A network-based approach to modelling bluetongue spread in France

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ABSTRACT

Bluetongue virus serotype 8 (BTV-8) was reported for the first time in Europe in 2006, causing the largest bluetongue outbreak ever recorded. France was mostly impacted in 2007/09. Trade restrictions were implemented all along. Vaccination became available from 2008: a limited number of doses was first administered in an emergency vaccination campaign, followed by two nationwide compulsory vaccination campaigns in 2009 and 2010. France regained a disease-free status in December 2012, but BTV may have kept circulating undetected as infected herds have been reported again since August 2015. We developed a stochastic dynamic compartmental model of BTV transmission in cattle and sheep to analyze the relative importance of vector active flight and host movements in disease spread, and assess the effectiveness of control measures. We represented BTV transmission both within and between French administrative subdivisions called cantons, during the 2007/09 outbreak and until the end of 2010, when compulsory vaccination was interrupted. Within-canton transmission was vector-borne, and between canton transmission could occur through three contact networks that accounted for movements of: *(i)* vectors between pastures located at close distance; *(ii)* cattle and sheep between pastures of the same farm; *(iii)* traded cattle. We estimated the model parameters by approximate Bayesian computation, using data from the 2007 French outbreak. With this framework, we were able to reproduce the BTV-8 epizootic wave. Host movements between distant pastures of the same farm were found to have a major contribution to BTV spread to disease-free areas, thus raising practical questions about herd management during outbreaks. We found that cattle trade restrictions had been well complied with; without them, the whole French territory would have been infected by winter 2007. The 2008 emergency vaccination campaign had little impact on disease spread as almost half vaccine doses had likely been administered to

already immune cattle. Alternatively, establishing a vaccination buffer zone would have allowed a better control of BTV in 2008: limiting its spatial expansion and decreasing the number of infected cattle and sheep. We also showed a major role of compulsory vaccination in controlling the outbreak in 2009 and 2010, though we predicted a possible low-level circulation after the last detection.

Keywords: Bluetongue, transmission dynamic modelling, contact network, host movement, vector-borne, vaccination

Abbreviations

AFSSA: French agency on food safety

BTV(-8): bluetongue virus (serotype 8)

CI95%: credible interval

CLC: CORINE land cover

CORINE: coordination of information on the environment

1. INTRODUCTION

Bluetongue (BT) is a non-zoonotic vector-borne viral disease of domestic and wild ruminants, mainly transmitted by biting midges of the genus *Culicoides*. Before the 21st century BT incursions into Europe used to be sporadic and limited to the southern part of the continent (Mellor et al., 2008). Since 1998, they became more frequent and BT spread further North, hence becoming one of the most important diseases of livestock in Europe with strong economic and social consequences (Rushton and Lyons, 2015). Bluetongue virus serotype 8 (BTV-8) which was reported for the first time on the European continent in 2006, caused the largest BT outbreak ever recorded (Carpenter et al., 2009) with over 95,000 infected holdings detected in two years' time. The strain that circulated in Europe surprised by its capacity to survive the coldest months and resume its spread after a winter break in a still poorly understood process referred to as overwintering.

France was mostly impacted from 2007: BTV-8 progressed in an epizootic wave from North-East to South-West, crossing the country in two years 'time. (Pioz et al., 2011). Trade restrictions were enforced in infected areas. An inactivated BTV-8 vaccine became available in spring 2008 in limited amount. Vaccination was first voluntary; vaccine doses were released progressively and attributed preferentially to areas that had already been affected by BTV in the previous year to allow farmers to return to normal production conditions (Sénat, 2008). Then, two nationwide state-funded compulsory vaccination campaigns were implemented in the winters of 2008/09 and 2009/10. The outbreak died off and was considered to be over by December 2009. Vaccination became voluntary and self-funded in 2011 and 2012. It was banned from 2013 onwards to preserve the national bluetongue free status regained in December 2012. BTV-8 remained undetected in Europe until August 2015, when a strain with an almost identical genome

sequence to the one that circulated in 2007/09 was detected in a ram in Central France (Bréard et al., 2016; Sailleau et al., 2017). The origin of the re-emergence remains unknown, with a possible silent circulation of BTV-8 in domestic ruminants between the two outbreaks (Courtejoie et al., 2017). Vaccination was re-introduced in autumn 2015.

Knowledge gaps remain about the epidemiology and management of the unexpected 2007/09 outbreak, in particular on the following points: *(i)* burden of infection given the high proportion of asymptomatic animals; *(ii)* relative role of host and vector movements in disease spread; and *(iii)* effectiveness of control measures that were implemented *vs* alternative measures that could have been considered.

In the past decades, mathematical models have been developed to study BT transmission and control in Europe (Courtejoie et al., 2018b). The challenging task of disentangling BTV spread *via* host and vector movements has rarely been addressed as many authors represented all routes of transmission together in a single probabilistic description (Szmaragd et al., 2009; Gubbins et al., 2010; de Koeijer et al., 2011; Boender et al., 2014; Bessell et al., 2016). Some authors explicitly considered long-distance host movements introduced by cattle trade (Turner et al., 2012; Ensoy et al., 2013; Sumner et al., 2017) but short-range and non-commercial host movements were rarely accounted for.

Here we developed a stochastic dynamic compartmental model of BTV spread in cattle and sheep from mainland France, representing long- and short-distance BTV transmission via three distinct contact networks explicitly accounting for different types of movements. The model was used to address remaining knowledge gaps on BTV spread and control.

2. MATERIAL AND METHODS

2.1. Study area and study period

We studied BTV-8 spread in mainland France (excluding overseas territories and Corsica) from summer 2007 to winter 2010, to cover the 2007/09 BTV-8 outbreak until the end of compulsory vaccination. We only focused on BTV-8, whereas BTV-1 circulated in the South of France in 2008 and 2009. We used administrative subdivisions called "cantons" as modelling units because sheep data were not available at smaller spatial scales. Each canton included on average 10 municipalities and covered about 150 km^2. There were 3,708 cantons in France during the study period; 3,432 of them hosted cattle and/or sheep.

2.2. Data sources

The number of cattle in each canton and all cattle movements between pairs of cantons were extracted from 2007 to 2010 from the National Identification Database, an exhaustive database maintained by the Ministry for Agriculture. The location and number of sheep in each canton were obtained from the 2010 Agriculture General Census of all holdings, conducted every ten years by the Ministry for Agriculture. We extracted pasture locations and the list of pastures belonging to the same farm from the Anonymized Land Registration System of 2011, provided by the French Agency for Services and Payment (Palisson et al., 2017). In this database, pastures were defined as grasslands, either permanent or temporary if part of a grass-arable rotation system. Temperature data were obtained from the SAFRAN atmospheric analysis system maintained by Météo France, with a spatial resolution of 8 km. We extracted all daily temperatures from 2007 to 2010. Land cover data were extracted from the 2012 version of the CORINE (Coordination of information on the environment) Land Cover (CLC) database,

provided by the European Environment Agency at a resolution of 100 m. Spatial data were aggregated by canton and temporal data were aggregated per week.

Surveillance data consisted in the list of farms with confirmed clinical cases detected from July 2007 until December 2009. Confirmed clinical cases were defined as diseased animals showing BTV-8 clinical signs and for which BTV-8 genomes (or anti-BTV antibodies in early 2007 only) had been detected. These data were provided by the French Ministry for Agriculture and processed by Pioz et al. (2011). Serological data consisted in the results of a cross-sectional retrospective serological study conducted in winter 2007/08 in seven and four French departments for cattle and sheep respectively (Durand et al., 2010); a department is an administrative subdivision containing on average 36 cantons. The number of vaccines administered in each department during the 2008 emergency campaign and during the 2009 and 2010 nation-wide compulsory vaccination campaigns was provided by the French Ministry for Agriculture.

2.3. Model design and parametrization

Stochastic compartmental models were used to capture BTV transmission in host populations in each canton. These models were operated with a weekly time step. Animals were grouped in species-specific compartments reflecting their health states (Figure 1). We did not implement a compartmental representation of vector populations due to the absence of abundance data needed for model parametrization. No systematic *Culicoides* trapping was indeed performed prior to 2009 on the French territory, except in Corsica and along the Mediterranean coast (Baldet et al., 2004). We used a non-Markovian representation of BTV transmission between hosts to account for vector-borne transmission, and we integrated environmental-based proxies of vector abundance, survival and activity to account for the spatial and temporal variations of vector

population dynamics. The size of cattle and sheep population by canton was matched to real data. For cattle, we updated the number of animals and births per canton every week. For sheep, we assumed a constant size in each canton and applied a weekly renewal proportion (Supplement S2.A).

At first, all animals of the canton were in the susceptible state. N_{inf} infected cattle were introduced in selected cantons: *(i)* on the observed date of first detection, the year when BTV-8 emerged (mid-July 2007); and *(ii)* at the beginning of each season of virus circulation (1st of June) afterwards. In 2007, infection was seeded in the six North-Eastern cantons where BTV-8 presence had first been confirmed. After 2007, the cantons where BTV was reintroduced in season *n+1* were simulation- and season-specific: they were those where BTV was still circulating before the winter break in season *n*, that is on the date when temperatures dropped below the T_{min} threshold in a proportion p_{ow} of cantons.

Each week, the number of animals that became infected in a given canton ($n_{inf}^{sp}(k,t)$) was the sum of two terms:

$$n_{inf}^{sp}(k,t) = n_{vect}^{sp}(k,t) + n_{intro}^{sp}(k,t)$$

with $n_{intro}^{sp}(k,t)$, the number of infectious animals introduced in canton *k* at time *t*, resulting from animal movements between trade partners or between distant pastures of the same farm; and $n_{vect}^{sp}(k,t)$, the number of susceptible animals infected by vector bites. This latter number depends on the force of vector-borne infection from female midges located in the canton and in other cantons within flight distance.

$$n_{vect}^{sp}(k,t) \sim Binom(S^{sp}(k,t) + L^{sp}(k,t), P_{inf}^{sp}(k,t))$$

where the probability of infection of susceptible individuals is given by:

$$P_{inf}^{sp}(k,t) = 1 - \exp\left(-\pi^{sp} * [\lambda_{int}(k,t) + \lambda_{vect}(k,t)]\right)$$

with π^{sp}, the relative preference of vectors for cattle or sheep (conditional on feeding on these species); $\lambda_{int}(k,t)$, the force of vector-borne infection from female midges located in canton *k*, and $\lambda_{vect}(k,t)$, the force of vector-borne infection from female midges located in other cantons within flight distance of canton *k*.

$\lambda_{int}(k,t)$ represents the force of vector-borne infection from female midges located in the canton that got infected locally while feeding on infectious ruminants in the previous time steps, that completed the extrinsic incubation period (EIP) required for BTV replication and dissemination up to the arthropod vector salivary glands, and survived up to time *t*. We made the simplifying assumption that, in a given canton, and during the vector activity period, the vector to host ratio was constant. Under this assumption, the vector-borne transmission can be represented by a non-Markovian force of infection, which accounts for the *Culicoides* cohorts that emerged in the preceding weeks.

$$\lambda_{int}(k,t) = \tau(k,t) * \sum_i (w_i * Prev(k,t-i))$$

with $Prev(k,t-i)$, the proportion of infectious animals at time *t-i* weighted by vectors species-specific trophic preferences; w_i, the fraction of *Culicoides* vectors that have completed their EIP in *i* weeks and survived over that period (Supplement S1.A, C); $\tau(k,t)$, the weekly effective contact rate at which vectors and hosts from canton *k* come into effective contact, given by:

$$\tau(k,t) = \beta_0 * Env(k) * b(k,t)$$

with β_0, a coefficient that represents the baseline exposure of hosts to vectors, defined here as the product of the baseline vector to host ratio, the host to vector and vector to host probabilities of successful transmission, and the trophic preference of *Culicoides* for cattle and sheep *vs* other warm-blooded species; *Env(k)*, the environmental variables used as proxy of host availability,

Culicoides presence and abundance; *b(k,t)*, the temperature dependent biting rate of *Culicoides* at time *t* in canton *k* that represents the seasonal variation in *Culicoides* activity.

Env(k) was defined under the assumption that bluetongue transmission in a given area depends on the proportion of surface covered in pastures (CLC code: 231), where hosts and vectors come into contact. We used additional landscape metrics to modulate the transmission that occurred on pastures: the spatial density of borders between pastures and arable lands (CLC code: 211-213), and between pastures and forests/semi-natural areas (CLC code: 331-335). Indeed, manure is spread on arable lands and provide suitable breeding sites for BTV vector species (Ninio, 2011), whereas forests/semi-natural areas provide shelter to the wild animals that may contribute to BTV sylvatic cycle (Rossi et al., 2014).

Between-canton movements of vectors and hosts occurred on three distinct contact networks: *(i)* the pasture network, representing midges flight; *(ii)* the farm network, representing movements of cattle or sheep between pastures of the same farm; and *(iii)* the trade network, representing movements of traded cattle. The nodes were cantons and a link existed between two cantons: *(i)* in the pasture network, if at least two pastures from each canton were less than one km apart, a distance used by Palisson et al. (2017) to represent the most likely routes of vector-borne disease transmission across the densely connected network of French pastures; *(ii)* in the farm network, if at least one farm had pastures located in each canton; *(iii)* in the trade network, if cattle had been traded between at least two farms located in each canton. The trade network was temporal and oriented, linking different donors and recipients every week, while the pasture and farm networks were static with links existing at all times and movements through these links as likely to go either way. Their topological properties are analyzed in Supplement S5.

BTV transmission due to midges dispersal was represented by applying to canton *k* a fraction Ψ_P of the force of vector-borne infection of its neighbors on the pasture network

($\lambda_{vect}(k,t)$), where Ψ_P is the proportion of canton surface that can be reached by vectors coming from each neighboring canton. The number of infectious animals introduced through the farm and trade networks ($n_{intro}^{sp}(k,t)$) depended on the number of animals moved towards canton *k* on each network and on the prevalence of infection in the source canton. The total number of cattle traded could be fully informed by data, while the total number of cattle and sheep movements on the farm network depended on Ψ_F, the weekly proportion of animals moved between pastures of the same farm. Movements of traded cattle was subjected to restrictions that were implemented and complied with, with a probability θ. All these processes and associated parameters are described in more details in Supplement S1.B.

Cantons with infected animals could be detected by passive clinical surveillance, given a probability Δ that infectious animals could show clinical signs and be detected (Supplement S2.B). Once at least one animal was detected, the canton became a "reporting canton". We recorded the date of first detection per canton and applied similar control measures to those actually implemented during the outbreak: movements were banned in cantons located in a 20 km radius around the reporting ones; those located in a 90 km radius were placed in a restricted zone: movements were allowed within that zone, but prohibited from the inside to the outside.

We represented three vaccination campaigns: the 2008 emergency vaccination campaign, conducted in times of outbreak, and the 2009 and 2010 compulsory campaigns, conducted in the first months of each year, when vectors were not active. In 2008, we attributed the limited number of vaccine doses following the Ministry for agriculture's vaccination schedule (Figure 6.A, D).

Most model parameters were informed from the literature, or from plausible assumptions then challenged in sensitivity analyses (Table 1). Three of them were estimated because they were specific to our study context and could not be inferred from previous studies.

2.4. Parameter estimation and model selection

We estimated three parameters: $\beta_{0,}$ the baseline exposure of hosts to vectors; Ψ_F, the proportion of animals moved weekly between pastures of the same farm; and θ, the probability that cattle trade control measures would be complied with. We used the Adaptive population Monte-Carlo approximate Bayesian computation method (ABC-APMC) (Lenormand et al., 2013), a likelihood-free method useful for complex, stochastic models where the full likelihood cannot be estimated. It is based on the generation of joint parameters values (particles) initially sampled from the joint prior distribution of each parameter, followed by the selection of the particles for which the model outputs (summary statistics) satisfy a proximity criterion with the target data (Supplement S4.A). We used the following settings: 0.5 for the quantile of the distribution of distances to observed data used to define tolerance thresholds; 0.03 for the minimal proportion of new particles satisfying the stopping criteria from the previous step; and a final size of 5,000 particles used to build posterior probabilities.

The summary statistics used for inference were built from surveillance and seroprevalence data from the 2007 epizootic wave. For surveillance data, we used the numbers of departments with, and without, reporting cantons by winter 2007/08. For seroprevalence data, we used the species-specific number of seropositive animals detected in each department sampled in the serosurvey conducted in winter 2007/08 (Supplement S4.B). We used uniform priors for all parameters (Supplement S4.C).

We investigated the need to make within-canton transmission rates vary with land-cover metrics, and the need for between-canton transmission to occur through only one or several contact networks. We built separate models including various combinations of the variables and contact networks of interest and compared them using a model selection procedure based on random forest classification methods (Pudlo et al., 2016). We selected the set of variables/networks providing the best fit to the observed data, then used it for all subsequent analyses (Supplement S3).

2.6. Model implementation, validation and exploitation

The model was coded in C++ and operated in R (version 3.3.2) using the Rccp package. ABC-APMC estimation and model comparison by random forest were conducted using the EasyABC and ABC-RF packages in R.

To assess the ability of our framework to estimate parameter values using the chosen summary statistics, we simulated 100 epidemics with parameters randomly drawn from the prior distributions, and we estimated back these parameters using the ABC-APMC procedure (Supplement S6). Model fit was evaluated by sampling 1,000 particles from the weighted joint posterior distributions and by generating summary statistics that we compared to the observed ones (used for parameter estimation). An external validation was performed by confronting simulated data with the observed spatio-temporal distributions of reporting cantons from 2007 to 2010 (not used for parameter estimation). From 2008, we excluded the southern areas where BTV-1 circulated as there may have been some cross-immunity.

A sensitivity analysis was performed to evaluate the effect on the estimated parameter values of two key parameters with values that were fixed: the proportion of canton surface reachable by vectors from neighboring cantons (Ψ_P) and the probability of detection upon clinical

277 suspicion (Δ). We compared *(i)* the relative error induced by a 25% change of each fixed
278 parameters on the average values of each estimated parameter, with *(ii)* the coefficient of
279 variation of the posterior distributions obtained with the default values. In addition, we
280 investigated the effect of fixed deviations of initial conditions (N_{inf}, p_{ow}) on model predictions
281 (Supplement S7).

282 We operated the parametrized model until the end of 2010, using 1,000 particles sampled
283 from the weighted joint posterior distributions, and computed various indicators. To address the
284 epidemiological contribution of the contact networks during the 2007 and 2008 epizootic waves,
285 we investigated the proportion of transmission that occurred through each of them. In every
286 simulation, we recorded the source of infection of each newly infected canton, *i.e.* whether a
287 canton previously free of infection had been contaminated through the pasture, farm or trade
288 network. Infections that occurred through multiple networks on the same week were randomly
289 allocated to either one of them. To address the true burden of infection, detected or not, and to
290 highlight local differences in the extent of BTV spread, we reconstructed for all French
291 departments: *(i)* the seroprevalence level in the winter after each season of virus circulation
292 (2007, 2008, 2009 and 2010); and *(ii)* the cumulative proportion of animals that had been infected
293 in each season of virus circulation. To evaluate the control measures, we estimated the proportion
294 and number of vaccines that had been administered to already immune animals in the 2008
295 emergency vaccination campaign.

296 Finally, we explored alternative control scenarios. We investigated four alternative
297 scenarios of movement restriction in 2007: one in which no control measures were applied on
298 trade movements of cattle, two in which they were applied and complied with at 90% and 95%,
299 and one in which movement restrictions, perfectly complied with, were extended to movements
300 of animals between pastures of the same farm. We investigated two alternative scenarios of

vaccination from 2008: one in which there was no vaccination at all, neither in 2008, nor in the compulsory campaigns of 2009 and 2010; and another one in which the 2008 emergency vaccination campaign was targeted to create a buffer zone beyond the previously affected areas (Figure S1), as recommended by the French agency on food safety at that time (AFSSA, 2008). In the latter scenario called the "AFSSA scenario", we released the same number of doses every week as in the baseline scenario, as vaccines were limiting at the time, but we distributed them in different order of priority, vaccinating less areas but with higher vaccination rates. We ran a 1,000 simulations in each scenario.

3. RESULTS

3.1. Description of the study area

The study area comprised the 3,432 French cantons that hosted cattle or sheep in 2007/10. There was a total of 19.6 million head of cattle and 5.5 million head of sheep hosted in 236 and 55 thousand farms, respectively. These domestic ruminants may have been put out to pasture on the three million parcels of grasslands defined as pastures (of 0.05 km^2 on average). The median number of cattle and sheep per canton was 3,042 [1^{st} – 3^{rd} quartile: 606 – 8,715] and 347 [80-1,135], respectively; and the median number of cattle and sheep farms per canton was 45 [15-92] and 8 [2-19], respectively. The median number of pastures was 573 [137-1,299] per canton, 7 [3-14] per farm and 9 [4-15] per farm with more than one pasture (*i.e.* 90% of all farms). 33% of all farms, and 37% of those with more than one pasture had pastures located in different cantons.

3.2. Model selection and parameter estimation

Model selection showed: *(i)* that the proportion of pastures was crucial to representing BTV within-canton transmission, with no benefit to model fit when including additional landscape metrics (Supplement S3.B); and *(ii)* that no network on its own was enough to represent BTV spread to new areas, with the best fit obtained when all networks were combined (Supplement S3.C). We thus selected the model in which the only environmental variable (*Env(k)*) was the proportion of canton surface covered in pastures, and which included the three contact networks. The framework and choice of summary statistics were validated based on pseudo-observations generated from randomly chosen parameter values (Supplement S6). Parameter estimates appeared satisfactory but estimates were regressed towards the mean of the prior distribution for extreme parameter values because of saturation in the summary statistics.

Then, we applied the framework to the observed data (Figure 2). The posterior distributions had the following median values: 5,543 (CI95%: 3,078-9,340) for the baseline exposure of hosts to vectors (β_0); 60.4% (CI95%: 27.4-96.0%) for the proportion of animals moved weekly between pastures of the same farm (Ψ_F); and 97.1% (CI95%: 92.0-99.7%) for the probability that control measures would be complied with (θ).

Simulated data allowed reconstructing the observed data used for parameter estimation (Figure S3), as well as the spatio-temporal distribution of reporting cantons (Figure 3). As in the observations, the simulations predicted a peak in detections in 2007, followed by a winter break and a second peak in 2008 when virus circulation resumed. The ability of the model to reconstruct the epizootic wave that crossed France in 2007 and 2008 was illustrated by mapping the newly reporting cantons every six weeks (Figure S4). In 2007, the map (Figure 3.A) and histogram (Figure 3.B) of reporting cantons showed slightly more notifications on average in simulations *vs* observations. By the end of winter, the area with reporting cantons in most simulations matched the area with most observed reporting cantons: apparent infection was mostly limited to the North-East of the country (Figure 3.A.1-2). Yet, in a few simulations, BT cases could have been detected in the whole territory during the 2007 epizootic wave (Figure 3.A.1). The 2008 epizootic wave progressed towards the South-West, reaching similar geographical areas in simulations and observations (Figure 3.A.3-4). In both case, two years of BTV circulation resulted in infected cases detected in >95% of the French departments (excluding those where BTV-1 circulated). In 2009, BTV kept circulating in the already detected areas, with no observed newly reporting cantons (Figure 3.B). However, in simulations, infection spread slightly further South-East in 2009, hence the few newly reporting cantons (Figure 3.B).

3.3. Model exploitation

In our simulations, most transmission to new areas occurred on the farm network (65%), followed by the pasture network (35%), and very little from trade (<1%) (Figure 4).

In 2007, the reconstructed seroprevalence levels (Figure 5.A.1, C.1) and cumulative proportion of infected animals per department (Figure 5.B.1, D.1) conveyed the same information: the burden of infection. They highlighted spatial contrasts, with some areas where more than 90% of the ruminants may have been infected by winter 2007/08. These maps diverged from 2008 (Figure 5.A-D.2-4), as several processes contributed to seroprevalence: past and present infection, population renewal, and vaccination. The contrasts between these maps gave an indication of the relative contribution of these processes. We predicted that BTV was still circulating in 2010 with similar low levels as in 2009 (Figure 5.B3-4, D.3-4), which would not have remained undetected in our setting (Figure S5), though the outbreak was considered as over from 2010 onwards.

In 2008, vaccination was conducted during the season of virus circulation. In our simulations, we highlighted spatial contrasts in the proportion of vaccines that had been administered to already immune animals (Figure 6.C, F) due to the relative timing of vaccination and infection (Figure 6.A, D). For both species, most of the vaccinated animals in the North-Eastern departments were already immune (>80% in some areas) and we estimated that >3 million vaccine doses had been administered to already immune cattle (41% of all vaccines), and <1 million (18%) to already immune sheep.

In 2008, vaccination, as it was conducted, had little impact on spatial spread in our simulations. The absence of vaccination would have only resulted in a 5% increase in the number of newly reporting cantons (Figure 7.B). However, there would have been a greater increase in the number of infected animals (about 10% increase in cattle and 55% in sheep) (Figure 7.A). The alternative AFSSA scenario would have allowed an additional 15% reduction in the number

of newly reporting cantons, and an additional 20% and 30% reduction in the number of infected cattle and sheep respectively. However, the infected cases would have been distributed differently than in the baseline scenario, with more cases in the North-East and less in the South-West (Figure 7.D). Overall, less vaccine doses would have been administered to immune animals, with only 5% reduction in the number of useless doses in sheep (0.8 *vs* 0.9 million) but over 60% reduction in cattle (1.2 *vs* 3.2 million). Finally, we predicted that from 2009, the absence of vaccination would have led to a dramatic increase in the number of infected animals in both 2009 and 2010, even greater in sheep than in cattle (Figure 7.A).

If movements on the farm network had been controlled similarly to the ones on the trade network in 2007, there would have been a 40% decrease in the number of newly reporting cantons compared to the baseline scenario (Figure 7.B, C.1), as well as a 40% decrease in the number of infected animals in that year (both in cattle and sheep) (Figure 7.A). On the other hand, if movements on the trade network had not been controlled in 2007, >65% of the French cantons would have reported BTV-8 infected cases by winter 2007 (Figure 7.B), >100% more than in the baseline scenario (Figure 7.C.2). There would have been a dramatic increase in the number of infected cattle and sheep (250 and 300% respectively, Figure 7.A), meaning that >70% and >45% of the total cattle and sheep populations respectively would have been infected. The effect would have been less dramatic but still substantial with a mere decrease of 5 and 10% in the compliance of movement restriction.

The sensitivity analysis showed little effect on parameter estimates of a 25% variation of the probability of detection upon clinical suspicion (Δ), but a stronger effect of a 25% of variation of the proportion of canton surface reachable by vectors coming from neighboring cantons (Ψ_P) (Supplement S7.A). However, we showed little difference on the variation of model predictions

for each couple of Ψ_P and associated parameter estimates. Lastly, the sensitivity analysis on model predictions showed little effect of variations of the initial conditions (Supplement S7.B).

4. DISCUSSION

In this work, we developed a stochastic dynamic model of bluetongue transmission in French cattle and sheep. We represented BTV vector-borne transmission in infected cantons, and used contact networks to represent BTV spread to disease-free areas. Our framework had the specificity of integrating two types of host movements: cattle traded between farms and cattle and sheep moved between distant pastures of the same farm. We combined multiple and high quality data sources to represent exhaustively population dynamics processes in hosts. Because of the absence of such data for *Culicoides* during the study period, we represented BTV vector-borne transmission in infected cantons by a non-Markovian formulation of the force of infection. This is equivalent to using a compartmental representation of vector populations with a fully Markovian dynamics, assuming that the vector to host ratio remains constant during the vector activity period (canton- and year-specific). This model may be adapted to the study of other vector-borne diseases of ruminants, in areas where the vector abundance does not show strong variations during the vector activity period.

We used our model to address the question of the relative contribution of the contact networks to disease spread between French cantons. Most transmission events between cantons were predicted to have happened on the farm network. Movements between distant pastures of the same farm are rarely considered in bluetongue transmission models because they are poorly documented. There is no precise record of grazing practices that may vary across geographical areas, breeding types and farmers. Our parameter estimation meant that grazing ruminants changed pasture on average every two weeks, which seems consistent given that French pastures

424 are small (0.05 km^2 on average) and that animals are frequently moved for grass renewal and
425 sanitary reasons such as the interruption of parasitic cycles (*e.g. Fasciola hepatica*).

426 The major contribution of movements between distant pastures of the same farm leads to
427 practical implications as we showed in a simulation study that controlling these movements may
428 have prevented many infections and limited the geographical spread. However, these findings
429 raise crucial questions about the feasibility of such control measures and about management
430 practices as grazing habits are at the discretion of farmers. Movements between distant pastures
431 of the same farm are also harder to regulate than trade exchanges, which are the subject of
432 specific protocols and are rigorously traced.

433 Among the many mathematical models of BTV-8 transmission developed after the
434 European outbreak (Courtejoie et al., 2018b), Sumner et al. (2017) were the only ones providing
435 a thorough quantification of the relative contribution of host and vector movements to
436 transmission events between farms. They attributed >90% of between-farm transmission to
437 vector-dispersal, which does not contradict our results given that the epidemiological units are
438 different (farms *vs* cantons), and that within-canton transmission is mainly driven by vectors in
439 our model. Here we provide an additional layer of information about the drivers of BTV spread
440 as we focus on the role played by different types of contact networks in BTV spread to new areas
441 at the wider scale of the canton, with a median number of 94 farms per canton.

442 In previous modeling studies, a greater attention has been paid to the diversity of vector
443 dispersal modes (*e.g.* active, passive, against the wind, Hendrickx et al., 2008; Ducheyne et al.,
444 2011; Sedda et al., 2012) than to the diversity of host movements. When the latter were explicitly
445 represented, only long-range movements of traded hosts were accounted for (Turner et al., 2012;
446 Ensoy et al., 2013; Sumner et al., 2017), and not non-commercial animal movements that may
447 happen at a similar distance to that of vector active flight. Only Graesbøll et al. (2012; 2014)

448 provided a detailed representation of both host and vector-related processes in BTV transmission:
449 in vectors, they separated active flight and passive wind-borne dispersal; in hosts, they
450 represented the movements of animals between pastures of the same farm under four different
451 grazing conditions, as well as the mixing of animals from neighboring farms. Yet, their highly
452 detailed framework did not allow quantifying the relative contribution of short-range active flight
453 by midges and movements of hosts on pasture because of the high sensitivity of their model to
454 parameter values, the poor knowledge on the flying parameters, and the lack of data on both host
455 and vector distributions (Graesbøll et al., 2012).

456 We provided a simpler representation of transmission processes designed to best use
457 available data and existing literature. We did not describe several modes of vector-borne
458 dispersal, but considered that, in addition to being responsible for BTV spread inside cantons,
459 vectors could spread infection between cantons through the pasture network, with flight distance
460 as only limiting criteria. It is possible that part of the transmission that we attribute to host
461 movements between pastures was actually due to vector active dispersal at a wider scale than that
462 considered (>5 km per week), or to passive wind-borne vector dispersal. On the other hand, part
463 of the transmission attributed to vector dispersal in previous studies may be due to non-
464 commercial host movements. Yet, results obtained for BTV spread in French livestock may differ
465 in other European countries as grazing habits depend on breeding types and country-specific
466 management practices.

467 Movements of traded cattle were the only ones allowing for long-distance jumps and fast
468 spreading. However, they hardly contributed to disease spread in simulations because the control
469 measures were almost perfectly implemented and complied with. The analysis of alternative
470 control scenarios stressed on the need for an efficient control of trade movements in times of
471 outbreak, as we predicted a dramatic increase on both BTV spatial spread and outbreak size if

472 they were only 5% less controlled, and a possible infection of the whole French territory by the
473 end of 2007. Animal transport restrictions had already been proven effective in substantially
474 slowing down BTV spatial spread in Europe in 2006 and 2007 (de Koeijer et al., 2011; Boender
475 et al., 2014), and in reducing outbreak sizes in Belgium in 2006 (Ensoy et al., 2013) and in
476 Eastern England in 2007 (Turner et al., 2012). Furthermore, when BTV was introduced in the UK
477 in 2007, the movement restrictions already in place as a result of foot-and-mouth disease control
478 were identified as one of the main factors explaining the relatively small 2007 outbreak in the
479 UK, compared with other European countries (Turner et al., 2019).

480 Our analysis of host movements was limited by available data. We represented only cattle
481 trade movements as there is no comprehensive record of the number of traded sheep in France.
482 However, there are over four times more cattle farms than sheep farms in France, and there is
483 little live sheep trade as most animals only leave their birth farm when sent to the slaughter
484 house. In addition, the movements we used were those that effectively took place as movements
485 remained possible under specific protocols (1266/2007/CE, October 26 2007). We may under-
486 estimate the movements that would have happened in 2007/09 in absence of outbreak, as
487 movement restrictions are likely to have impacted: *(i)* the number of sales, with a 21% decrease
488 estimated in a beef cattle breed in which most calves are sold for fattening (Tago et al., 2014); *(ii)*
489 export destination, in relation to the evolution of restricted zones; and *(iii)* timing, as practical
490 constraints add export delays. However, the analysis of the French cattle trade network from
491 2005 to 2009 did not show any significant difference between the years of the study period at the
492 national scale (Dutta et al., 2014).

493 We also retrospectively investigated the usefulness of vaccination. The 2008 emergency
494 vaccination campaign did not prevent disease expansion to new areas. Vaccination targeted in
495 priority the North-Eastern departments where most animals had already been infected in 2007, so

that most vaccine doses were administered to already immune animals. Vaccination targeted ahead of the front would have limited BTV spatial spread: it would have been preventive in the areas that had not been reached by the epizootic wave in 2007, and the 2008 outbreak would have remained constrained to the already infected areas. Back in 2008, the design of the vaccination strategy had been individual-based, to protect the farmers that had already suffered from the 2007 epizootic wave, rather than population-based, to prevent disease expansion to new areas. Here we show that both vaccination strategies, individual or population-based, have –or would have- met their respective goals.

Whatever the vaccination strategy, only vaccination performed by July 2008 may have provided protective immunity on time and influenced the course of the outbreak as vaccination was conducted simultaneously with virus circulation and that there is a few weeks' delay between vaccination and acquisition of protective immunity. Vaccination was more preventive in sheep than in cattle because it started earlier in this species, which is more sensitive to BTV, and because only one vaccine dose was required in sheep *vs* two in cattle.

Vaccination became truly preventive from 2009, when vaccines became available in sufficient quantity to vaccinate all domestic ruminants outside of the periods of vector activity. The course of the outbreak was truly changed by widespread compulsory vaccination which allowed maintaining high seroprevalence levels. Without vaccination, BTV would have kept reemerging every year with a significant level of infected cattle and sheep, suggesting that the situation may have become endemic. This is consistent with the results obtained by the EFSA Panel on Animal Health and Welfare (EFSA, 2017) whose mathematical model indicated that BTV could persist for several years without any vaccination, reaching an endemic situation with low level of prevalence of infection (1.5% in cattle, 0.6% in sheep).

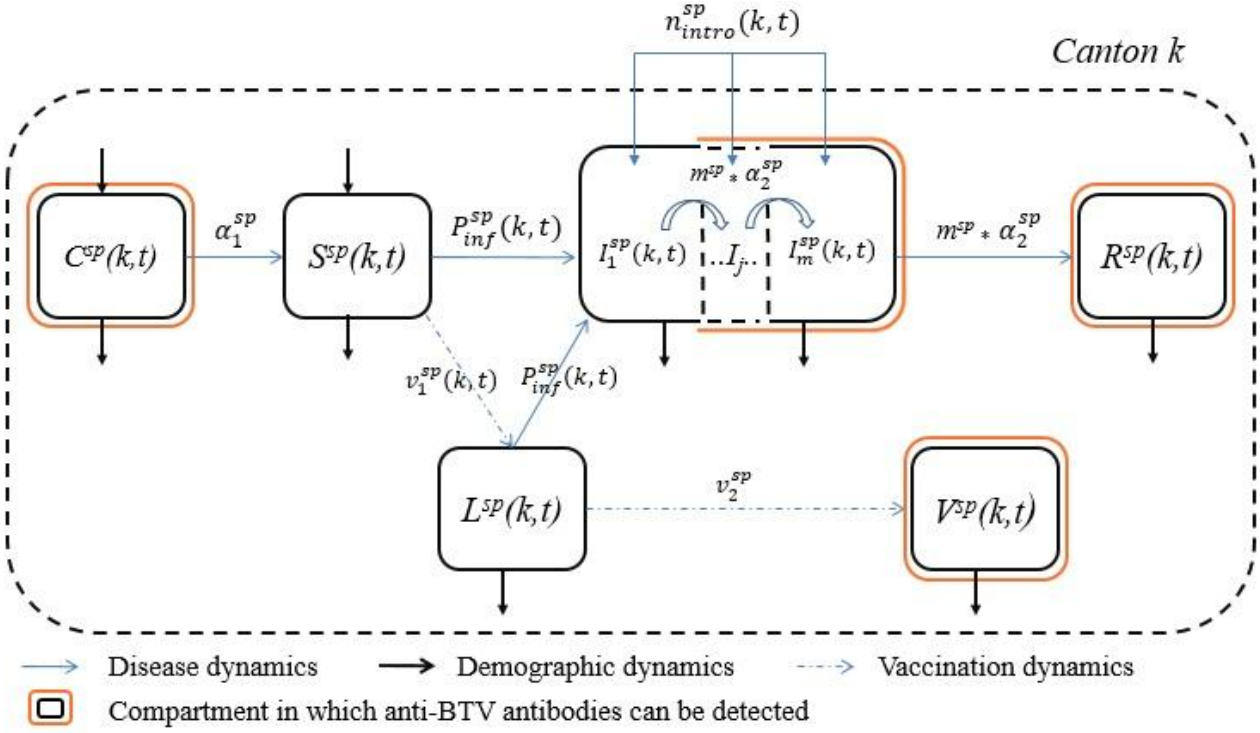
519 We still do not know whether widespread compulsory vaccination allowed a real
520 eradication of BTV as our model predicted a potential residual level of circulation even after the
521 last case detection in 2009. The model developed by EFSA experts predicts that five years of
522 vaccination of 95% of susceptible French cattle and sheep would have been required to reach a
523 prevalence of infection close to eradication levels (EFSA, 2017). If vaccination went on after
524 2010, it became voluntary and there is little knowledge on vaccine uptake at that time. We
525 suggested in a previous study that vaccination have been only little implemented, even less in
526 2012 than in 2011 (Courtejoie et al., 2018a). It would be interesting to model alternative
527 vaccination scenarios after 2011, such as one or two additional compulsory campaigns, and
528 assess whether the 2015 re-emergence could have been prevented.
529 Some of our modelling assumptions need to be discussed. The resurgence after each
530 winter break was obtained providing assumptions on BTV overwintering, a phenomenon that
531 remains poorly understood and most likely results in the combination of several processes
532 (Takamatsu et al., 2004; Napp et al., 2011). It may be explained by the persistence of adult
533 vectors in the coldest months by taking shelter inside farm buildings (Baldet et al., 2008;
534 Carpenter et al., 2009); or by vertical transmission in hosts, with a cumulative duration of
535 infectious viremia in heifer and calve lasting longer than the vector inactivity period (Wilson et
536 al., 2008). Our model does not have the granularity allowing to represent BTV overwintering, but
537 we assumed that BTV resumed its spread in the cantons where it was still circulating when
538 temperatures dropped in the end of each season of circulation. The sensitivity analysis showed
539 little variation of model predictions with reasonable variations of the initial conditions used for
540 BTV reintroduction.
541 The surveillance system was based on clinical suspicion and we used a single probability
542 of detection of infected animals upon clinical suspicion, though this may have varied in time, in

place, according to the main breeding type and to the sensitization of farmers. In 2010, we predicted low-level virus circulation, which would have been detected if applying the same probability of detection. Yet, no case had been detected in this year. We may have re-seeded infection too strongly in 2010: our assumption for overwintering may not be adapted to the epidemiological context after 2009 when there was no, or low-level, virus circulation. On the other hand, the probability of detecting animals upon clinical suspicion may have decreased in time, allowing for an undetected low-level BTV circulation in 2010 and potentially up to the 2015 reemergence. Indeed, the 2015 BTV-8 strain, though almost genetically identical to the one isolated in 2007, has been shown to induce less clinical signs in sheep experimentally infected with both strains (Flannery et al., 2019).

In conclusion, we built a framework that allowed the reconstruction of the 2007/09 BTV outbreak in France. We showed a major contribution to BTV spread between cantons of host movements between distant pastures of the same farm, raising practical questions of herd management in times of outbreak. We provided an assessment of the effectiveness of the control measures that had been conducted, stressing on the crucial impact of the restriction of cattle trade movements, and providing a better understanding of the impact of the successive vaccination campaigns until the outbreak died off. This adaptable framework could be further used to reproduce and understand past events such as the cumulative impact of vaccination and population renewal in shaping the immunity landscape in French ruminants until the 2015 re-emergence. In the future, this framework might become a management tool to explore and compare various control scenarios in times of outbreak.

FIGURES

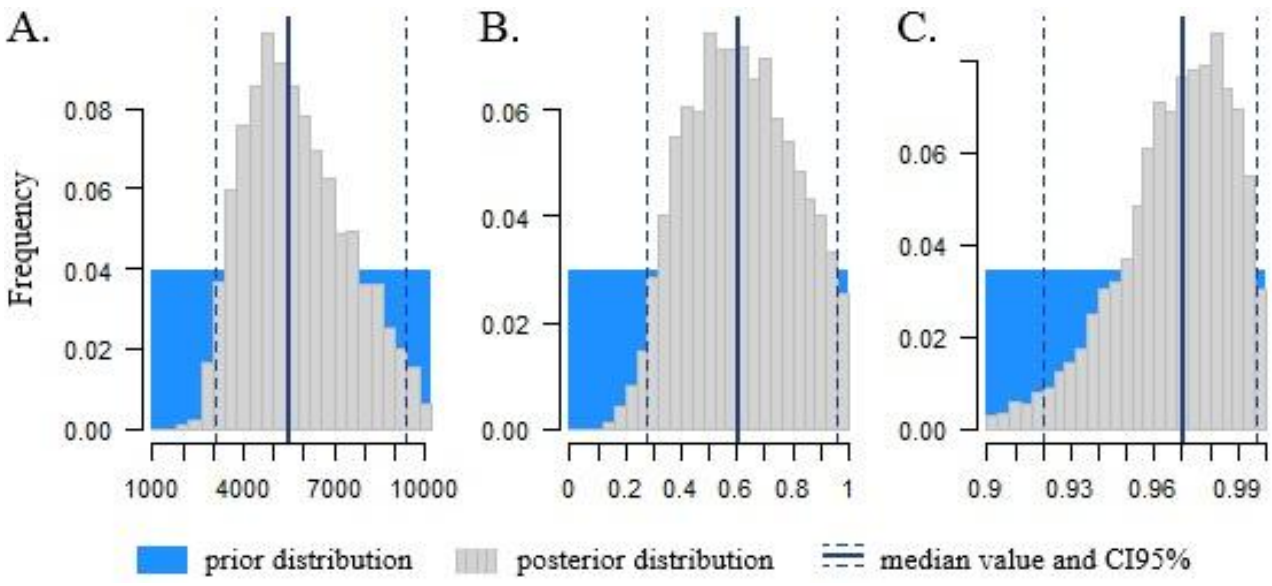
Figure 1. Schematic representation of the species-specific compartmental model.



Superscripts *c*, *s* and *sp* are used to indicate parameter values specific to cattle, sheep or to either one of the species respectively. Cattle or sheep could be in one of the following health states: *C*: protected by colostral antibodies within their first months of life if born from seropositive mothers; *S*: susceptible, *i.e.* uninfected and immunologically naive; *I*: infectious, with enough BTV in the blood stream to infect *Culicoides* when feeding; *R*: recovered and protected against further infection by persistent antibodies; *L*, latent-vaccinated, between vaccination and acquisition of protective immunity against BTV; *V*, vaccinated, for vaccinated individuals protected against BTV infection. The infectious health state was subdivided into m^{sp} stages so that the time spent in that state followed a flexible gamma distribution. We denoted: $C^{sp}(k,t)$, $S^{sp}(k,t)$, $I^{sp}(k,t)$, $R^{sp}(k,t)$, $L^{sp}(k,t)$ and $V^{sp}(k,t)$, the number of animals of species *sp* in each health state in canton *k* at time *t;* $n_{intro}^{sp}(k,t)$, the number of infectious animals of species *sp* introduced in canton *k* at time *t*. $\alpha_1^{sp}, \alpha_2^{sp}, P_{inf}^{sp}(k,t), v_1^{sp}(k,t), v_2^{sp}$ were the transition

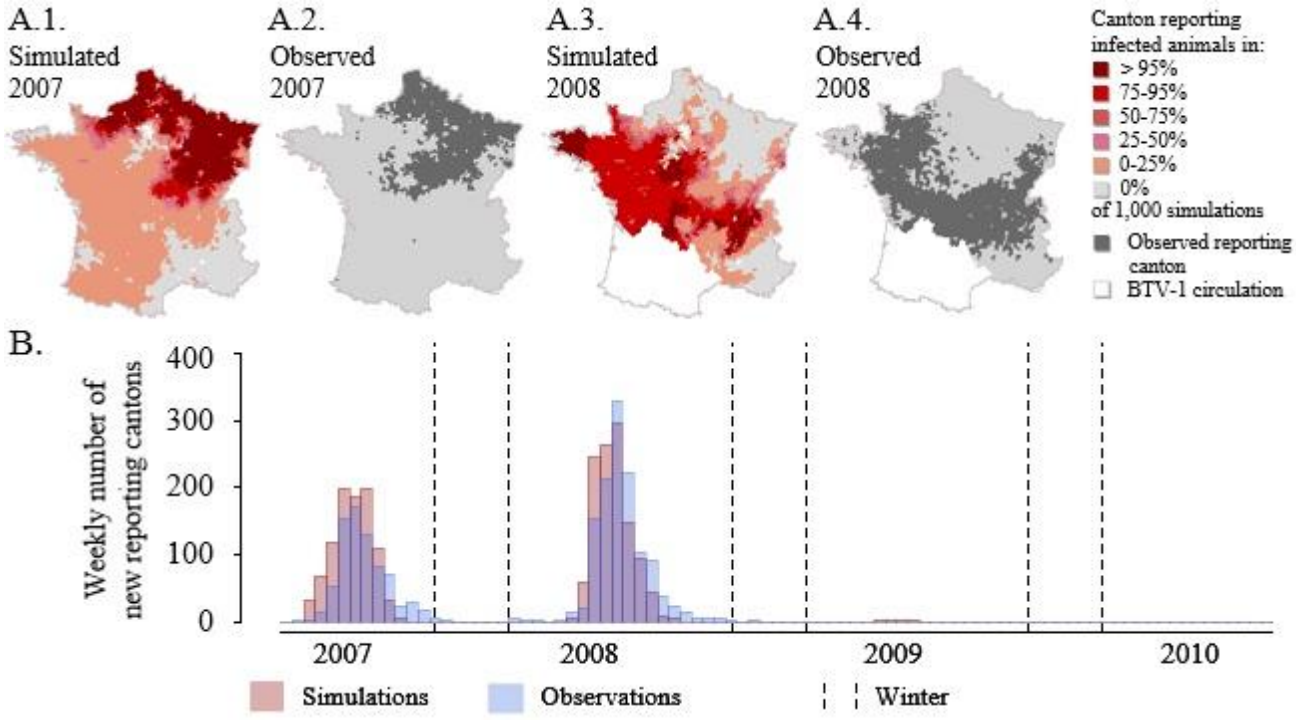
probabilities for species *sp* with: α_1^{sp}, 1/length of persistence of colostral antibodies; α_2^{sp}, 1/viremia; $P_{inf}^{sp}(k,t)$, probability of infection (vector-borne) in canton *k* at time *t*; v_1^{sp}, vaccination rate in canton *k* at time *t*; v_2^{sp}, rate of acquisition of protective immunity.

Figure 2: Posterior distributions of the three estimated parameters.



A. Baseline exposure of hosts to vectors (β_0); B. Proportion of animals moved weekly through the farm network (Ψ_F); C. Probability of control measures being implemented on movements of cattle through the trade network (θ). CI95%: credible interval.

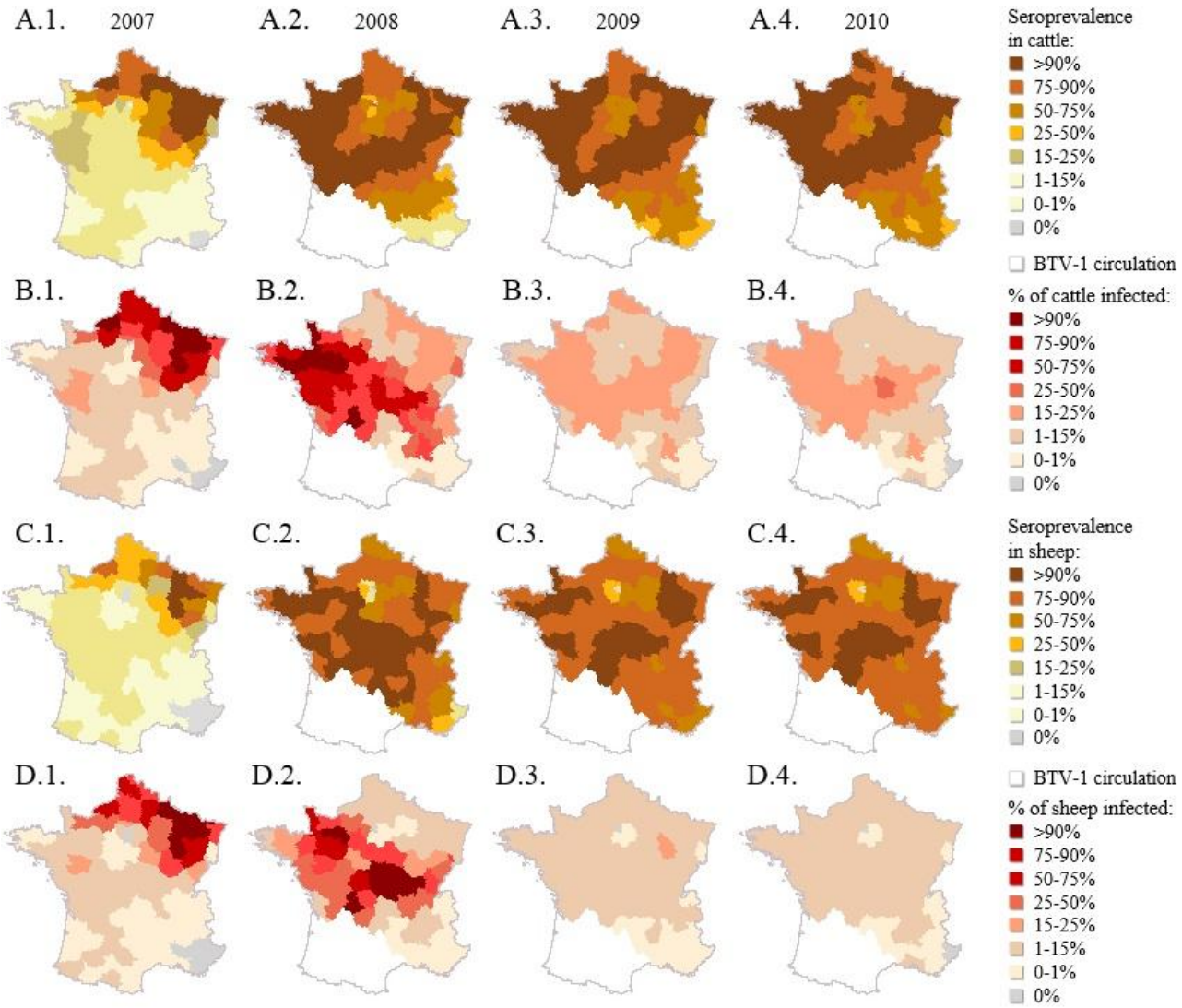
587 **Figure 3: External validation: spatio-temporal pattern of the apparent infection**.



588

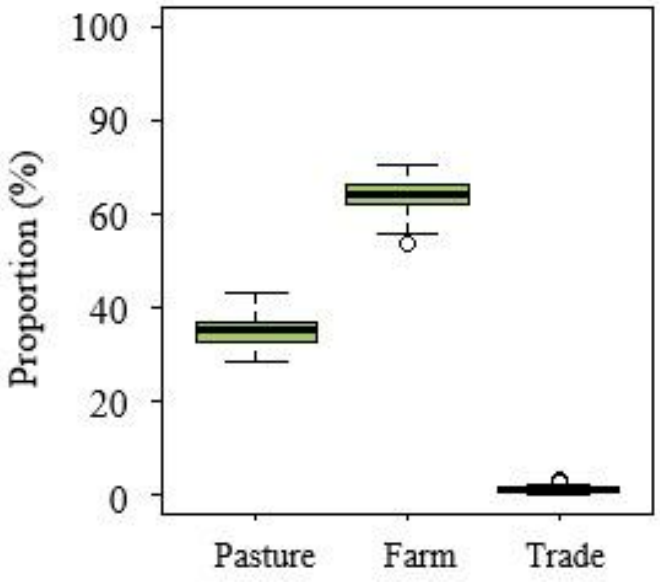
589 A. Spatial pattern of detection of infection in cantons: frequency of reconstructed detection (1,000
590 simulations: A.1, A.3) *vs* observations (A.2, A.4), in 2007 (A.1, A.2) and in 2008 (A.3, A.4); B. Temporal
591 pattern of detection: histogram of observed and simulated reporting cantons in 2007/10 (median value of
592 1,000 simulations).

Figure 4: Initial source of infection.



Proportion of BTV introduction to new areas that happened on each contact network (pasture, farm or trade networks). The boxplots indicate the mean, interquatile interval, minimal and maximal values.

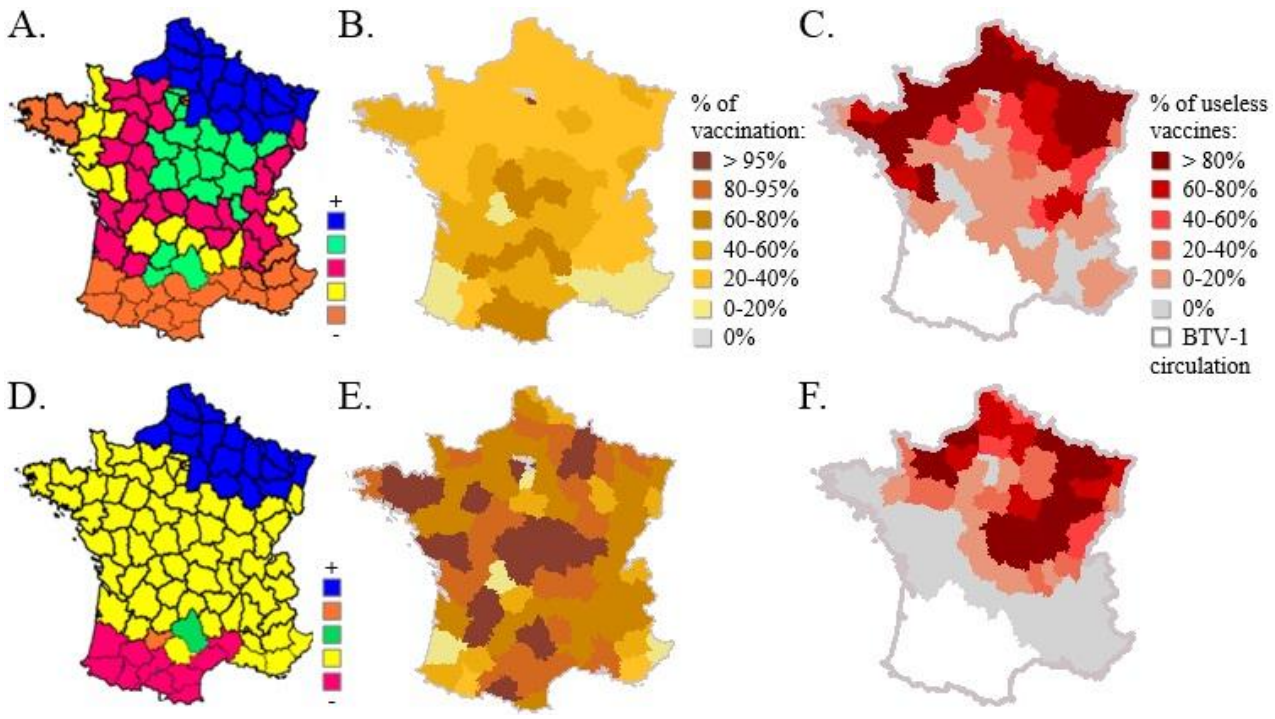
598 **Figure 5 : Reconstructed seroprevalences and proportions of livestock infected per department,**
599 **from 2007 to 2010.**



600

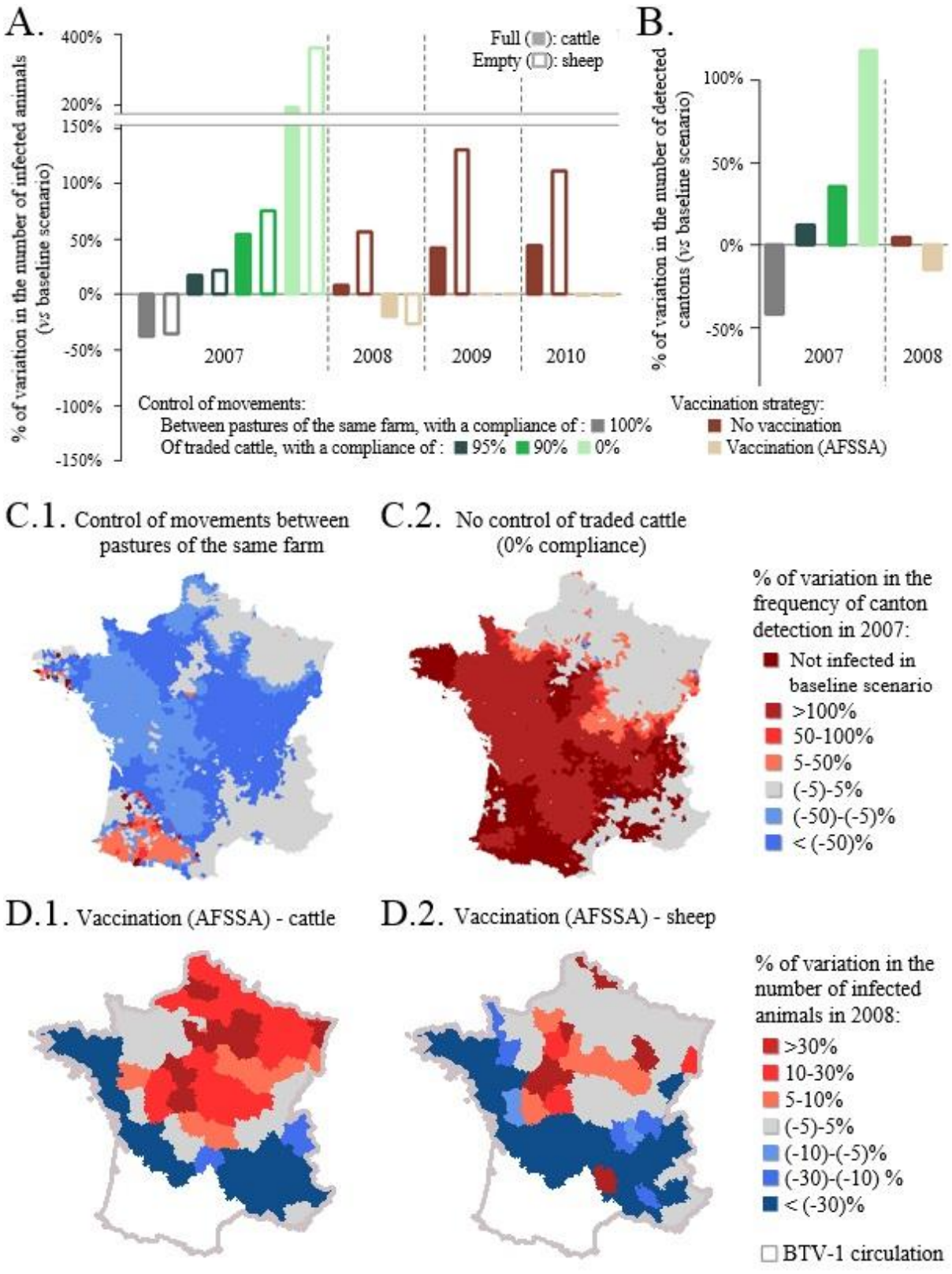
601 A, C. Seroprevalences (due to natural infection or to vaccination) after each season of virus circulation in
602 cattle (A) and sheep (C); B, D. Cumulative proportion of animals infected in each season of virus
603 circulation in cattle (B) and sheep (D) ; 1-4. season of virus circulation: 2007 (1), 2008 (2), 2009 (3) and
604 2010 (4).

Figure 6: Evaluation of the 2008 emergency vaccination campaign per department.



A, D. Vaccination schedule: order of priority for the distribution of the limited number of vaccine doses spread out between May and September 2008 (DGAL/SDSPA, 2008), in cattle (A) and sheep (D), the order of priority is indicated by the color code; B, E. Vaccination coverage achieved by the end of the campaign (October 2008) in cattle (B) and sheep (E); C, F. Proportion of doses administered to already immune animals in cattle (C) and sheep (F).

612 **Figure 7: Impact of the alternative control scenarios on spatial spread and outbreak size.**



613

614 A, B. Country-wide percentage of variation compared to the baseline scenario of alternative measures of
615 movement restrictions and of alternative vaccination strategies: number of infected cattle and sheep from
616 2007 to 2010 (A); number of cantons first detected in 2007 and 2008 (B). C. Simulated variation of the
617 frequency of canton detection in 2007 (1,000 simulations) in two alternative scenarios of movement
618 control: with additional control of movements between pastures of the same farm (C.1), with no control of
619 trade movements (C.2). D. Variation of the number of infected cattle in 2008, per department, in the
620 AFSSA vaccination scenario: in cattle (D.1) and sheep (D.2).

TABLES

Table 1: Fixed parameter.

Symbol	Description	Value	Reference
α_1^c	1/ length of persistence of colostral antibodies	0.0625 (1/16 wk)	(Vitour et al., 2011)
α_2^c	1/ viremia	0.25 (1/4 wk)	(Singer et al., 2001; Martinelle et al., 2011; Di Gialleonardo et al., 2011)
m^c	number of viremic stages in cattle	3	
α_1^s	1/ length of persistence of colostral antibodies	0.07 (1/14 wk)	(Oura et al., 2010)
α_2^s	1/ viremia	0.33 (1/3 wk)	(Eschbaumer et al., 2010; Worwa et al., 2010)
m^s	number of viremic stages in sheep	2	
π^c	trophic preference for cattle *vs* sheep (if feeding on these species)	0.87	(Ayllón et al., 2014; Elbers and Meiswinkel, 2014)
$b(k,t)$	biting rate (wk^{-1})	[0.00002 * $Tp(k,t)$ * ($Tp(k,t)$ - 3.7) * (41.9 – $Tp(k,t)$)$^{0.37}$]*7	(Mullens et al., 2004)
μ^v	daily mortality proportion of *Culicoides* vectors	6% (17-25°C)	(Goffredo et al., 2004)
EIP	extrinsic incubation period	11 days (17°C)	(Carpenter et al., 2011)
T_{min}	threshold temperature for virus replication	12°C	(Carpenter et al., 2011)
v_2^c	weekly rate of acquisition of protective vaccinal immunity in cattle	0.35 (t_v^c=7 wk)*	(Merial, BTVPUR®, AlSap8)
v_2^s	weekly rate of acquisition of protective vaccinal immunity in sheep	0.52 (t_v^s=4 wk)*	(Intervet, BOVILIS BTV8 ®)
Ψ_P**	proportion of canton surface reachable in a week by vectors from neighboring cantons	0.4	Flight distances (Kluiters et al., 2015), cantons surface (Supplement S2.C)
Δ**	probability of clinical onset and detection of infectious animals in newly infected areas	0.02	(Durand et al., 2010; Mounaix, B. et al., 2010; Courtejoie et al., 2018a) (Supplement S2.B)
N_{inf}***	number of infected cattle introduced to seed infection	5	
p_{ow}***	proportion of canton with $Tp(k,t)<T_{min}$, used to model overwintering	90%	

c for cattle, *s* for sheep, *v* for vectors; *wk*, weeks; $Tp(k,t)$, temperature in canton *k* at time *t*

* so that $(1-(1-v_2^{sp})^{t_v^{sp}}) = 95\%$, with t_v^{sp} the time before reaching immunity in 95% of the vaccinated animals

** varied in a sensitivity analysis on parameter estimates

*** varied in a sensitivity analysis on model predictions

SUPPLEMENTARY FILES AND FIGURES

Supplementary files

Supplement S1: Model details

S1.A. Detailed within-canton transmission

S1.B. Detailed between-canton transmission

S1.C. Discussion of modelling assumptions

Supplement S2: Details on fixed parameters

S2.A. Demography

S2.B. Detection

S2.C. Proportion of canton surface reachable by *Culicoides* from neighboring cantons

Supplement S3: ABC-RF for model comparison

S3A. Model selection by random forest

S3.B. Environmental variables included in BTV within-canton transmission

S3.C. Contact networks included in BTV between-canton transmission.

Supplement S4: Details on parameter estimation

S4.A. Adaptive population Monte-Carlo approximate Bayesian computation method

S4.B. Summary statistics

S4.C Prior distributions

Supplement S5: Network analysis

Supplement S6: Validation of the framework (POC)

Supplement S7: Sensitivity analyses

S7.A. Sensitivity analysis on parameter estimates

S7.B. Sensitivity analysis on model predictions

Supplementary figures

Figure S1: Alternative strategy for the 2008 emergency vaccination campaign

Figure S2: Validation of the framework in an in-silico analysis.

Figure S3: Model fit: comparison of observed vs simulated summary statistics.

Figure S4: External validation: spatio-temporal pattern of the apparent infection.

Figure S5: Reporting cantons after the 2007/09 outbreak.

Figure S6 and S7 : Results of the sensitivity analysis on parameter estimates and model predictions

DECLARATIONS

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Competing interests

Co-authors do not have any competing interest.

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