Valorisation of surveillance data and assessment of the sensitivity of a surveillance system for an equine infectious disease using a unilist capture-recapture model

JP AMAT[1],[2]*, T VERGNE[3], A HANS[1], B FERRY[4], P HENDRIKX[5], J TAPPREST[1], B DUFOUR[6], A LEBLOND[2]
[1]Laboratory for Equine Diseases, French Agency for Food, Environmental and Occupational Health and Safety (Anses), Goustranville, France; [2]Animal Epidemiology Unit UR[346], National Institute for Agricultural Research (INRA), Saint-Genès-Champanelle, France; [3]Veterinary Epidemiology, Economics and Public Health Group, Royal Veterinary College, London, United Kingdom; [4]French horse and riding institute (IFCE), Paris, France. [5]Directorate for Laboratories, Anses, Lyon, France; [6]EpiMAI Unit – joint Anses, Veterinary School of Maisons-Alfort, Maisons-Alfort, France

* jean-philippe.amat@anses.fr

Abstract
Whether surveillance is based on serological tests, the exact number of detected cases may remain unknown because identifying seroconversion can be difficult. Moreover, incomplete cases / outbreaks detection is a recurrent issue in surveillance. Our study addresses these two issues, regarding equine viral arteritis (EVA) surveillance. Our goals were to establish suitable rules for identifying seroconversion to estimate the number of EVA outbreaks detected by the French breeding stock surveillance system between 2006 and 2013, and to assess surveillance sensitivity by estimating the total number of outbreaks that occurred during this period using a capture-recapture model.

Data from mares with at least one positive result using viral neutralization test between 2006 and 2013 were used for analysis (n=1,645). Data consisted of annual antibody titers and mares' location (towns). Seroconversion was defined as a change in antibody titer from negative to at least 32 or a three-fold increase. The number of seroconversions was counted for each town and modeled using a zero-truncated binomial capture-recapture model with R software.

From 2006 to 2013, 239 cases of seroconversion located in 177 towns (outbreaks) were identified. Total number of outbreaks in breeding stock was estimated at 215 ($CrI_{95\%}$ 195-249) and the surveillance sensitivity at the town level at 82% ($CrI_{95\%}$ 71%-91%).

The estimated surveillance sensitivity is relatively high. The proposed rules may be used to analyze other serological surveillance data, including testing before sales or international trade. This study shows how capture-recapture methods may help to estimate surveillance sensitivity and to valorize surveillance data.

Introduction
Equine viral arteritis (EVA) is an equine respiratory and reproductive disease which can lead to abortions and neonatal deaths. EVA is caused by a virus of the *Arteriviridae* family and is mainly transmitted horizontally by aerosols or venereal contact, including frozen semen (1, 2). EVA is monitored in many countries in breeding stock to avoid its spread during breeding activities (3). In France, the breeding stock surveillance (BSS) is mainly based on serological tests, but difficulties in interpreting certain series of results may impair the estimation of the number of outbreaks. Moreover, only a part of breeding horses are tested, depending on the studbooks' regulations. The first objective of this study was to establish suitable rules for identifying seroconversion in order to estimate the number of EVA cases and outbreaks detected by the BSS between 2006 and 2013. The second goal was to estimate the sensitivity of the BSS, after having estimated the total number of out-breaks that occurred in breeding stock during this period (including undetected outbreaks) using a capture-recapture method.

Keywords: *Surveillance sensitivity, horse, capture-recapture model, equine viral arteritis, seroconversion*.

Materials and methods
Breeding stock surveillance
In France, breeding stock surveillance (BSS) is mandatory for mares producing racehorse foals, for around 20 breeds of stallions used for natural mating and for all stallions used for semen collection. A serological test (viral neutralization test, VNT) is used, which is the standard test for EVA prescribed by the OIE.

Data
We used data collected by the French institute for horse and riding (IFCE) related to all breeding horses having at least one positive result using VNT between January 2006 and December 2013: identification number, location, dates and results of VNT. We did not used data pertaining to stallions be-cause the number of males with positive VNT results was very low (n=32) compared to mares (n=1,645) and some had uninterpretable results. Location was recorded, at the beginning of each year, as the town of the holding.

Definitions
A 'case' was defined as 'a mare with seroconversion, detected by the interpretation of several VNT results'. Due to difficulties in the interpretation of certain series of titers, a panel of four experts was gathered to establish suitable rules for identifying seroconversion. The goal of the rules was to

allow the estimation of the number of EVA cases detected by the BSS between 2006 and 2013. An 'outbreak' was defined as 'a town where at least one EVA case occurred within one year' (an outbreak is a 'town-year' infected).

Capture-recapture model

A unilist capture-recapture model was used to estimate the total number of outbreaks that occurred in breeding stock (N_{occ}) between 2006 and 2013 (4). N_{occ} was estimated using an extension of the Horvitz-Thompson estimator proposed by van der Heijden and colleagues (5):

$$\widehat{N_{occ}} = \sum_{i=1}^{N_{det}} \frac{1}{1 - \Pr(Y_i = 0)},$$

with N_{det} being the number of detected outbreaks, Yi the number of detected cases within outbreak *i* and Pr(Y_i =0) the probability that no infected mare was detected in outbreak *i* (i.e. outbreak *i* is not detected).

Pr(Y_i=0) depends on the sensitivity of the proposed rules (*Se*) and on the real number of cases within the outbreak *i* (C_i, that ranges from 1 to n_i the number of tested mares in outbreak *i*), which depends on the incidence rate within an outbreak *(In)*. For each outbreak, Pr(Y_i=0) was calculated as the sum of the probabilities that Y_i=0 for all possible values of c_i:

$$\Pr(Y_i = 0) = \sum_{c_i=1}^{n_i} \{(1 - Se)^{c_i} * \frac{\frac{n_i!}{c_i!*(n_i-c_i)!} * In^{c_i} * (1-In)^{n_i - c_i}}{1-(1-In)^{n_i}}\},$$

Sum for all possible values of c_i

Probability that $Y_i = 0$ knowing that $C_i = c_i$, assuming that Y_i follows a binomial distribution of parameters C_i and *Se*

Probability that $C_i = c_i$, assuming that C_i follows a zero-truncated binomial distribution of parameters n_i and *In*

Then, the BSS's sensitivity was calculated as the ratio of the number of detected outbreaks (N_{det}) by the estimate of the total number of outbreaks that occurred (N_{occ}). The parameters were estimated in a Bayesian framework using the WinBUGS software (6). Priors of the parameters *In* and *Se* were determined as beta distributions of parameters (4.6, 9.3) and (44.9, 11.3) respectively, using an expert opinion elicitation. We ran three simulation chains of 10,000 iterations, to determine the posterior distributions.

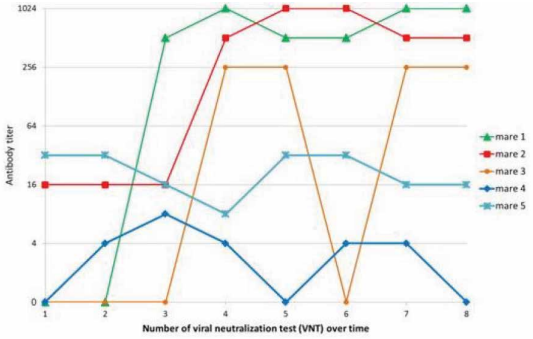
Results

Rules for identification of seroconversion

Mares are not vaccinated in France. Therefore, an increase in antibody titer can be due to either infection/re-infection or other reasons, such as slight differences in laboratory practices. In order to focus only on the mares which have a true seroconversion, the panel tried to define rules able to exclude mares that were likely infected many months or years ago, i.e. with a mix of negative and low positive results (see Mare 4 in Figure 1) or with little variations in antibody titer (see Mare 5 in Figure 1). The goal was to take into account only the new true seroconversions (such as Mares 1 and 2 in Figure 1), even if some data entry mistake occurred (see 6th test of Mare 3).

Finally for this research, seroconversion was defined by the panel as a change in antibody titer from negative to at least 32 (*i.e.* infection) or as a three-fold or greater increase in antibody titer in mares with previous positive results (*i.e.* reinfection).

Figure 1. Examples of EVA antibody titer curves in five brood mares tested each year over an eight-year period.



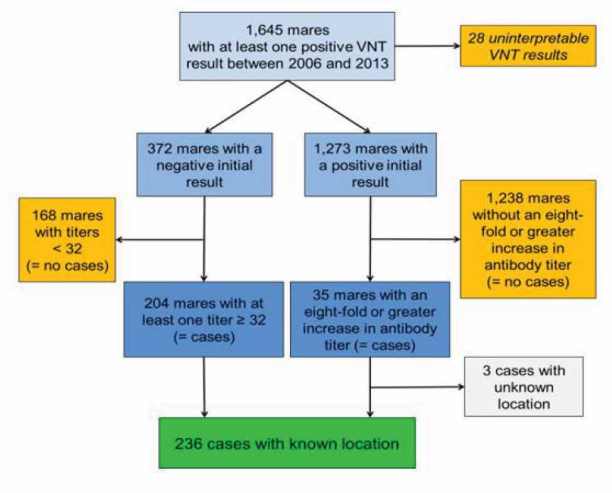
Number of EVA cases and outbreaks detected by the BSS

By applying the proposed rules for identifying seroconversion, we observed 239 EVA cases detected in brood mares by the BSS between 2006 and 2013 (Figure 2). The town was not available for three of these mares. Then we counted the number of cases in each town, considering each year separately, for the 236 cases with a known location: 177 outbreaks were identified (Table 1).

Table 1. Number of EVA cases detected in the outbreaks identified by the BSS in French breeding stock between 2006 and 2013.

Number of EVA cases detected per outbreak	1	2	3	4	7	30	Total
Number of outbreaks identified using the seroconversion definition proposed by the panel	158	13	1	3	1	1	177

Figure 2. Flow chart documenting the proposed rules used to identify EVA cases among the brood mares tested between 2006 and 2013 in France using VNT.



Estimation of the total number of outbreaks and of the BSS's sensitivity

According to the model, the total number of EVA outbreaks that occurred during this period was estimated at 215 (95% credible interval $CrI_{95\%}$ 195-249), on average around 30 per year. Thus the overall sensitivity of the BSS (i.e. N_{det}/N_{occ}) was estimated at 82% ($CrI_{95\%}$ 71-91).

Discussion

Due to the lack of accurate information in the literature about the serological response in naturally infected horses over months and years, we needed to define *ad hoc* rules for identifying seroconversion. Although they are probably imperfect, the high antibody titers usually measured in horses naturally and experimentally infected (7,8) seem to support the proposed rules for research purposes (not for the replacement of the current guidelines for international movements of horses or other policy goals). These *ad hoc* rules may be used to analyze other EVA surveillance datasets based on serology, such as testing before sales or international trade.

The number of cases and outbreaks detected by the BSS is not negligible and confirms EVA circulation in French breeding stock. Of the 239 cases, 35 mares (15%) had positive results before showing a sharp rise in antibody titer, suggesting that a proportion of mares have been reinfected, although natural infection is generally recognized as resulting in durable immunity. The total number of outbreaks estimated by our model seems plausible when trying to compare with other countries (9,10), although comparison is difficult because other studies usually estimate serological point prevalence rather than annual incidence (number of *new* cases or outbreaks) and focus on an individual scale rather than holding/town scale.

The BSS's sensitivity on a town scale seems relatively high. This result supports the relevance of EVA surveillance in breeding stock to prevent the disease spreading through mating.

Conclusion

This study shows that the number of cases and outbreaks is not negligible in the French breeding stock. The estimate of the BSS's sensitivity between 2006 and 2013 is relatively high. However, it could be improved by a closer relationship between surveillance components and more detailed information about the horses' location. Expanding access to serological results collected in circumstances other than pre-mating surveillance (especially before sales or international trade) and using common rules for identifying seroconversion would improve future incidence investigations. The proposed rules may be used to analyze other serological surveillance data, such as testing before sales or international trade. This study also shows how capture-recapture methods may help to estimate surveillance sensitivity and to valorize surveillance data.

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