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ABSTRACT

Bluetongue virus is a vector-borne pathogen affecting ruminants that has caused major epidemics in France. Reconstructing the history of bluetongue in French cattle under control strategies such as vaccination has been hampered by the high level of sub-clinical infection, incomplete case data and poor understanding of vaccine uptake over time and space. To tackle these challenges, we used three age-structured serological surveys carried out in cattle (N = 22,342) from ten administrative subdivisions called departments. We fitted catalytic models within a Bayesian MCMC framework to reconstruct the force of seroconversion from infection or vaccination, and the population-level susceptibility per semester between 2007 and 2016. In the departments of the study area, we estimated that 36% of cattle had been infected prior to vaccine rollout that became compulsory from July 2008. The last outbreak case was notified in December 2009, at which time 83% of the animals were seropositive, under the cumulative effect of vaccination and infection. The probability of seroconversion per semester dropped below 10% after 2010 when vaccination became optional. Vaccine uptake was smaller during the 2012 campaign than during the one in 2011, with strong regional contrasts. Eighty four percent of cattle were susceptible when bluetongue re-emerged in 2015. Thus, serological surveys can be used to estimate vaccine uptake and the magnitude of infection, the relative effect of which can sometimes be inferred using prior knowledge on reported incidence and vaccination dates.

1. Introduction

Bluetongue is a non-zoonotic vector-borne viral disease of domestic and wild ruminants that is mainly transmitted by biting midges of the genus *Culicoides*. In 2006, bluetongue virus serotype 8 (BTV-8) was reported for the first time on the European continent, causing a massive outbreak (Carpenter et al., 2009), though disease outcome was mostly subclinical in cattle (> 90%, (Durand et al., 2010)). France was mostly impacted over the 2007–2009 period with more than 43,400 infected holdings. Seventy nine percent of these holdings were detected following clinical suspicion (French Ministry for Agriculture) while the rest were detected through pre-export testing. The disease progressed in an epidemic wave from North-East to South-West France (Pioz et al., 2011). An inactivated BTV-8 vaccine became available in summer 2008. Two state-funded compulsory vaccination campaigns were implemented in 2008/09 and 2009/10. After the notification of the last case of BTV-8 in December 2009, vaccination became voluntary and self-funded in 2011 and 2012. Vaccination was subsequently banned from 2013 to preserve the national bluetongue free status regained in December 2012 and a national surveillance program was implemented. BTV-8 remained undetected in Europe until August 2015, when it re-emerged in Central France with a strain almost identical to the one detected in 2007–2009 (Sailleau et al., 2017; Bréard et al., 2016). 93% of infected holdings were detected through pre-export testing (Bournez et al., 2017). Vaccination was re-introduced in autumn 2015, first limited to exported animals.

Given the high levels of sub-clinical infections, the true proportion of the population infected in the 2007–2009 epidemics remains unknown. Further, little is known about vaccine uptake over time and space, especially during the 2011–2012 period when vaccination had to be paid for by farmers themselves, with no systematic record of the number of doses released or strategy of administration. There are also questions about possible silent circulation of BTV-8 in domestic or wild ruminants between the 2007–2009 and the 2015 epidemics (Courtejoie

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et al., 2018a).

The complex history of bluetongue disease spread in French cattle and its control by vaccination thus remains unclear. Insights could be gained by reconstructing the time-varying forces of seroconversion from infection or vaccination, exerted on French cattle. Methods to reconstruct forces of infection from age-stratified serological studies have previously been used with other pathogens to overcome the limits of infectious diseases surveillance systems and estimate the size of past epidemics (Metcalf et al., 2016; Salje et al., 2016; Rodríguez-Barraquer et al., 2015; Ferguson et al., 1999). As natural infection and vaccination induce the production of similar antibodies in cattle, we extended the existing framework to reconstruct the history of bluetongue virus circulation in French cattle under successive vaccination campaigns and determine when seroconversions could be allocated to either infection or vaccination.

We applied our models to three age-stratified serological studies in cattle, conducted in ten French departments in 2007/08, 2014/15 and 2015/16 to reconstruct the force of seroconversion and the population-level susceptibility for each semester over a ten-year period (2007–2016) and answer key questions regarding bluetongue spread and control.

2. Material and methods

2.1. Study area

We used data from three retrospective surveys based on the analysis of stored sera from cattle sampled in the winters of 2007/08 (Durand et al., 2010), 2014/15 (Courtejoie et al., 2018b) and 2015/16 (Courtejoie et al., 2018a) in ten French administrative subdivisions called departments, with a mean surface of about 6000 km^2. The departments were chosen along an East-West transect, to provide a variety of epidemiological situations during the two BTV-8 epidemics (Fig. 1A). Four departments were sampled in 2007/08 only, four in both 2014/15 and 2015/16, and two in 2007/08, 2014/15 and 2015/16. To study regional contrasts, we grouped the ten departments into two regions: 'W' consisting of the five western departments (Ille-et-Vilaine, Maine-et-Loire, Manche, Orne, Sarthe), and 'E' consisting of the five eastern departments (Allier, Cher, Indre, Indre-et-Loire, Loir-et-Cher). The departments of each region shared a similar epidemiological situation and, in both outbreaks, departments from region E were affected earlier than those from region W (Fig. 1B).

2.2. Sampling design, exclusion criteria and biological samples

All sera came from serobanks locally maintained by veterinary laboratories, in charge of the yearly collection of sera for brucellosis and infectious bovine rhinotracheitis detection in animals over one year old. The sampling protocols are fully described elsewhere (Durand et al., 2010; Courtejoie et al., 2018b, a). Briefly, two studies were carried out to estimate seroprevalence in 2007/08 and 2014/15, using the serobanks as a sampling base. In each department, stored sera were retrieved for testing from 50 randomly selected herds, with 30 animal samples randomly selected in each herd. A third study was carried out to address the question of undetected BTV-8 circulation in the winters preceding and following the re-emergence of BTV-8 on the French territory, using sera collected in 2014/15 and 2015/16. At least 100 sera were randomly selected from the serobanks per department and per winter, preferentially from cattle born after 2013. Across the three studies, the sera were tested for antibodies against BTV by a competitive ELISA test (IDVet), specific of the BTV-serogroup (estimated > 99% sensitivity and > 99% specificity (IDVet, 2014)).

The 898 animals sampled in 2014/15 and 2015/16 that had stayed in herds outside the study area between the emergence of BTV-8 in 2007 (or their birthdate if later) and their sampling date were excluded, as they could have seroconverted elsewhere. For each animal, we obtained the day of birth. This information was not available for the 2007/08 study, but all animals in this dataset were ≥1 year of age and therefore present at the start of the bluetongue epidemic in France. We assumed that all these animals were susceptible prior to 2007.

2.3. Reconstruction of the historical pattern of exposure

2.3.1. Reconstruction of the semestrial probability of seroconversion

We developed a methodological framework, hereafter called the "baseline model", to estimate time-dependent forces of seroconversion (from either natural infection or vaccination) from age-stratified serological data. The framework was used to derive the probability of seroconversion for each semester (*i.e.* the proportion of the susceptible population seroconverting per six-month period) between 2007 and 2016 and by geographic area.

In each area, animals were considered exposed to the risk of seroconversion from January 2007 or from their birthdate (whichever was later), to their sampling date. We denoted $\lambda(t)$ the force of seroconversion at time *t*, *i.e.* the instantaneous risk that a seronegative animal seroconverted at time *t*. The probability that an animal born at time t_1 had seroconverted by the time of sampling t_2 can be characterized by: $1-exp\left(-\int_{t_1}^{t_2}\lambda(t)dt\right)$. In practice, we modelled the force of seroconversion with a step function equal to λ_i during time period $i = 1\ldots N$, with *N*, the total number of periods. The contribution to the likelihood from an animal *j* that was seropositive by the time of sampling was: $1-exp(-\sum_i \lambda_i T_i \alpha_{i,j})$ where T_i was the duration of period *i* (six months for a semester) and $\alpha_{i,j}$ was the proportion of time animal *j* lived in the study area during the time period. Parameters λ_i had a lognormal prior distribution (with parameters $\mu = 0$, $\sigma^2 = 4$). The model was fitted in a Bayesian Markov chain Monte Carlo (MCMC) framework, using the RStan package in R. We computed the posterior mean and 95% credible intervals (95% CI) for parameters.

2.3.2. Reconstruction of the susceptible population across the study period

For each semester, we used the inference results to estimate the proportion of seropositive animals in the sampled population. As we had no animal under one year old in our datasets, we used the National identification database that records information, including dates of birth, on all cattle on the French territory to estimate these proportions in the whole cattle population in the study area (about 1,100,000 head of cattle in region E and 2,700,000 in region W).

2.3.3. Simulation study for model validation and evaluation

We carried out a simulation study to assess the ability of our baseline model to accurately recover known forces of seroconversion, using a population structure identical to the sampled population. We used arbitrary, but realistic semestrial probabilities of seroconversion to compute animal-level probabilities of being seropositive at sampling dates. Twenty simulated serological datasets (ELISA positive/negative) were built by successive binomial draws for all animals in the dataset, and analysed with our statistical model. For each area and semester, we computed the mean absolute deviation (*i.e.* the average difference between the means of the posterior distributions and the input forces of seroconversion), and the proportion of 95% CIs that included the input value. A sensitivity analysis was also conducted to compare four different priors in the Bayesian parameter estimation. Additional information can be found in supplementary materials (Table S2).

2.3.4. Evaluating the relative contribution of infection and vaccination

We attempted to disentangle the relative contribution of natural infection and vaccination to the overall force of seroconversion at each time point using two approaches. In the first approach, we used available data about the timing of the epidemic and of the vaccination campaign to *a priori* identify time periods when seroconversions could be unambiguously attributed to either infection or vaccination in the

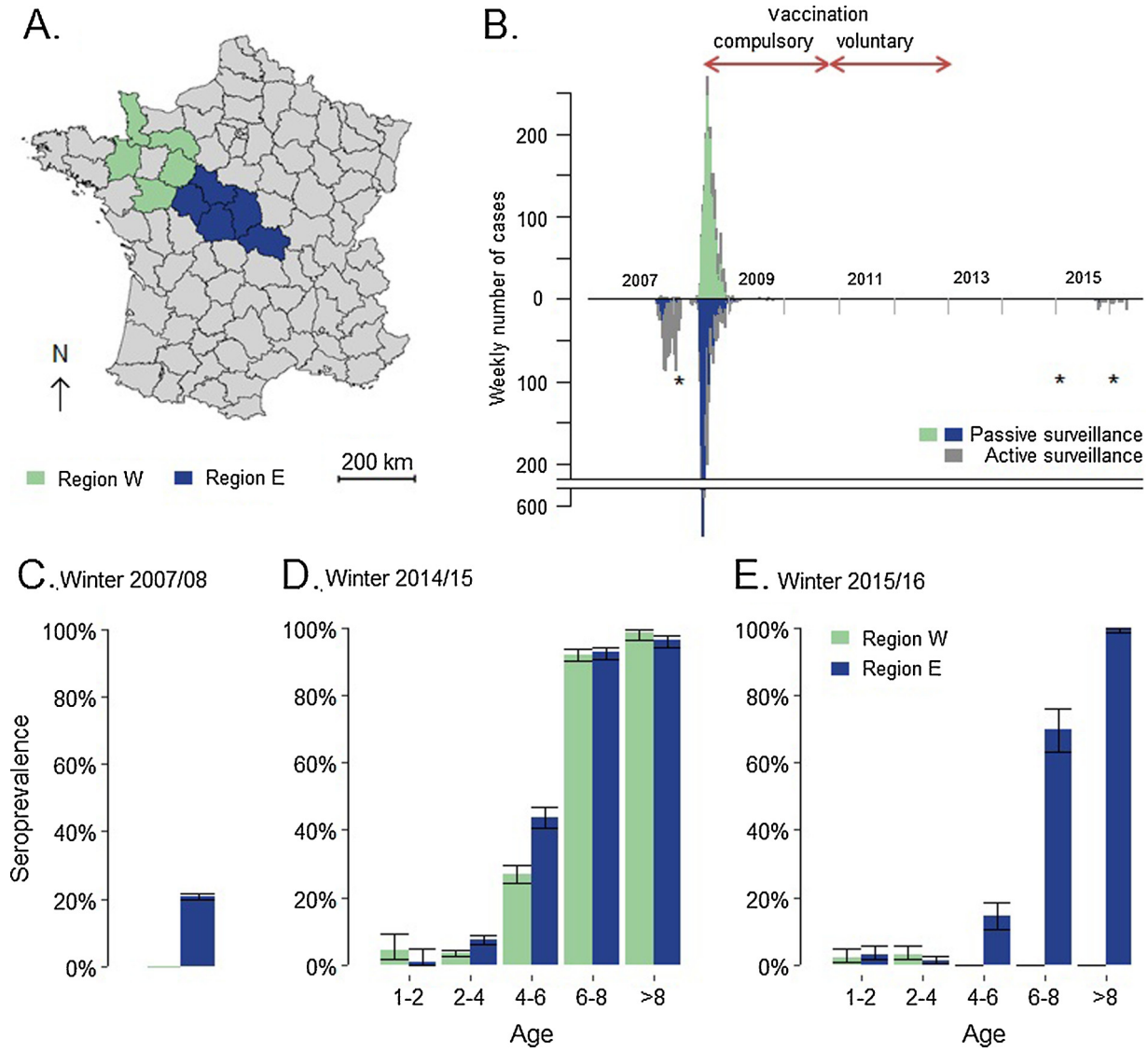

Fig. 1. Study area and epidemiological context for the three seroprevalence studies. A) Map of France, showing the location of the ten departments in which the study was performed along an east-west transect, regions W and E. B) Number of infected holdings reported weekly in regions W (top panel) and E (bottom panel), by passive surveillance (clinical suspicion) or active surveillance (including pre-export testing), during the 2007/09 and 2015/16 outbreaks; *: winter of sampling; the first arrow shows the notification date of the last BTV-8 case; the second arrows shows the date of recovery of the BTV-8 free status. C) Seroprevalence in winter 2007/08 in regions W and E, not stratified by age as dates of birth were not available. D) and E) Age-stratified seroprevalence in the winters 2014/15 (D) and 2015/16 (E) in regions W and E. No animal > 3 year-old was sampled in region W in 2015/16. Ages were calculated at the dates of sampling, meaning that the 46 years old sampled in 2014/15 were more likely exposed to vaccination than the 46 years old sampled in 2015/16 (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

baseline model output. In a second approach, we built an alternative model using prior knowledge on reported disease incidence and vaccination dates that explicitly captured each mechanism. Under the assumption that the force of seroconversion due to infection was proportional to the number of infected holdings (Tsang et al., 2016), we modelled the force of seroconversion for time period i as $\lambda_i = \gamma I_i + \lambda^{vacc}{}_i I_i$ was the reported number of infected holdings for time period i. We also assumed that the force of seroconversion due to vaccination λ^{vacc} would be zero before July 2008 and after January 2013.

2.3.5. Model performance and adequacy to the data

In order to assess model fit, we randomly selected 80% of the animals in the dataset as a training dataset and kept the remaining 20% for validation. The baseline model and the alternative model were fitted on the training dataset, and then used to predict the seroprevalence in the validation dataset. In addition, to investigate the adequacy of each model to the data, we split the dataset in yearly birth cohorts and compared the observed and expected seroprevalence at the dates of sampling in each cohort.

3. Results

We obtained serological test results from 22,342 serum samples: 11,248 in 2007/08, 8,761 in 2014/15 and 2,333 in 2015/16 (Fig. 1C–E). In the winter of 2007/08, we found that 13.5% of animals were seropositive (N = 1,549/11,248), with significant geographical heterogeneity: 20.5% (N = 1,547/7,468) in region E *vs* < 0.1% (N = 2/3,780) in region W. In the winter of 2014/15 a strong increase in seroprevalence with age was observed in both regions with 96.7% (N = 879/910) of those over eight years old having detectable antibodies against BTV compared to 5.5% (N = 220/4,030) for those under

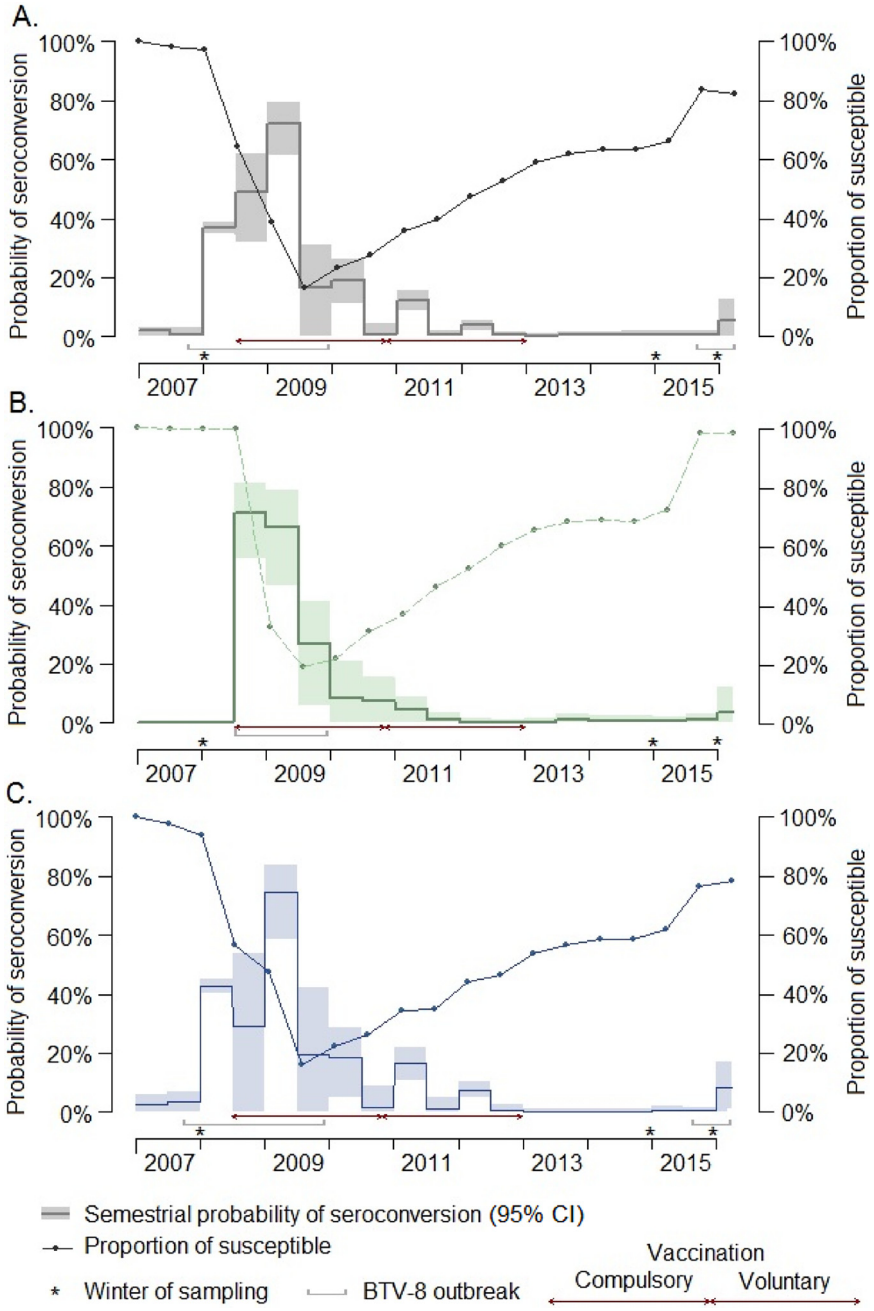

Fig. 2. Reconstruction of the semestrial probability of seroconversion and proportion of susceptible cattle between 2007 and 2016. Model estimates in the whole sampled population (A), in region W (B) and in region E (C). *: winter of sampling.

four years old. A similar age pattern was observed in 2015/16 but only in region E as no animal over three years of age was sampled from region W.

We combined the results from the three studies to estimate overall trends in the probability of seroconversion by semester (Fig. 2). We found that the probability of seroconversion rose from 37.0% (95% CI: 35.1%, 38.9%) in the first semester of 2008 to 72.0% (95% CI: 61.7%, 79.5%) in the first semester of 2009. Most cases had been notified by then, and the probability to seroconvert subsequently dropped. We observed seasonal peaks in the first semesters of 2009, 2010, 2011 and 2012, the most likely periods for vaccination. Vaccination was still compulsory in 2010 but it became voluntary in 2011 and 2012. We estimated that the probabilities of seroconversion dropped from 18.9% (95% CI: 11.3%, 26.1%) in the first semester of 2010 to 3.9% (95% CI: 2.1%, 5.5%) in the first semester of 2012. We estimated a very low probability of seroconversion between the vaccination ban (2013) and the detected re-emergence of BTV-8 (2015) (average of 0.5% per semester, 95% CI: 0.0%, 1.8%, Fig. 2). Yet we found evidence of seroconversion over that period when looking at serological data: of the 520 animals born after the vaccination ban and sampled in 2014/15 (*i.e.* prior to the detected re-emergence of BTV-8 in France), 14 were seropositive. One of these positive sera was tested and confirmed by seroneutralization assay in another study (Courtejoie et al., 2018a).

We reconstructed the proportion of susceptible animals in the sampled population over the study period (Fig. 2, Table S3). We estimated that 64.3% (95% CI: 61.8%, 66.8%) of the population remained susceptible when compulsory vaccination was initiated in July 2008. By July 2009, that proportion had dropped to 16.5% (95% CI: 13.8%, 19.7%). But it was of 83.6% (95% CI: 82.3%, 84.7%) when BTV-8 re-emerged in August 2015. We obtained similar trends in the proportion

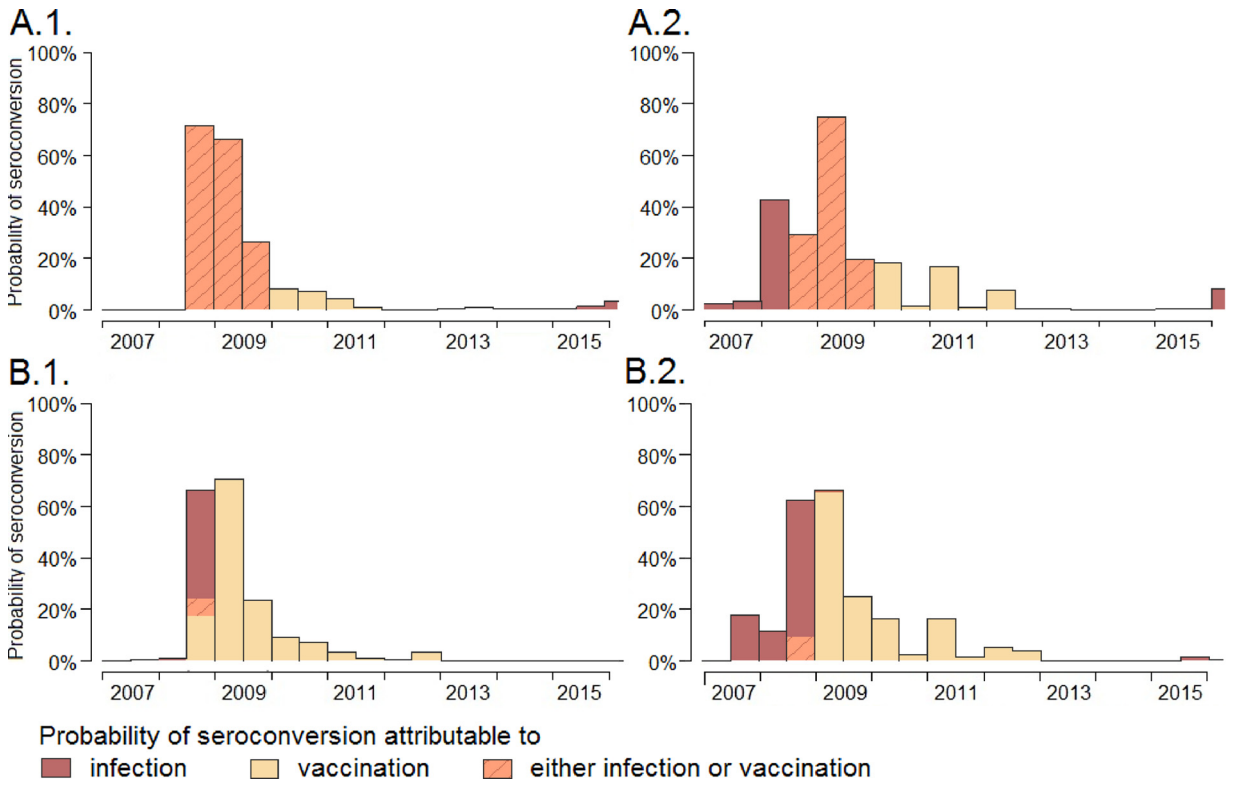

Fig. 3. Use of prior knowledge to evaluate the relative contribution of vaccination and infection in each semester between 2007 and 2016. Dates of reported outbreaks and vaccination campaigns were used to attribute seroconversion reconstructed with the baseline model to either infection or vaccination in both regions W (A.1) and E (A.2). Incidence data and dates of vaccination campaigns were incorporated in the alternative model to evaluate the relative contribution of vaccination and infection to seroconversion, even when these processes occurred simultaneously in both regions W (B.1) and E (B.2).

of susceptible animals in the whole cattle population in the sampling areas (Fig. S1).

We observed regional contrasts with no evidence of seroconversion prior to vaccine release in region W, whereas we estimated that 500,000 animals (42.7% of all cattle) from region E had seroconverted by that time (Table S1). The probabilities of seroconversion during voluntary campaigns were lower in region W (4.3% in 2011, 95% CI: 0.04%, 9.0%; and about zero in 2012: 0.3%, 95% CI: 0.0%, 1.5%), than in region E (16.8% in 2011, 95% CI: 10.8%, 21.9%; and 7.6% in 2012, 95% CI: 4.9%, 10.1%). Almost all animals in region W were susceptible when BTV-8 re-emerged in August 2015 (98.3%, 95% CI: 95.6, 100%), compared to 78.6% (95% CI: 76.8%, 80.3%) in region E.

We attempted to allocate the reconstructed forces of seroconversion to either infection or vaccination (Fig. 3). From the dates of known outbreak events and vaccination campaigns, we could attribute all seroconversion to natural infection before July 2008 and from 2013 onwards, and to vaccination from 2010 to 2013 (Fig. 3A). However, using this approach, we could not separate the two processes from the second half of 2008 to 2010, as they occurred simultaneously (Fig. 3A). In order to separate out the force of infection due to infection and vaccination during this period, we used an alternative model built upon prior knowledge on incidence data and vaccination dates (Fig. 3B). This model estimated that when vaccination was introduced in the second half of 2008, most seroconversions were due to vaccination in region W (Fig. 3B1) but to infection in region E (Fig. 3B2).

The overall probabilities of seroconversion estimated by the two models were similar (Fig. 3), although the alternative model suggested that, in region E, the force of seroconversion was high in the second semester of 2008 instead of the first semester in the baseline model. Both models provided good predictions of the proportion of seropositive animals (Fig. S2). The estimated proportion of seropositive animals in each birth cohort was consistent with that measured in each study area (Fig. S3). The simulation study confirmed the ability of the baseline model to correctly estimate seroconversion parameters (Fig. S4, Table S2). Results were found to be robust to the choice of priors (Table S2).

4. Discussion

In this paper, we explored how age-specific serological surveys can be used to gain insights into the exposure of French cattle to bluetongue virus considering both natural infection and vaccination. We used three serosurveys to reconstruct the complex history of spread and control of BTV-8 in French cattle, from the initial emergence in 2007 to its re-emergence in 2015. Understanding the dynamics of seroconversion had not been previously possible because national surveillance protocols evolved with the spread of the outbreak and after recovery of the disease free status, asymptomatic infections were frequent and vaccine uptake was poorly documented.

We did not find evidence of infection until 2008 in the sampled population, though the virus had circulated in region E from September 2007. We estimated that over 40% of all cattle from the whole region E seroconverted prior to vaccine release, corresponding to about 500,000 animals, while only 155 bovine herds (estimated 2000 clinically infected animals (Mounaix et al., 2008)) had been notified in the area at that time (French Ministry for Agriculture). These results are consistent with widespread natural infection from East to West, with a vast majority of asymptomatic cases (Durand et al., 2010; Méroc et al., 2008). Our reconstruction provides an approximation of the magnitude of the epidemic in terms of infected animals, which complements existing farm-level surveillance that detected infected holdings, mainly through symptomatic case detection.

We were able to reconstruct the semestrial probabilities of seroconversion over a ten-year period from serological results, but the

relative contribution of infection and vaccination to seroconversion could not be inferred without additional knowledge. Two approaches were considered to attribute a seroconversion event to infection or vaccination. First, within our baseline framework, the known timing of outbreaks and vaccination campaigns was used to identify time periods when seroconversion events could unambiguously be allocated to one of the mechanisms. Of course, we cannot completely rule out the possibility that a small part of seroconversion allocated to vaccination after the 2007–2009 outbreak could have been unnoticed infections. We also developed an alternative model that performed a probabilistic attribution even during periods when both processes occurred. However, this latter model relied on the strong assumption that the force of infection was proportional to the observed incidence, which is questionable in a context when the probability of detection is likely to have varied over time and space.

We found that the vast majority of animals had seroconverted by late 2009, under the cumulative effect of compulsory vaccination and natural infection. The last BTV-8 case was notified in December 2009. We observed that all vaccine campaigns from 2009 to 2012 were mostly implemented in the first semester of each year, which seems consistent with the period chosen to apply vaccines, as reported by professionals in the field, but that had not been well documented for bluetongue. Yet, we found that only a small proportion of animals underwent vaccination once it became voluntary after 2010. This is an important insight in a context where we did not have any prior knowledge on the number of vaccine doses used during voluntary vaccination, let alone on the places and dates when they were administered. During future outbreaks, these findings could help inform any switch from compulsory to voluntary vaccination.

Understanding regional contrasts in terms of epidemiological context and local practices can be important to inform control strategies. For example BTV-8 circulated first in region E before moving to region W. Therefore, in 2008, mandatory vaccination in region E was largely performed on animals that had already been infected. Vaccine doses may have been saved by targeting preferentially disease free areas. Under voluntary vaccination, the diverging patterns in E and W regions likely reflect differences in local contexts. As vaccination was self-funded, farmers' behaviour may have been shaped by their personal experience of the outbreak that affected more severely region E (Figs. 1B and 3), and by vaccination awareness raised by farmers unions.

This study did not detect evidence of substantial viral circulation in the sampled population between the recovery of bluetongue free status in December 2012 and the re-emergence in 2015 despite evidence of some seroconversions. Unfortunately, this period is also the least informed by our data, with few animals born after the vaccination ban and prior to BTV-8 re-emergence. The presence of a small number of seroconversions could be due to a low level circulation of BTV-8 in cattle, possible transmission from other ruminant species acting as reservoirs or reintroduction. BTV-8 circulation seems to have reached non-negligible levels in early 2016. More sera from animals born after 2014 and sampled in the winter of 2015/16, and sera from other potential host species (sheep or red deer) would have been useful to better understand the drivers of the re-emergence.

The present analysis was carried out using serological results from surveys that had been conducted for other purposes (Durand et al., 2010; Courtejoie et al., 2018a, b). The corresponding protocols had been satisfactorily implemented and, for each study purpose, the sampled population was considered as representative of the cattle population over one year old in the study area. In addition, we corrected for the deficit in young animals in the sampled population to compute the proportion of susceptible animals in the whole cattle population in the study area.

The two catalytic models rely on a number of assumptions. Serological results are used to draw insights on the various exposure experienced by all animals from their birthdates (or 2007) to their sampling dates, assuming that BTV-8 natural infection and vaccination leaves a life-long serological signature. However, long-term trajectories of antibody levels against BTV-8 remain poorly documented. Natural infection is expected to provide life-long immunity (Eschbaumer et al., 2012), while vaccine-induced immunity may decrease more quickly. In a recent study, antibodies could still be detected up to five years after vaccination (Courtejoie et al., 2018b). This suggests that waning of antibodies can be ignored given the short life expectancy of cattle: about five years for dairy cattle (15% of the dataset) and two to six years for suckler cattle (85% of the dataset) (Ellies, 2014)). As all animals sampled were more than one year old, we ruled out the presence of maternal antibodies, expected to disappear within the first four months of life (Vitour et al., 2011). We also assumed that animals could not have been exposed to BTV-8 prior to 2007 as France was mostly affected by the outbreak over the 2007/08 period, and as merely three clinically infected animals were reported in 2006.

Overall, our approach makes it possible to reconstruct the history of viral transmission and vaccine uptake from serological studies, though evaluating the relative effect of vaccination and infection on seroconversion requires good prior knowledge on the occurrence of both processes. We provide an innovative way of using data from already existing serobanks that could be used in the future to supplement the surveillance of infectious agents.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.epidem.2018.05.005.

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