Evidence-based early clinical detection of emerging diseases in food animals and zoonoses

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SYNOPSIS

In case diseases of food-producing animals or zoonoses (re-)emerge, early clinical decision making is of major importance. In this particular condition, it is difficult to apply a classical evidence-based veterinary medicine process, because of a lack of available published data. A method based on the partition of field clinical observations (evidences) could be developed as an interesting alternative approach. The classification and regression tree (CART) analysis was used to improve the early clinical detection of two selected emerging diseases: bovine spongiform encephalopathy (mad cow disease) and bluetongue due to the serotype 8-virus in cattle.

ABSTRACT

Background: In case diseases of food-producing animals or zoonoses (re-)emerge, early clinical decision making is of major importance. In this particular condition, it is difficult to apply a classical evidence-based veterinary medicine process, because of a lack of available published data. Objective: A method based on the partition of field clinical observations (evidences) could be developed as an interesting alternative approach. Method and principal findings: The classification and regression tree (CART) analysis was used to improve the early clinical detection of two selected emerging diseases: bovine spongiform encephalopathy (mad cow disease) and bluetongue due to the serotype 8-virus in cattle. Conclusion and significance: The use of CART analysis is a way to improve the early clinical detection of diseases of food-producing animals or zoonoses as well as conditions of emergence. The development of a veterinary structured, informed and interactive clinical platform is highly suggested.
Evidence-based veterinary medicine (EBVM) is the application of evidence-based medicine (EBM) to the veterinary field (1). By definition, it is the conscientious, explicit and judicious use of the best scientific evidence to inform clinical decisions with a view to improve the clinical outcome at the individual level (2-3). However, in the veterinary profession, a great deal of time is spent in making diagnostic, therapeutic and preventive decisions in a complex and uncertain environment where optimal evidence often lacks (4).

Medical care is the art of making decisions without adequate information (5). Medical decision making has been studied extensively and follows a mainstream trend, labelled ‘rational optimising’ (6). It is usually based on cognitive rational models, such as decision analysis, decision tables, decision trees and Bayes’ theorem (7-11). When decision refers to diagnosis, the consideration of the possible causes of a disease, its prevalence and an initial evaluation of clinical signs will lead to a differential diagnosis about which clinical judgment, informed by evidence clinical data, is exercised (3). Diagnosis may involve the choice and interpretation of an appropriate confirmatory diagnostic test.

To detect and identify emerging or rare diseases, a good clinical approach is essential as few biological and epidemiological data and/or laboratory tests are available. The approach aims at establishing the limits between normality and abnormality as veterinarians cannot relate the clinical signs to those of a known disease or to their experience. These limits should be built on the ability to detect biological variations in physiological and environmental conditions. The various actors involved in epidemiosurveillance networks (e.g. breeders, veterinarians, and slaughterhouse staff) should be prepared to this clinical approach to fulfil their responsibility in health monitoring (12). Part of this training should develop knowledge of disease biology and epidemiology, and skills in a rigorous, standardized and evidence-based clinical approach including that of differential diagnosis (13-16).
However, since with emerging diseases, the implementation of classical EBVM is difficult because few published cases are available and/or accessible via web searches, other options are necessary.

The current paper aims to describe a method to improve the early clinical detection of emerging diseases in food animals and zoonoses. This approach is based on the analysis of field clinical observations collected on the first cases suspected of disease using a method called “classification and regression tree” (CART) (17-19). Those clinical facts become the only evidences available. Two practical examples are developed to illustrate the feasibility of the method in cattle. Future prospect is also proposed like the implementation of a structured, well-informed and interactive veterinary web clinical data mining platform.

CASE DESCRIPTION

Two examples are developed to illustrate the use of CART analysis for stimulating the early warning of emerging animal diseases. This is a key parameter of health control strategy (20). CART analysis is a non-linear and non-parametric model fitted by binary recursive partitioning of data (including clinical signs). Using CART 6.0 software (Salford Systems, San Diego, CA, USA), the analysis successively splits the dataset into increasingly homogeneous subsets until it is stratified and meets specified criteria (clinical signs) (Figure 1). Further details about CART are presented in previously original papers or reviews (17-19, 21).

Case 1: Early detection of bovine spongiform encephalopathy

Background: Bovine spongiform encephalopathy (BSE) emerged in 1986 (22). It is a neurodegenerative disease characterised by a very long incubation period compared to the life of the host species (23). BSE started a dramatic chain of events in the United Kingdom and subsequently in other countries (24). The peak of interest was the discovery of its potential
zoonotic character after the first description of a new variant of Creutzfeldt-Jakob disease (vCJD) in 1996 (25-27). The presence of clinical signs seems to be linked to the localisation and degree of vacuolisation of neurones. The main warning signs are psychic disorders (apprehension, temperament change, abnormal ear position and abnormal behaviour), sensory disorders (exaggerated responses to stimuli, excessive licking) as well as postural and locomotion abnormalities (ataxia and tremors). Their identification requires a clinical approach: a thorough veterinary clinical examination of the animal when on a halter and when moving in an uncustomary environment (16).

Now the evolution of BSE incidence in many European countries is in decline (28). Because of the favourable BSE epidemiological situation of most Member States in the European Union, a lowering of control measures, by reducing testing procedure, was recently suggested. However, in such a context, the reporting of clinically suspected cattle by the veterinarians is the most common method for detecting sporadic cases of BSE (18). The improvement of clinical diagnosis and decision-making remains crucial.

Veterinary data collection: A comparison of clinical patterns captured by veterinarians, consisting in 25 signs, was carried out between BSE cases confirmed in Belgium before October 2002 (N = 30), and 272 suspected cases that were subsequently determined to be histologically, immunohistochemically, and scrapie-associated-fiber negative (10).

Epidemiological methods and principal findings: Seasonality in reporting suspected cases was observed, with more cases being reported during wintertime when animals were kept indoors. The median duration of illness was 30 days. Using odds ratio, the 10 most relevant signs of BSE were kicking in the milking parlour, hypersensitivity to touch and/or sound, head shyness, panic-stricken response, reluctance to enter in the milking parlour, abnormal ear movement or carriage, increased alertness behaviour, reduced milk yield, teeth grinding and
temperament change. Ataxia did not appear to be a specific sign of BSE. A classification and regression tree was constructed by epidemiologists using the following four features: age of the animal, year of birth, number of relevant BSE signs noted, and number of clinical signs typical of listeriosis reported. The model presented a 100% sensitivity and a 85% specificity (Figure 2).

**Veterinary significance:** The originality of the approach resides in the fact that, first; it involved both veterinarians and epidemiologists. Secondly, it offers an explorative and interactive tool based of clinical observations (evidences) captured by veterinarians and, then, the results and conclusions arrived at are independent of BSE prevalence, through the use of odds ratios. The late feature is especially appealing for rare events. A similar decision tree, allowing the distinction of `highly suspected BSE cases’ from all other suspected BSE cases, could be applied in other countries, with or without the use of rapid tests. The continued addition of standardized clinical data by veterinarians would permit further improvement of the current model tree, even if the clinical BSE pattern would be modified in time. Based on the CART analysis results, veterinarians could more appropriately identify affected cows and retrieve them from the food chain in a public health perspective.

**Case study 2: Early detection of bluetongue**

**Background:** Bluetongue (BT) is a non-contagious disease affecting ruminants and is caused by the bluetongue virus (BTV). BTV is transmitted by blood-feeding midges of the genus *Culicoides* (Diptera: Ceratopogonidae) (29). A broad spectrum of wild and domestic ruminants can be infected and severe clinical signs are mainly seen in certain breeds of sheep and some *Cervidae* species (30-31). The severity of infection depends on various factors, such as species, breed, age, nutritional and immune status of animals, and environmental stresses, as well as the virulence of the BTV strain involved (32). Although clear differences in virulence of BTV isolates are known, the determinants of virulence are still poorly defined.
Clinical manifestations are closely linked to virus-induced vascular injuries and the role of species-specific endothelial cell-derived inflammatory and vasoactive mediators has been highlighted (33). The European BTV-8 outbreak was characterised by peculiar features (34). Among these features, a remarkable severity of the lesions in cattle was noticed (35).

**Veterinary data collection:** Forty-one cattle from seven Belgian farms and two French farms confirmed as infected with bluetongue virus serotype 8 (BTV-8) were monitored from the onset of clinical signs in order to describe the disease pattern (19). On each visit, a standardised clinical form was filled in for each animal by a veterinarian (Table I) (36).

**Epidemiological methods and principal findings:** A clinical score was calculated for every week until the end of clinical signs. A CART analysis was conducted by epidemiologists to determine the most important clinical signs every week for the first seven weeks. The highest scores were recorded within two weeks of clinical onset. The first recorded clinical signs were quite obviously visible (conjunctivitis, lesions of nasal mucosa and nasal discharge). Skin lesions, a drop in milk production and weight loss appeared later in the course of the disease. A biphasic pattern regarding nasal lesions was noticed: the first peak concerned mainly congestive and ulcerative lesions, whereas the second peak mainly concerned crusty lesions.

**Veterinary significance:** These results should ensure a more accurate detection of BT in cattle by veterinarians in order to increase the early detection of emerging diseases (Table II).

**DISCUSSION AND CONCLUSION**

The clinical expression of a disease in an animal depends on several parameters: the nature of the causal agent (dose, virulence) (37), the location of induced lesions (38), the host (resistance, general condition, immune status) and the environment; certain clinical signs may be exacerbated when the environment of the animal is altered (39-40). The quality of observation plays an essential role and is proportional to the breeders’ and veterinarians’ level
of information, awareness and training. The intensity of observation is also important, and seems to depend directly on herd size. According to the United States of America, National Animal Health Monitoring System (NAHMS), the rate of neurological problems in breeding females in beef herds, expressed in affected cattle per thousand, doubles when herd size is less than 100 heads, and is nil when herd size is over 300 heads (41). In addition to these parameters, there is a degree of variability that depends on the individual animal and the observer (clinical picture, pre-patent phase and course of the disease). To improve knowledge regarding diseases, especially (re-)emerging animal diseases, it is important: i) to improve awareness, training and information available for breeders and veterinarians, ii) to use a uniform method for clinical examination by veterinarians, iii) to make more systematic use of confirmatory diagnostic tests, iv) to create sentinel networks of highly-motivated breeders and veterinarians, v) to transcribe the results of observations in a codified and standardised form, regarding both nature and course, vi) to compile and validate existing information by epidemiologists vii), to enrich a relational database and viii), to discuss actual experience in a focus group.

In case of early clinical detection of emerging animal diseases, an EBVM approach is difficult to perform. However an alternative approach based on new structured and harmonized clinical observations (evidence) should be used (standardized clinical form compiled by veterinarians). With two practical examples we demonstrated the usefulness of joint effort involved veterinarians and epidemiologists in CART analysis to improve the early clinical detection of (re-) emerging animal diseases. The strategy is based on analysis of clinical observations (evidences) captured by veterinarians in the field. Selection criteria are based on signs captured by a structured and harmonized clinical form. A presumptive clinical diagnosis performed by veterinarians implies confirmatory diagnostic test(s). Results are analyzed taking into account all clinical signs registered. The CART analysis carried out by
epidemiologists allows producing a robust clinical tree that improves the early clinical detection of diseases by any veterinarian who has not faced the considered emerging disease before.

The CART approach is characterised by i) its exploratory and interactive aspects, ii) its independence from sample size and disease prevalence, which is usually imperfectly known, and iii) its spatio-temporal universality (adaptation is possible when the clinical profile of disease evolves in function of time or region; adaptation is also possible for other diseases). The use of tools to improve the detection of (re-)emergent diseases will lead to more effective veterinary epidemiomveillance networks. The efficacy of these networks requires regular evaluations together with the elaboration and a continuous follow-up of performance indicators. The recent episodes of both human and animal (re-)emergent diseases have also highlighted the important role of global health information systems. These systems require abilities, resources, collaborative and coordinated actions of medical and veterinary regulatory authorities.

To improve early clinical detection of (re-)emerging diseases, a future prospect should consist in developing a veterinary structured and informed clinical platform. Whilst some interesting diagnostic support systems for veterinary medicine exist, like the “Consultant” support system from the Cornell College of Veterinary Medicine (http: www.vet.cornell.edu/consultant/consult.asp) (42), no interaction and partition of clinical data are currently available.

Facing the emergence of diseases, the translation of the support system to an interactive platform should be interesting. Involving sentinel veterinarians in this platform is crucial. Veterinarians should be stimulated in a pilot research project to ensure the collection of field clinical data through the filling of structured and harmonized clinical forms. The connection between validated clinical data and results of confirmatory diagnostic tests using CART
analysis by epidemiologists permits to build useful clinical decision trees to improve the
evidence-based early clinical detection of diseases of food-producing animals in the field.

More interactions between veterinarians and epidemiologists should be stimulated in a
clinical perspective.

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REFERENCES


6. Janis I.L., Mann L. Decision making: A psychological analysis of conflict, choice, and


14. Brown C. Importance des maladies émergentes pour la santé publique et animale et pour les échanges commerciaux. 69ème Session Générale du Comité International de


335 37. Schlech W.F. Listeriosis epidemiology, virulence and the significance of contaminated

337 38. George L.W. Localization and differentiation of neurologic diseases. In Large animal


341 40. Saegerman C., Dechamps P., Vanopdenbosch E., Roels S., Petroff K., Dufey J., Van
342 Caeneghem G., Devreese D., Varewyck H., De Craemere H., Desmedt I., Cormann
343 A., Torck G., Hallet L., Hamerijckx M., Leemans M., Vandersanden A., Peharpre D.,
344 Brochier B., Costy F., Muller P., Thiry E. & Pastoret P.-P. Épidémiosurveillance de
346 de Médecine Vétérinaire 1999;143:423-436.

347 41. Centers for Epidemiology and Animal Health (CEAH). National Animal Health
348 Monitoring System. Beef’97, Part II: Reference of 1997 beef cow-calf health and
349 health management practices. United States Department of Agriculture, Fort Collins,

351 42. White M.E. Consultant. A diagnostic support system for veterinary medicine. Cornell
352 College of Veterinary Medicine (www.vet.cornell.edu/consultant/consult.asp accessed
353 on 13 November 2011).
Figures and tables

**Figure 1.** Flowchart of the CART approach with implication of veterinarians (on the left: process; on the right: actors involved)

**Figure 2.** Classification and regression tree modelling for clinically suspected bovine spongiform encephalopathy cases in Belgium (10)

Legend: BSE, bovine spongiform encephalopathy; LIS, listeriosis; Score, number of clinical signs that are present.

**Table I.** Bluetongue standardized clinical form for the use in different species (36)

**Table II.** Variable importance in CART analysis during the first seven weeks of cattle naturally infected by BTV-8 (19)
Table I. Bluetongue standardized clinical form for the use in different species (36)

**General information**: Identification number of the herd; Identification number of animal; Animal species; Breed; Sex; Date of birth; Date of last calving; Stage of pregnancy; Date of clinical examination; Name of clinician.

**General clinical signs**: Hyperthermia; Decreased milk production; Wasting, emaciation, weight loss; Tiredness; Oedema of head, ears, sub-mandibular region, or the peri-orbital region; Hypertrophied lymph nodes.

**Clinical signs of skin and annexes**: Lesions of the muzzle, lips (congestion > ulcers > necrosis); Conjunctivitis, tears, peri-ocular dermatitis; Photosensibilisation-like lesions; Presence of petechias, contusions, ecchymoses; Erythema, inflammation of the skin, crusts; Cyanosis of the skin or limbs; Skin lesion of the udder, teats or vulva; Scrotal skin lesions; Wool loss (sheep).

**Clinical loco-motor signs (musculo-arthro-skeletal)**: Incapacity to lift up or prostration; Reluctance to move or limited movement; Lameness, stiffness of front limbs; Lameness, stiffness of hind limbs; Oedema of coronary bands; Swelling of pastern, fetlock, cannon, carpal or hock joint; Pododermatitis; Contracture of front limbs; Contracture of hind limbs; Arched back; Amyotrophy; Torticollis or neck bended.

**Digestive clinical signs**: Loss of appetite; Anorexia; Difficulties in grasping the food; Regurgitation; Congestion, erythema of the oral mucosa; Ulcerative lesions of the oral mucosa, excoriations; Salivation, drooling, foam out of the mouth; Oedema and/or protrusion of the tongue; Cyanosis of the tongue; Haemorrhagic stool; Diarrhoea.

**Respiratory clinical signs**: Ulcerative lesions of the nasal mucosa; Purulent nasal discharge; Mucous, serous, aqueous nasal discharge; Halitosis or bad breath; Dyspnoea, oral breathing, stridor.

**Neurological clinical signs**: Apathy, lethargy; Generalised weakness, paresis or paralysis.

**Reproductive clinical signs**: Anoestrus; Abortion or premature calving; Stillbirth; Abnormalities of newborns.

**Duration of evolution**: Date of the first clinical signs; Comments on the evolution of the disease within the herd.

**Post-mortem (PM)**: Has a PM examination been performed?; If « yes », please attach a copy of the PM record(s) (with the animals identification mentioned).

**Concomitant pathologie(s)
Table II. Variable importance in CART analysis during the first seven weeks of cattle naturally infected by BTV-8 (19)

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis, lacrimation, peri-ocular dermatitis</td>
<td>100</td>
<td>38</td>
<td>33</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ulcerative lesions of nasal mucosa, crusts</td>
<td>32</td>
<td>100</td>
<td>100</td>
<td>91</td>
<td>76</td>
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<td></td>
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<tr>
<td>Mucous, serous, aqueous nasal discharge</td>
<td>26</td>
<td>1</td>
<td>100</td>
<td>28</td>
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<tr>
<td>Congestion, erythema, redness of buccal mucosa and/or muzzle</td>
<td>21</td>
<td>19</td>
<td>61</td>
<td></td>
<td></td>
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<tr>
<td>Loss of appetite</td>
<td>18</td>
<td>71</td>
<td>18</td>
<td>3</td>
<td>28</td>
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<td>Purulent nasal discharge</td>
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<td>13</td>
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<td>Ulcerative lesions of buccal mucosa, excoriation</td>
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<td>24</td>
<td>44</td>
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<td>Swelling of coronary bands</td>
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<td>Skin lesions of udder, teat or vulva</td>
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<td>9</td>
<td>32</td>
<td>18</td>
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<td>Swelling of the head, tongue, sub-maxillary area, jaws</td>
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<td>Incapacity to stand up, prostration</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<td>Anorexia</td>
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Figure 1.
Figure 2.