SOCIETY FOR VETERINARY EPIDEMIOLOGY AND PREVENTIVE MEDICINE

Proceedings of a meeting held in

Ghent, Belgium

25th – 27th March 2015

Edited by H.-H. Thulke and K. Verheyen

and the SVEPM Executive Committee

Cite as: Thulke, H.-H. and Verheyen K. (eds). Proceedings of the Society for Veterinary Epidemiology and Preventive Medicine annual meeting held in Ghent, SVEPM

ISBN 978-0-948073-30-4

ACKNOWLEDGEMENTS

The following bodies provided financial support for the conference and the publication of these proceedings:

Research Foundation Flanders

Federal Agency for the Safety of the Food Chain

Zoetis

Boerenbond

Flemish Society for Veterinary Epidemiology and Economics

Boehringer-Ingelheim

Avia-GIS

Ghent University

CODA-CERVA

Scottish Rural College

Royal Veterinary College

University of Liverpool

Merial

BioMed Central

CONTENTS

CANINE HEALTH

PIG HEALTH AND PRODUCTION

ECONOMICS APPLIED TO ANIMAL HEALTH

DISEASE MODELLING

ROBUSTNESS OF STATISTICAL METHODS

SOCIO-CULTURAL ANALYSIS

ANALYSIS OF SURVEILLANCE DATA

ZOONOSES AND ANTIBIOTIC RESISTANCE

***

Society for Veterinary Epidemiology and Preventive Medicine

CANINE HEALTH

PREVALENCE AND SURVIVAL OF DOGS WITH DEGENERATIVE MITRAL VALVE DISEASE ATTENDING PRIMARY-CARE PRACTICE IN ENGLAND

M.J. MATTIN*, A. BOSWOOD, D.B. CHURCH, P. MCGREEVY, D.G. O'NEILL, P. THOMSON AND D.C. BRODBELT

SUMMARY

This study aimed to evaluate survival of dogs with degenerative mitral valve disease (DMVD). A retrospective cohort study of dogs with DMVD attending primary-care practices in England was undertaken. Cases of DMVD were identified within the electronic patient records (EPRs) of practices sharing data with VetCompass. Kaplan-Meier curves were used to explore survival and Cox regression models identified factors associated with hazard of death. The EPRs from 111,967 dogs identified 405 cases of DMVD. A further 3,557 dogs were classified as possible cases (heart murmurs consistent with DMVD). In the multivariable analysis, Cavalier King Charles Spaniels and other purebreds had higher hazards of death than crossbreds. Dogs weighing ≥ 20.0 kg and older dogs had an increased hazard of death compared with those < 20.0 kg and younger dogs, respectively. These results could aid clinical prognostication and help assessment of the impact of DMVD at a population level.

INTRODUCTION

Degenerative mitral valve disease (DMVD) has a high prevalence in the domestic dog population, with estimates ranging between 3.6% - 69.7% (Detweiler & Patterson, 1965; Whitney, 1974; Thrusfield et al., 1985). The disorder is generally straightforward to diagnose from the presence of a characteristic heart murmur that can be detected on physical examination (Borgarelli & Haggstrom, 2010). However, dogs with DMVD form a heterogeneous population and only a proportion of affected animals will develop congestive heart failure or die as a result of their cardiac disease (Borgarelli et al., 2012). The challenges for practitioners therefore increasingly centre on prognostication and identifying patients at greater risk of death.

Survival times have been reported for cohorts of dogs with DMVD recruited to clinical trials (Ettinger et al., 1998; The Bench Study Group, 1999; Haggstrom et al., 2008) and those included in observational studies monitored by specialist veterinary cardiologists (Borgarelli et al., 2008; Moonarmart et al., 2010; Borgarelli et al., 2012; Hezzell et al., 2012). The results of specialist treated studies may be poorly generalizable to wider DMVD populations because referral caseloads may include complex cases requiring more advanced care (Bartlett et al., 2010) and non-consent bias may occur if patients enrolled into clinical trials are not

---

[*] Madeleine Mattin, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire, AL9 7TA, UK. Email: mmattin@rvc.ac.uk

representative of the eligible population (Marcus, 1997). Further, the time of entry into existing survival studies was generally defined as the time of referral or randomization, rather than the time the disease was initially detected, limiting the application of these results to the primary-care setting. The current literature lacks median survival time (MST) estimates from the time of disease detection to time of death in primary-care practice populations of dogs with DMVD.

Risk stratification could improve prognosis and management of DMVD cases. For example, more frequent monitoring or targeted therapy may be warranted in patients at high risk of progressive disease (Hezzell et al., 2012). Previous survival studies have largely focussed on the predictive value of echocardiographic and radiographic measurements (Haggstrom et al., 2008; Moonarmart et al., 2010; Lord et al., 2011; Borgarelli et al., 2012; Hezzell et al., 2012; Reynolds et al., 2012) and circulating concentrations of cardiac biomarkers (Fonfara et al., 2010; Moonarmart et al., 2010; Hezzell et al., 2012; Eriksson et al., 2014) in dogs with DMVD. However, it is not always possible to perform these diagnostic tests in primary-care practice due to limited availability of equipment, clinical expertise or financial constraints. Some of these studies also evaluated the prognostic value of demographic variables, such as sex, breed, age and bodyweight (Haggstrom et al., 2008; Moonarmart et al., 2010; Hezzell et al., 2012; Reynolds et al., 2012), which can be easily ascertained in the primary-care setting. However, the latter studies yielded conflicting results and may have limited external validity as their study populations were referred to veterinary cardiologists, which may be subject to selection bias.

Estimating MST and evaluating the predictive value of demographic factors in the primary-care setting would be of value as these results would be relevant to the wider primary-care population and could aid prognostication. The objectives of this study were to estimate the MST of dogs with DMVD and to identify demographic risk factors associated with all-cause mortality in affected animals attending primary-care veterinary practices in England. It was hypothesised that crossbred dogs would have a lower hazard of death than purebred dogs.

MATERIALS AND METHODS

A retrospective cohort study followed cases of DMVD identified within the electronic patient records (EPRs) of dogs attending veterinary practices sharing de-identified data with the Veterinary Companion Animal Surveillance System database (VetCompass, 2014) between 1st January 2010 and 31st December 2011. The practices were primary-care companion animal clinics, mainly located in central and southeast England. Data shared included demographic (date of birth, sex, breed, bodyweight, insurance status, microchip number, partial postcode, veterinary clinic ID) and clinical data (free-text clinical notes, VeNom diagnostic terms (VeNom coding group, 2014), treatments prescribed). The study received ethics approval from the Royal Veterinary College ethics and welfare committee.

Case finding was achieved by searching for EPRs containing key diagnostic terms relating to DMVD (e.g. ‘mitral’, ‘valv*’, ‘MVD’, ’murmur’) and reviewing the free text clinical notes of potential cases. Two case definitions were developed to account for different levels of diagnosis: diagnosed DMVD and possible DMVD cases. Diagnosed DMVD cases were defined as dogs with a stated diagnosis of DMVD (or synonym) in their clinical notes or VeNom diagnostic terms. Possible DMVD cases were defined as dogs over one year old with a documented heart murmur consistent with DMVD without a specific cardiac diagnosis.

Dogs reported to have continuous or diastolic murmurs were excluded as cases. Dogs that had murmurs only detected during pregnancy or clinically significant systemic disease (e.g. moderate to severe anaemia, pyrexia, severe hypovolaemia or dehydration) and those with murmurs or mitral valve regurgitation due to other diagnosed cardiac disorders (e.g. aortic stenosis, ventricular wall defects etc.) were also excluded. Evidence of a point of maximal intensity (thoracic location where the heart murmur is heard most loudly) inconsistent with DMVD on chest auscultation was not used as an exclusion criterion. Diagnosed and possible DMVD cases were combined to form a population of dogs with heart murmurs consistent with DMVD for the prevalence estimates, hereafter described as heart murmur cases. Incidence estimates were reported separately for possible and diagnosed cases.

Where follow up consultations occurred, the EPRs of all diagnosed cases up to May 2014 were examined in detail. The date of the first veterinary consultation, the date the disease was detected and the date, cause and modality of death were extracted where applicable. Incident cases were defined as dogs that were newly diagnosed with DMVD or recorded with a heart murmur during the study period. Dogs alive at the end of the study period were censored on the date of the last entry in their clinical notes. Death as a result of cardiac disease was defined as euthanasia or death due to worsening of clinical signs associated with DMVD or when veterinary surgeons stated that heart disease was the primary cause of death in the clinical notes. Cases were not classified as cardiac deaths if alternative or multiple causes of death were listed, or if the cause of death was not specified. Due to the large number of possible cases, a random sample of possible DMVD cases was selected from the denominator of all possible cases using an electronic random number generator (www.random.org) to enable comparison between the survival of diagnosed and possible cases. The date of murmur detection and the date, cause and modality of death in incident possible cases were recorded.

Data were exported to a spreadsheet (Microsoft Office Excel 2010, Microsoft Corp, Redmond, WA), checked, cleaned and exported to Stata Version 13 (Stata Corporation, TX) for analysis. Prevalence and 95% confidence intervals (95% CI) were calculated for heart murmur cases (including both diagnosed and possible cases) and for diagnosed DMVD cases only. Prevalence was adjusted for clustering at the practice level using survey commands (StataCorp., 2013). Further analyses relate to incident cases only.

The MST for all-cause mortality and cardiac death were calculated for diagnosed and possible cases when possible. Kaplan-Meier survival curves were generated for all-cause mortality and cardiac-related death and log-rank tests were used to explore survival differences between diagnosed and possible cases. Univariable and multivariable Cox proportional hazard models were used to evaluate associations between the following explanatory variables and hazard of death (all-cause mortality): breed, sex, insurance status, maximum recorded bodyweight (kg), age at diagnosis (years) and level of diagnosis (diagnosed and possible cases). Breeds were categorised into ‘crossbred’, ‘Cavalier King Charles Spaniel’ (CKCS) and ‘other purebred’. CKCS were evaluated as a separate group as this represented the most common breed within the data and has frequently been a comparator group in the current literature. Additional analyses evaluating a binary breed variable (‘purebreds’ and ‘crossbreds’) were performed. Maximum bodyweight was further dichotomised based on published literature (< 20.0 kg and ≥ 20.0 kg) (Borgarelli et al., 2004; Borgarelli et al., 2012). Age at diagnosis (years) was categorised into four groups (< 5.0, 5.0 - < 10.0, 10.0 - < 15.0, and ≥ 15.0 years) and evaluated for a linear association. Level of diagnosis and breed were forced variables to account for the sampling technique and *a priori* interest, respectively. Variables significant at the 20% level in univariable analyses were taken forward for consideration in the mixed effects multivariable model. Manual stepwise backward elimination regression was used to sequentially remove variables with a P-value > 0.05 in the multivariable model (Dohoo et al., 2009). Each eliminated variable was then added to the final model to assess for important confounding by the change in parameter estimates. Interactions between final model explanatory variables were evaluated. Veterinary clinic was evaluated as a shared frailty term to account for clustering at the practice-level. The proportional hazards assumption was tested using Schoenfeld residuals and visual inspection of log-cumulative hazard and Kaplan-Meier Cox plots. Goodness of fit was evaluated using Cox-Snell residuals. Dogs with any missing data were excluded from the multivariable Cox proportional hazards model.

It was estimated that a sample size of approximately 160 individuals would be required to detect a hazard ratio (HR) for all-cause mortality of two for a variable to which 75% of individuals were exposed, at a confidence level of 95% and power of 80%. This calculation was based on the estimated proportion of purebred dogs in the VetCompass database (O'Neill et al., 2014), an accrual time of 24 months, a follow-up time of 24 months and a MST of 20 months for exposed individuals (PS Power and Sample Size Calculations, 2014).

RESULTS

Descriptive statistics

The denominator population consisted of 111,967 individual dogs attending 93 veterinary clinics on one or more occasions between 1st January 2010 and 31st December 2011. Four hundred and five dogs were identified as having a diagnosis of DMVD, giving a prevalence, adjusted for the clustering effect of clinic, of 0.36% (95% CI: 0.29 – 0.45%). A further 3,557 dogs were classified as possible cases, having a heart murmur consistent with DMVD recorded within their EPRs. Generally, the age, bodyweight and breed distributions of possible and diagnosed DMVD cases were similar; with DMVD typically affecting older small to medium sized dogs (data not shown). A total of 3,962 dogs were heart murmur cases (with possible or diagnosed DMVD), giving a prevalence, adjusted for the clustering effect of clinic, of 3.54% (95% CI: 3.26 – 3.84%).

Survival times of incident diagnosed and possible DMVD cases

Incident diagnosed DMVD cases: One hundred and sixteen (28.6%) of the diagnosed DMVD cases were incident cases, newly diagnosed with DMVD or recorded with a heart murmur during the study period. The mean age at which DMVD was diagnosed or the presence of a heart murmur was first recorded in diagnosed cases was 9.52 years (standard deviation 3.20 years). The median follow-up time was 17.9 months (IQR: 6.0 – 27.9 months, range: 0.0 – 45.2 months). Fifty-eight (50.0%) of the incident diagnosed cases died during the study period. Twenty (34.5%) deaths were primarily due to cardiac disease, 9 (15.5%) deaths occurred due to multiple causes including cardiac disease and 16 (27.6%) deaths occurred due to non-cardiac causes. In 13 (22.4%) cases, cause of death was not recorded. Euthanasia accounted for 43 (74.1%) deaths. The MST for all-cause mortality was 25.4 months (95% CI: 20.4 – 34.4 months) after the disease was initially detected (Table 1). MST for cardiac death could not be calculated for these cases as the cumulative proportion of dogs surviving failed to drop below 0.5.

Incident possible DMVD cases: One hundred and twenty one (29.7%) from a random sample of 407 possible DMVD cases were incident cases, based on the presence of a heart murmur consistent with DMVD newly detected during the study period. The mean age at which the presence of a heart murmur was first recorded in possible cases was 9.73 years (standard deviation 4.01 years). The median follow-up time for possible cases was 14.4 months (IQR: 2.5 – 27.6 months, range 0.0 – 43.5 months). Forty-nine (40.5%) possible cases died during the study period. Eight (16.3%) deaths were primarily attributed to cardiac disease, two (4.1%) deaths occurred due to multiple causes including cardiac disease and 29 (59.2%) deaths occurred due to non-cardiac causes. In 10 (20.4%) cases, cause of death was not recorded. Euthanasia accounted for 45 (91.2%) deaths. The MST for all-cause mortality was 33.8 months (95% CI: 23.7 – 43.1 months) after a heart murmur was initially detected. MST for cardiac related death was 42.0 months (95% CI: 31.2 – 52.7 months). There was no evidence of a difference in the survival functions of diagnosed and possible DMVD cases for all-cause mortality (log rank test, P = 0.63) (Fig. 1). However, there was a statistically significant difference in survival for cardiac mortality (log rank test, P = 0.034) (Fig. 2).

Table 1. Mean age at diagnosis and survival characteristics of incident cases of diagnosed and possible degenerative mitral valve disease in dogs attending primary-care practices in the UK

	Diagnosed DMVD	Possible DMVD[a]
Incident cases, number (%)	116 (28.6)	121 (29.7)
Mean age in years at DMVD diagnosis / murmur detection (standard deviation)	9.52 (3.20)	9.73 (4.01)
All-cause mortality		
Deaths, number (%)	58 (50.0)	49 (40.5)
Median survival time in months (95% CI)	25.4 (20.4 – 34.4)	33.8 (23.7 – 43.1)
Cumulative proportion surviving at 1 year (95% CI)	0.72 (0.64 – 0.80)	0.71 (0.62 – 0.79)
Cumulative proportion surviving at 2 years (95% CI)	0.55 (0.45 – 0.65)	0.57 (0.47 – 0.67)
Cardiac related death		
Cardiac deaths, number (%)	20 (17.2)	8 (6.6)
Median survival time in months (95% CI)	n/a	42.0 (31.2 – 52.7)
Cumulative proportion surviving at 1 year (95% CI)	0.91 (0.85 – 0.97)	0.95 (0.91 – 0.99)
Cumulative proportion surviving at 2 years (95% CI)	0.84 (0.76 – 0.91)	0.93 (0.88 – 0.99)

[a] Possible DMVD cases were defined as dogs over one year old with a documented heart murmur consistent with a diagnosis of DMVD without a specific cardiac diagnosis

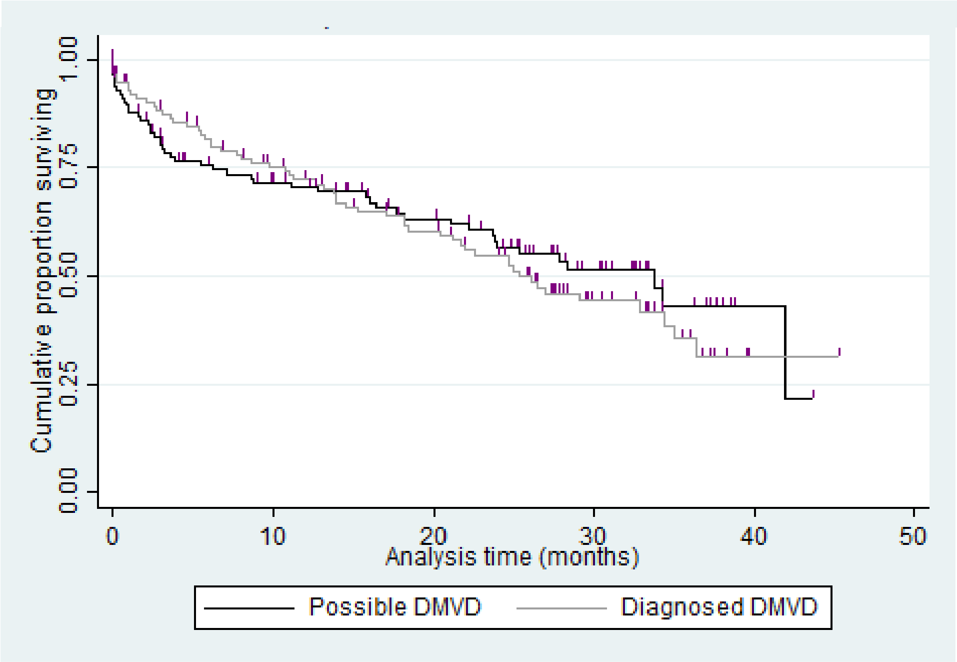


Fig. 1 Kaplan-Meier survival curve of all-cause mortality in incident cases of diagnosed and possible degenerative mitral valve disease in dogs attending primary-care practices in England. Survival time represents the time from when the disease was initially detected until the time of death due to all-cause mortality.

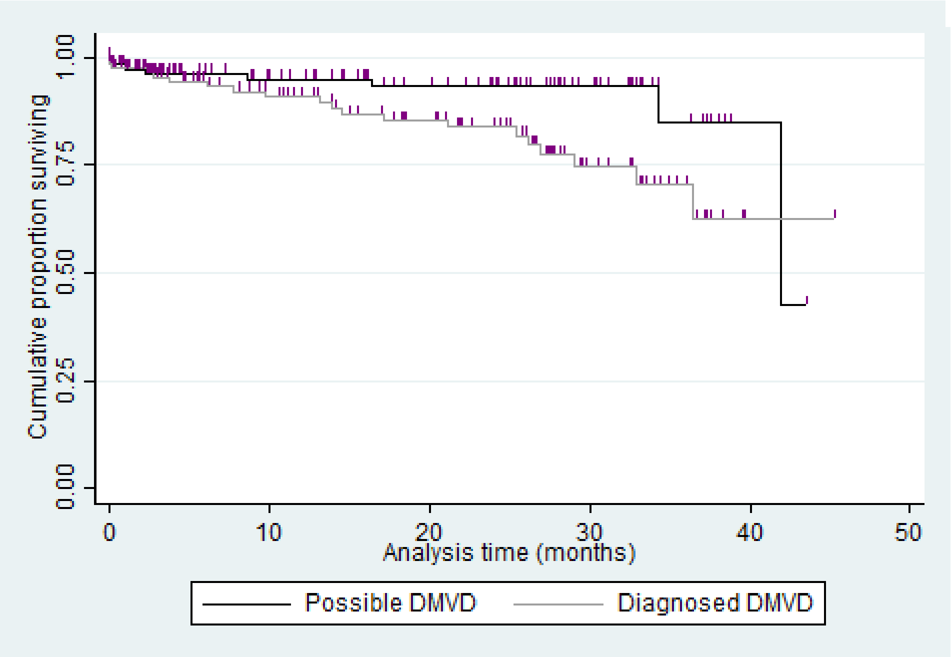


Fig. 2 Kaplan-Meier survival curve of cardiac death in incident cases of diagnosed and possible degenerative mitral valve disease in dogs attending primary-care practices in England. Survival time represents the time from when the disease was initially detected until the time of death due to cardiac disease. Deaths due to other causes were censored.

Cox proportional hazards models: In the univariable analysis, there was a non-statistically significant trend for an association between breed and survival (P = 0.083). CKCS had a lower hazard of death than crossbred dogs (HR 0.44, 95% CI 0.21 – 0.96), whereas there was no difference observed between the survival of crossbreds and other purebreds. Dogs with a maximum recorded bodyweight of 20.0 kg or greater had almost twice the hazard of death in univariable analysis (HR 1.87, 95% CI: 1.24 – 2.83). For each 5 year increase in age group, hazard of death increased by a factor of 2.80 (95% CI: 2.09 – 3.75). There was no evidence for an association between survival and sex, insurance status or level of diagnosis (diagnosed versus possible cases) (Table 2). When CKCS were combined with other purebreds, no association between breed and survival was detected (P = 0.2454). Twelve dogs had missing bodyweight data and 10 dogs did not have insurance status recorded.

Table 2. Descriptive statistics and univariable Cox regression analysis for risk factor association with death (all-cause mortality) among 237 dogs with diagnosed or possible degenerative mitral valve disease attending primary-care veterinary practices

Variable	Number (%)	Hazard ratio	95% confidence intervals	P-value
Breed				0.0834
Crossbred	43 (18.1)	Baseline	~	
Cavalier King Charles Spaniel	31 (13.1)	0.44	0.21 – 0.96	
Purebred other	163 (68.8)	0.82	0.52 – 1.32	
Sex				0.4034
Female	111 (46.8)	Baseline	~	
Male	126 (53.2)	0.85	0.58 – 1.24	
Insurance status				0.9409
Not insured	88 (38.8)	Baseline	~	
Insured	139 (61.2)	0.98	0.65 – 1.49	
Maximum bodyweight				0.0040
<20.0 kg	163 (72.4)	Baseline	~	
≥20.0 kg	62 (27.6)	1.87	1.24 – 2.83	
Age group (years)				<0.0001
<5.0 years	27 (11.4)	Baseline	~	
5.0 - <10.0 years	97 (40.9)	2.80[a]	2.09 – 3.75	
10.0 - <15.0 years	99 (41.8)			
≥ 15.0 years	14 (5.9)			
Level of diagnosis				0.6306
Possible DMVD	121 (51.1)	Baseline	~	
Diagnosed DMVD	116 (48.9)	1.10	0.75 – 1.61	

[a] Hazard ratio relates to each 5 year increment in age

In the multivariable analysis, CKCS (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred dogs (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs. Dogs weighing ≥ 20.0 kg had almost three times the hazard of death than dogs < 20.0 kg (HR 2.81, 95% CI: 1.72 – 4.59). For each 5 year increase in age, hazard of death increased 3.85 fold (95% CI: 2.61 – 5.69). Veterinary clinic was included as a shared frailty term (P = 0.027). No important confounding or interactions were identified. There was no evidence that the proportional hazards assumption was violated and model fit was good. When the breed variable with three groups (CKCS, other purebreds and crossbreds) was substituted for the binary breed variable (purebreds and crossbreds) in the multivariable model, the association between breed and survival persisted; with purebreds having approximately double the hazard of death compared with crossbred dogs (HR 1.84, 95% CI: 1.06 – 3.18).

Table 3. Multivariable Cox regression analysis for risk factor association with death (all-cause mortality) among dogs with diagnosed or possible degenerative mitral valve disease attending primary-care veterinary practices. Observations from 225 of the 237 incident cases (12 had a missing value for one of the final model variables).

Variable	Hazard ratio	95% confidence intervals	P-value
Breed			0.0533
Crossbred	Baseline	~	
Cavalier King Charles Spaniel	2.78	1.05 – 7.36	
Purebred other	1.86	1.07 – 3.23	
Maximum bodyweight			0.0001
<20.0 kg	Baseline	~	
≥20.0 kg	2.81	1.72 – 4.59	
Age group (years)			<0.0001
<5.0 years	Baseline	~	
5.0 - <10.0 years	3.85[a]	2.61 – 5.69	
10.0 - <15.0 years			
≥ 15.0 years			
Level of diagnosis			0.6093
Possible DMVD	Baseline	~	
Diagnosed DMVD	1.12	0.72 – 1.73	
Veterinary clinic (included as a shared frailty term)			0.027
Theta	0.23		

[a] Hazard ratio relates to each 5 year increment in age

DISCUSSION

This study identified a prevalence of diagnosed DMVD of 0.36% (95% CI: 0.29 – 0.45%) and a substantially greater proportion of dogs with heart murmurs consistent with DMVD (3.54%, 95% CI: 3.26 – 3.84%). The MST following detection of the disease was approximately 2 – 3 years in both diagnosed and possible DMVD cases. Purebreds, older dogs and those weighing ≥ 20.0 kg had a higher hazard of death compared with crossbreds, younger and lighter dogs, respectively.

The MSTs for all-cause mortality were 25.4 (95% CI: 20.4 – 34.4) and 33.8 (23.7 – 43.1) months for diagnosed and possible cases, respectively. Considering that the disease was initially detected in older dogs (mean age 9.52 and 9.73 years in diagnosed and possible cases, respectively) and the MST was relatively long, DMVD appeared to have minimal impact on longevity in many dogs. Further, the median age of death in our DMVD cohort was 12.2 years (IQR: 10.5 – 14.3 years), similar to median longevity reported for 5,095 dogs with confirmed deaths within the VetCompass population (12.0 years, IQR 8.9 – 14.2 years) (O'Neill et al., 2013). The median age of death of crossbreds (14.3 years, IQR: 12.3 – 15.2), purebreds (11.7 years, IQR: 10.0 – 13.6) and CKCS (10.0 years, IQR 8.6 – 10.7) in the current DMVD cohort were similar to those reported within the overall VetCompass population (13.1 years, IQR: 10.1 – 15.0; 11.9 years, IQR 8.4 – 14.0 and 9.9 years, IQR 8.1 – 12.3, respectively) (O'Neill et al., 2013). However, 34.5% of dogs with diagnosed DMVD died due to their cardiac disease, emphasising that dogs with DMVD are a heterogeneous population and that it is therefore important to identify those most at risk of progressive disease and death. When only cardiac related deaths were considered, dogs with diagnosed DMVD had shorter survival times than possible cases. Given the age at detection of murmurs and disease in possible and diagnosed cases respectively were very similar and the shorter survival of diagnosed DMVD cases, it would appear that dogs with more advanced cardiac disease may be more likely to receive a diagnosis.

The estimated MST in the current study was generally longer than those reported in the literature. Two studies evaluating survival in dogs presenting to Italian referral centres reported MST of approximately 20 months for all-cause mortality (Borgarelli et al., 2008, Borgarelli et al., 2012). A cohort of dogs with DMVD enrolled to a research clinic in the UK had a MST of 11.1 months (range 0.1 – 32.7 months) (Moonarmart et al., 2010). Randomised controlled trials evaluating different interventions in dogs with heart failure due to DMVD have reported MST from the time of randomisation until cardiac death or treatment failure. In the BENCH study, MST was 14.5 months in the intervention group and 5.0 months in the placebo group (The Bench Study Group, 1999). MST for dogs recruited to the LIVE and QUEST studies were approximately 5 - 6 months (Ettinger et al., 1998; Haggstrom et al., 2008). The discrepancies between the MST reported in the current study and those published in the literature may be due to differing inclusion criteria and primary end-points. The current study included dogs at all stages of the disease and the primary-end point was death, whereas some previous studies focused only on dogs in congestive heart failure and, for ethical reasons, included treatment failure among their the primary end-points. A delay between disease detection by the primary-care practitioner and subsequent referral for inclusion into survival studies may also account for MST differences. Moreover, referral populations may be prone to preferentially select dogs with more advanced disease (Bartlett et al., 2010) than the entire canine DMVD population. The MSTs reported by the current study may thus be of greater relevance to primary-care practitioners, who manage most DMVD cases.

Cavalier King Charles Spaniels (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred dogs (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs in the multivariable analysis. Interestingly, in the univariable analysis, CKCS had a significantly decreased hazard of death (HR 0.44, 95% CI: 0.21 – 0.96) and purebreds had a similar hazard of death compared with crossbreds. The differences between the results of univariable and multivariable analyses were largely due to the confounding effect of age at diagnosis; CKCS and other purebreds were significantly younger when they developed DMVD compared with crossbred dogs and, after adjusting for age at diagnosis, the trend to reduced hazard in the purebred categories disappeared and these breeds were associated with increased hazard of death.

In the current study, dogs weighing 20 kg or more had nearly three times the hazard of death compared with dogs less than 20 kg (HR 2.81, 95% CI: 1.72 – 4.59). It has been suggested that heavier dogs and larger breed types with primary mitral valve disease may have a different clinical course compared with smaller dogs (Borgarelli et al., 2004). An alternative explanation for the association between survival and bodyweight in the current study population is that heavier dogs were more likely to be misclassified as DMVD cases. It is possible that some of these dogs had heart murmurs due to other causes, such as dilated cardiomyopathy, which is more common in large breeds and carries a poorer prognosis than DMVD (Martin et al., 2009). Finally, population-based studies consistently report that larger dogs have reduced longevity compared with smaller dogs (Michell, 1999; Galis et al., 2007; Greer et al., 2007; O'Neill et al., 2013). As the multivariable analysis in the current study explored only all-cause mortality, the association between bodyweight and hazard of death may reflect reduced longevity in general in larger dogs rather than cardiac deaths specifically.

In agreement with a previous study (Hezzell et al., 2012), there was strong evidence for an association between age and all-cause mortality in dogs with DMVD, with hazard of death increasing 3.85 fold (95% CI: 2.61 – 5.69) for each 5 year increase in age at diagnosis. In addition to being an independent predictor of outcome, age at diagnosis confounded the associations between breed and hazard of death, highlighting the importance of multivariable analyses when interpreting the effect of explanatory variables in epidemiological studies.

Including veterinary practice as a shared frailty term improved model fit, suggesting that practice-level factors influenced the outcome. Treatment may influence survival of dogs with DMVD (The Bench Study Group, 1999; Haggstrom et al., 2008), so if therapeutic management of cases within a practice are more similar than between practices, the survival experience of individuals attending the same practice may be more similar than those of individuals from different practices. Further, most deaths resulted from euthanasia, rather than unassisted death. A poor prognosis given by the attending veterinary practitioner was identified as an important factor influencing the decision to euthanase dogs with congestive heart failure (Mallery et al., 1999). The timing of death may therefore be influenced by human factors and highlights the importance of optimising evidence-based prognostic guidelines.

This study had several limitations. Firstly, individuals with heart murmurs due to other causes could have been misclassified as cases as a definitive diagnosis of DMVD requires echocardiographic confirmation (Borgarelli & Buchanan, 2012). However, the presence of a left apical systolic heart murmur in a dog of typical signalment is highly suggestive of DMVD (Borgarelli & Haggstrom, 2010). Further, the breed, age and sex distributions of possible and diagnosed cases were similar, suggesting that most of the possible cases were as likely to have DMVD as those diagnosed by the attending veterinarian. Secondly, the current study evaluated only factors associated with hazard of death for all-cause mortality. However, within the all-cause mortality group, based on the pre-study power calculations, the number of cases identified substantially exceeded the calculation requirements, suggesting the study had ample power to detect biologically meaningful associations with hazard ratios of 2 or above. A higher powered study evaluating both all-cause and cardiac related mortality could help further elucidate the identified associations. Finally, a convenience sample of corporate and independently owned, exclusively companion animal veterinary clinics was studied. Nonetheless, data from just under 100 practices distributed across England were analysed, so the main conclusions are likely to be relevant for the practice-attending dog population in the UK.

In summary, heart murmurs consistent with DMVD were frequently documented in the EPRs of dogs attending primary-care practices in England. A DMVD diagnosis was reported in about 0.4% of this population. Dogs with DMVD had a MST of 2 – 3 years following detection of the disease, although purebreds, those weighing ≥ 20.0 kg and older dogs may have a less favourable prognosis. Further studies evaluating associations between demographic factors and other clinical and biochemical variables with both cardiac related and all-cause mortality in primary-care practice are warranted.

ACKNOWLEDGEMENTS

The authors are grateful to the Medivet group and other veterinary practices and their clients who participated in this project. We also thank Peter Dron, Noel Kennedy and James Hoontrakul (Royal Veterinary College) for database development and management.

REFERENCES

Bartlett, P.C., Van Buren, J.W., Neterer, M. and Zhou, C., (2010). Disease surveillance and referral bias in the veterinary medical database. Prev. Vet. Med. 94, 264-271

Borgarelli, M. and Buchanan, J.W., (2012). Historical review, epidemiology and natural history of degenerative mitral valve disease. J. Vet. Cardiol. 14, 93-101

Borgarelli, M., Crosara, S., Lamb, K., Savarino, P., La Rosa, G., Tarducci, A. and Haggstrom, J., (2012). Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration. J. Vet. Intern. Med. 26, 69-75

Borgarelli, M. and Haggstrom, J., (2010). Canine degenerative myxomatous mitral valve disease: natural history, clinical presentation and therapy. Vet. Clin. North. Am. Small Anim. Pract. 40, 651-663

Borgarelli, M., Savarino, P., Crosara, S., Santilli, R.A., Chiavegato, D., Poggi, M., Bellino, C., La Rosa, G., Zanatta, R., Haggstrom, J. and Tarducci, A., (2008). Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. J. Vet. Intern. Med. 22, 120-128

Borgarelli, M., Zini, E., D'Agnolo, G., Tarducci, A., Santilli, R.A., Chiavegato, D., Tursi, M., Prunotto, M. and Haggstrom, J., (2004). Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. J. Vet. Cardiol. 6, 27-34

Detweiler, D.K. and Patterson, D.F., (1965). The prevalence and types of cardiovascular disease in dogs. Ann. N. Y. Acad. Sci. 127, 481-516

Dohoo, I.R., Martin, S.W. and Stryhn, H., (2009). Veterinary epidemiologic research. VER, Inc. Charlotte, P.E.I.

Eriksson, A.S., Haggstrom, J., Pedersen, H.D., Hansson, K., Jarvinen, A.K., Haukka, J. and Kvart, C., (2014). Increased NT-proANP predicts risk of congestive heart failure in Cavalier King Charles spaniels with mitral regurgitation caused by myxomatous valve disease. J. Vet. Cardiol. 16, 141-54

Ettinger, S.J., Benitz, A.M., Ericsson, G.F., Cifelli, S., Jernigan, A.D., Longhofer, S.L., Trimboli, W. and Hanson, P.D., (1998). Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group. J. Am. Vet. Med. Assoc. 213, 1573-1577

Fonfara, S., Loureiro, J., Swift, S., James, R., Cripps, P. and Dukes-McEwan, J., (2010). Cardiac troponin I as a marker for severity and prognosis of cardiac disease in dogs. Vet. J. 184, 334-339

Galis, F., Van der Sluijs, I., Van Dooren, T.J., Metz, J.A. and Nussbaumer, M., (2007). Do large dogs die young? J. Exp. Zool. B Mol. Dev. Evol. 308, 119-126

Greer, K.A., Canterberry, S.C. and Murphy, K.E., (2007). Statistical analysis regarding the effects of height and weight on life span of the domestic dog. Res. Vet. Sci. 82, 208-214

Haggstrom, J., Boswood, A., O'Grady, M., Jons, O., Smith, S., Swift, S., Borgarelli, M., Gavaghan, B., Kresken, J.G., Patteson, M., Ablad, B., Bussadori, C.M., Glaus, T., Kovacevic, A., Rapp, M., Santilli, R.A., Tidholm, A., Eriksson, A., Belanger, M.C., Deinert, M., Little, C.J., Kvart, C., French, A., Ronn-Landbo, M., Wess, G., Eggertsdottir, A.V., O'Sullivan, M.L., Schneider, M., Lombard, C.W., Dukes-McEwan, J., Willis, R., Louvet, A. and DiFruscia, R., (2008). Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. J. Vet. Intern. Med. 22, 1124-1135

Hezzell, M.J., Boswood, A., Chang, Y.M., Moonarmart, W., Souttar, K. and Elliott, J., (2012). The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral valve disease. J. Vet. Intern. Med. 26, 302-311

Lord, P.F., Hansson, K., Carnabuci, C., Kvart, C. and Haggstrom, J., (2011). Radiographic heart size and its rate of increase as tests for onset of congestive heart failure in Cavalier King Charles Spaniels with mitral valve regurgitation. J. Vet. Intern. Med. 25, 1312-1319

Mallery, K.F., Freeman, L.M., Harpster, N.K. and Rush, J.E., (1999). Factors contributing to the decision for euthanasia of dogs with congestive heart failure. J. Am. Vet. Med. Assoc. 214, 1201-1204

Marcus, S.M., (1997). Assessing non-consent bias with parallel randomized and nonrandomized clinical trials. J. Clin. Epidemiol. 50, 823-828

Martin, M.W., Stafford Johnson, M.J. and Celona, B., (2009). Canine dilated cardiomyopathy: a retrospective study of signalment, presentation and clinical findings in 369 cases. J. Small Anim. Pract. 50, 23-29

Michell, A.R., (1999). Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease. Vet Rec 145, 625-629

Moonarmart, W., Boswood, A., Luis Fuentes, V., Brodbelt, D., Souttar, K. and Elliott, J., (2010). N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. J. Small Anim. Pract. 51, 84-96

O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C. and Brodbelt, D.C., (2013). Longevity and mortality of owned dogs in England. Vet. J. 198, 638-643

O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C. and Brodbelt, D.C., (2014). Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England. PLoS ONE 9, 1-16

PS Power and Sample Size Calculations, (2014). PS Power and Sample Size Calculations. Available at http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize. Accessed May 20, 2014

Reynolds, C.A., Brown, D.C., Rush, J.E., Fox, P.R., Nguyenba, T.P., Lehmkuhl, L.B., Gordon, S.G., Kellihan, H.B., Stepien, R.L., Lefbom, B.K., Meier, C.K. and Oyama, M.A., (2012). Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: the PREDICT cohort study. J. Vet. Cardiol. 14, 193-202

StataCorp., (2013). Stata: Release 14. Statistical Software. College Station, TX: StataCorp LP

The Bench Study Group, (1999). The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. J. Vet. Cardiol. 1, 7-18

Thrusfield, M.V., Aitken, C.G.G. and Darker, P.G.G., (1985). Observations on breed and sex in relation to canine heart valve incompetence. J. Small Anim. Pract. 26, 709-717

VeNom coding group, (2014). VeNom Veterinary Nomenclature. Available at http://venomcoding.org 2013. Accessed May 20, 2014

VetCompass, (2014). VetCompass: Health surveillance for UK companion animals. Available at: http://www.rvc.ac.uk/VetCompass. RVC ElectronicMedia Unit; 2013. Accessed May 20, 2014

Whitney, J.C., (1974). Observations on the effect of age on the severity of heart valve lesions in the dog. J. Small Anim. Pract. 15, 511-522

DOGSLIFE: A COHORT STUDY OF LABRADOR RETRIEVER HEALTH

C.A. PUGH*, B.M. DE C. BRONSVOORT, I.G. HANDEL, K.M. SUMMERS AND D.N. CLEMENTS

SUMMARY

Studies of animals that visit primary and secondary veterinary centres dominate companion animal epidemiology. Dogslife is a research initiative that collects data directly from owners about the health and lifestyle of Kennel Club (KC) registered, Labrador Retrievers (LR) in the UK. The ultimate aim is to seek associations between canine lifestyle and health. Analyses of a selection of data from Dogslife regarding the height, weight and health of 4,307 LR up to four years of age are reported here. There was considerable variation in height and weight measurements indicative of a highly heterogeneous population. Chocolate coloured dogs were heavier than their yellow and black counterparts. Illness reports were dominated by gastrointestinal and skin-related signs that were not associated with veterinary visits. Illness incidence rates peaked before the dogs reached six months of age. These data provide a unique insight into the young lives of LR in the UK.

INTRODUCTION

In human medicine, it has been well demonstrated that lifestyle has health impacts, such as links between smoking tobacco and lung cancer (Doll & Hill, 1950), or exercise levels and mortality (Irwin et al., 2011). Understanding how people live, and identifying associations between their lifestyle and health can facilitate investigations of disease mechanisms, which in turn may suggest avenues for intervention. Medical professionals are able to give patients evidence-based guidance on how to best maintain their health. By contrast in academic literature regarding canine health, there is a paucity of the most basic lifestyle information; knowledge about what is 'normal' for a dog in the UK is missing. Collecting lifestyle information and linking lifestyle with health is an obvious avenue for future exploration.

The disease burden of dogs visiting veterinarians in the UK is currently being assessed by two large-scale projects, SAVSNET (SAVSNET, 2014a) and VetCompass (VetCompass, 2014). Both have automated the collection of electronic records directly from veterinary practices and SAVSNET also collect diagnostic test results directly from laboratory facilities. These two projects report that they have information on the veterinary care of over 800,000 dogs; comprising 89,000 pets in the SAVSNET database between September 2012 and February 2014 (SAVSNET, 2014b) and over 800,000 dogs in VetCompass' database (VetCompass, 2014). Both of these projects offer great scope to investigate disease in dogs that are taken to a veterinarian. However, they cannot gather information about illnesses that do not precipitate veterinary visitation and do not address the environment dogs are kept in, nor other data of interest such as diet and exercise regimes.

---

[*] The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush, Midlothian, Scotland, EH25 9RG. Email: Carys.Pugh@roslin.ed.ac.uk

There is not just a lack of information regarding how dogs live, but also about the dogs themselves. Morphologically, pedigree dogs are supposed to meet certain breed standards (The Kennel Club, 2014). Standards such as these have been used to show that smaller breeds have greater longevity (Li et al., 1996; Adams et al., 2010) but exhibit more behaviours that might be considered undesirable (McGreevy et al., 2013). However, it is not known how many pedigree dogs actually meet the specified breed standard. If the breed standard is an ideal rather than a reality, then a major input of such analyses would not represent individual subjects, reducing the chances of finding associations.

A more detailed understanding of dog lifestyle and morphology would facilitate future studies. Initial results regarding a cohort of LR will be reported here with the aim of initiating investigations of the impact of lifestyle and morphology on dog health and wellbeing.

MATERIALS AND METHODS

Owners of KC registered LR, born on or after the 1st January 2010 and based in the UK, were eligible for ongoing recruitment into the Dogslife project as described in Clements et al. (2013). Owners were recruited using emails and postcards and registered with Dogslife via the project website (www.dogslife.ac.uk). Registration included giving basic information about the household, and a questionnaire was used to gather information on dog height, weight, exercise levels, diet and health. Participants were prompted to fill in the online questionnaire every month for the first year of their dogs' lives and quarterly thereafter. With the exception of dog weight, all questions required an answer before the owner could continue through the questionnaire. Data collected up to and including 31st December 2013 were used to describe the growth, health and lifestyles of LR up to the age of four years in the UK.

Questionnaire details

Exercise data were collected by asking how much time on average the dog spent on six different types of activity on a weekday and a weekend day. The owner was able to choose from a drop-down list with options 'none'; '1 – 5 minutes'; '5 – 15 minutes'; '15 – 30 minutes'; '30 minutes – 1 hour'; '1 – 2 hours' and 'over 2 hours'. The six different types of exercise were 'fetching, chasing and retrieving'; 'obedience training'; 'lead walking'; 'lead running'; 'off the lead' and 'other'. Owners were also asked whether the exercise levels were restricted for any reason and given the following options to choose from: 'restricted due to your own time constraints'; 'restricted due to your own exercise ability'; 'restricted because of where you live'; 'restricted because your dog has a problem'; 'as recommended by my dog breeder / my own experience'; 'unrestricted (you give as much exercise as you think your dog should have)'.

Owners were asked whether their dog had had any of the following potential problems: 'vomiting'; 'diarrhoea'; 'coughing'; scratching themselves'; 'licking or chewing themselves'; 'limping or lameness' and 'other'. If they answered yes then they would be asked when it happened and whether they took their dog to the vet with the problem. All reports were coded into presenting signs and diagnoses by a single veterinarian (DN Clements) using the VeNom coding system (VeNom Coding Group, 2014).

Measurements taken by owners included the height of their dog to the shoulder until the dog was 18 months of age (demonstrated via an online video). They were also asked to weigh their dog when possible, irrespective of age. Owners were asked to weigh their dogs' meals then report the average daily food intake in addition to meal frequency and type of diet (for example 'dried' or 'home-prepared'). Use of SI units in the UK is inconsistent so owners were given the option to enter a measurement and choose their preferred units from a drop down box (centimeters (cm) or inches for height; kilograms (kg) or pounds for dog weight and grams (g) or ounces (oz) for food weight). Entries made in inches were automatically multiplied by 2.54 and stored in cm. Entries made in pounds were divided by 2.20 and stored in kg. Entries made in ounces were multiplied by 28.3 and stored in g.

Statistical analyses

Data were extracted from the Dogslife database using the *RMySQL* package (James & DebRoy, 2012) and analyses were performed using R 3.0.2 (R Core Team, 2013).

Dog heights: Early explorations were undertaken of the raw, database-recorded heights of the cohort as they aged (Fig. 1). There were two distinct growth curves and it was hypothesised that the lower curve, which was approximately 2.5 times shorter than the main curve, was generated by owners who had taken measurements in inches but reported them as cm. It was also thought possible that some of the very high heights were measured in cm and reported in inches.

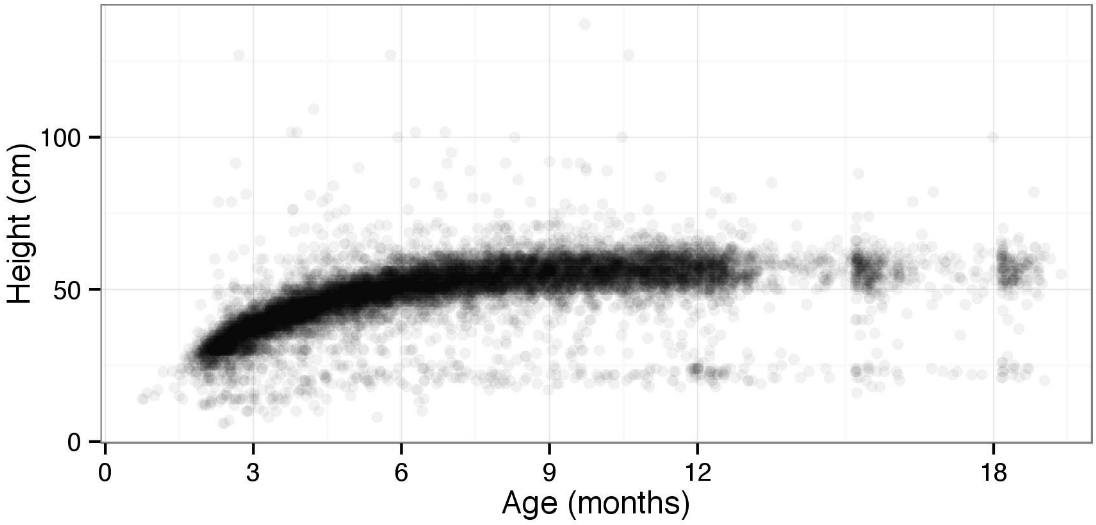


Fig. 1 Heights as the dogs aged (data uncleaned)

A probabilistic model was used to estimate whether entries might have been made in the correct or incorrect units. Equations (1-3) describe the heights which were assumed to be normally distributed with a mean height that changed exponentially with age. Each height would also fit one of three classes: measured in cm and reported in inches; measured and reported in the same units; measured in inches and reported in cm.

$$\mathrm{HEIGHT} = \mathcal{N}(\mathrm{M}, \mathrm{T}) \tag{1}$$

$$\mathrm{M_I} = \mathrm{A}\left\{1 - \mathrm{E}^{(-\mathrm{B}(\mathrm{AGE_I} - \mathrm{C}))}\right\} * \mathrm{CLASS_I} \tag{2}$$

$$\text{CLASS} = \begin{pmatrix} \frac{1}{2.54} \\ 1 \\ 2.54 \end{pmatrix} \tag{3}$$

The model required Bayesian priors, shown in Eqs. (4-9). Variable a is the mean full height of the dogs and was taken from the UK KC breed standard for LR which was 55-56 cm for females and 56-57 cm for males (The Kennel Club, 2014). Variable b is a proxy for growth rate. The height was growing half way closer to its maximum height, a, every $^{ln2}/_{b}$ days. Variable c is an offset term that allowed the height to have a non-zero value when the pups were born. Variable pi is the prior probability of a measurement belonging to each different error class: i.e. estimated 10% chance of being subject to each type of inches-cm error and 80% chance of having the correct units. Once identified, the mis-reported heights were corrected using a multiplier of 2.54 or $^{1}/_{2.54}$.

$$a = \mathcal{N}(56, 0.01) \tag{4}$$

$$b = Uniform(0, 1.5) \tag{5}$$

$$c = Uniform(0, 100) \tag{6}$$

$$\tau = Gamma(0.001, 0.001) \tag{7}$$

$$sd = \sqrt{\frac{1}{\tau}} \tag{8}$$

$$pi = Dirichlet(0.1, 0.8, 0.1) \tag{9}$$

The model was estimated under a Bayesian framework using the *rjags* package (Plummer & Stukalov, 2014). Each sex was modeled separately. One thousand iterations were used for adaptation and 2,000 were discarded as ‘burn-in’. The final model was based on a further 5,000 iterations and the mixing of the models was checked to ensure that sufficient iterations had been performed using the *coda* package (Plummer et al., 2006).

Dog weights: Weights of dogs over one year were modelled using a linear mixed model, utilising the *nlme* package in R (Pinheiro et al., 2013). The reported model had the lowest Akaike Information Criterion (AIC) of all possible models, found using the *MuMIN* package (Bartoń, 2014). Identifiers for both owners and pets were included as random terms and an auto-correlation structure was used to account for the repeated measurements.

Illnesses: Illness reports were described and incidence rates were investigated using the *survival* package in R (Therneau, 2014). Owners might report co-occurring signs, such as vomiting and diarrhoea. If they started within three days of each other, they were considered to be part of the same event. Early validation work with the veterinary records of a subset of dogs indicated that owner reports of illness signs were accurate but that there was recall decay resulting in under-reporting (data not shown). Reports of potential illnesses were therefore only included in rate estimates if they fell within a period of 40 days prior to each questionnaire answer. Dog ages (in months) came from the dog age in days when the illness started, divided by 365.25 then multiplied by 12. The age categories were right-continuous.

RESULTS

The registered cohort comprised 4,148 owners and 4,307 dogs but owners of 1,058 dogs did not fully complete the questionnaire. Over 96% of owners registered just one dog; 127 owners had two dogs and a further 12 owners had registered three or more. Owners reported that the majority of their households comprised either families (1862; 45%) or more than one adult (1673; 40%) but there were also retired households (273; 6.6%), single adults (218; 5.3%) and some owners did not describe their household (122; 2.9%). Information regarding other pets in households indicated that 1,284 households had at least one other dog, 922 had at least one cat and 641 had other pets. Household location details were captured as postcodes and compared to the postcode locations of owners of dogs eligible to join during the study period. As reported in Clements et al. (2013), the first year's recruitment were geographically distributed in proportion to all eligible dogs.

The 4,307 Dogslife dogs comprised 2,041 females and 2,266 males and the median age of recruitment was 92 days. Their main purposes were reported to be pets (2941; 68%), working dogs (253, 5.9%), assistance dogs (33, 0.77%), multi-purpose (20, 0.46%), show dogs (10, 0.23%), breeding dogs (2, 0.046%), other (24, 0.56%) and not reported (1,024, 24%). On 31st December 2013, 26.9% (95% CI: 25.6 – 28.3%) of dog histories were up to date and completed questionnaires were available for 3,249 of 4,307 dogs, relating to a total of 3,098 dog years at risk.

Dog heights

Extreme heights such as zero or one were excluded before modelling which resulted in the complete removal of some dogs. The model results, based on 3,180 of 3,249 dogs and 12,479 heights, are shown in Table 1.

Table 1. Height model parameters

Constant	Female (95% CI)	Male (95% CI)
A	55.1 (54.9 – 55.4) cm	59.0 (58.7 – 59.2) cm
B	0.0132 (0.0128 – 0.0137)	0.0126 (0.0122 – 0.0131)
C	7.03 (4.43 – 9.63) days	9.37 (6.77 – 11.9) days
τ	4.67 (4.59 – 4.76) cm	5.01 (4.92 – 5.10) cm

It was estimated that 470 heights had been reported in the wrong units. The maximum height for each sex (constant a) would theoretically only be reached at an infinite age but the mean heights at 18 months were similar at 55.1 cm for females and 58.9 cm for males. The mean male height was 2-3 cm higher than the UK breed standard (The Kennel Club, 2014) and there was wide variation in heights to the shoulder ($\tau = 4.67$ and 5.01 cm for females and males respectively). Of all measurements of males over one year, only 12.9% (95% CI: 10.5 – 15.7%) met the breed standard. Even for females, whose average height fitted the UK standard, only 20.5% (95% CI: 17.6 – 23.6%) of measurements met the standard.

Dog weights

The dog weight model was based on 1,049 dogs, 1,016 owners and 4,260 weights. The fixed effects parameters are shown in Table 2. The random effect of ownership had an intercept standard deviation of 3.01 and the dog effect nested within the owner effect had an intercept standard deviation of 1.50. The correlation structure was autoregressive of order 1, with φ = 0.686, indicating a high degree of autocorrelation.

Table 2. Fixed parameters of weight model for dogs over one year of age

		Value	95% Confidence interval		*p*-value
			lower	upper	
	Intercept	18.4	16.8	19.9	5.10e-113
	Dog age (years)	0.890	0.762	1.02	3.23e-41
	Height^2 (cm)	2.24e-03	1.76e-03	2.72e-03	1.39e-09
Neuter status	Entire	0			
	Neutered	-0.120	-0.366	0.126	0.339
Coat colour	Black	0			
	Chocolate	1.39	0.775	2.00	1.50e-04
	Fox red	-0.843	-2.46	0.773	0.316
	Yellow	0.189	-0.347	0.725	0.495
Dog sex	Female	0			
	Male	3.65	3.15	4.16	1.02e-13
Dog purpose	Pet	0			
	Working dog	-2.13	-3.01	-1.25	6.98e-05
	Other[a]	2.49	0.745	4.24	9.60e-03
Owner smoking	Non-smoker	0			
	Smoker	1.09	0.412	1.77	1.72e-03
Status	Not reported	-1.40	-3.49	0.688	0.189
Other pets	Dog	-0.477	-0.986	0.0306	0.0658
Daily time spent	Fetching, chasing and retrieving (hours)	-0.218	-0.354	-0.0822	1.66e-03
	Other (hours)	-0.0864	-0.181	8.16e-03	0.0735
Exercise restrictions	None	0			
	Owner location	0.947	0.326	1.57	2.82e-03
	Owner ability	0.250	-0.133	0.632	0.201
	Dog problem	-0.0228	-0.341	0.296	0.888
	As recommended	0.0365	-0.179	0.252	0.740
	Owner time	-0.194	-0.411	0.0238	0.0811
Daily quantity	Food (g)	5.73e-04	9.89e-05	1.05e-03	0.0179

[a] Other dog purpose included show, breeding, multi-purpose and all ‘other’ dogs. Assistance dogs were excluded because they typically left the project at one year.

Surprisingly chocolate LR were, on average, 1.39 kg heavier than their yellow and black counterparts and neutering apparently had minimal effect. A closer look at the weights associated with neutered and entire dogs indicated that only after the dogs reached three years of age did the weights of neutered dogs become greater than that of entire dogs but that there were not enough dogs of this age to affect the model parameters.

Illness reports

Over 7,000 signs of potential illness were reported. Once co-occurring signs were grouped, there were 6,115 events comprised of one or more signs of potential illness, affecting 2,099 dogs. Just 47.8% (95% CI: 46.1 – 48.6%) of events were associated with a veterinary visit. The twenty most frequently reported event types included 90% of all reports. They are shown grouped in Table 3 with the proportion of events in that field that precipitated a veterinary visit.

Table 3. Twenty most frequently reported illness events grouped by system or event type

	Frequency	Proportion involving veterinary visit	95% Binomial confidence interval
Gastrointestinal [a]	2672	0.273	0.256 – 0.290
Skin-related [b]	1079	0.408	0.378 – 0.438
Musculoskeletal [c]	813	0.659	0.626 – 0.692
Respiratory [d]	307	0.713	0.659 – 0.763
Eye-related [e]	201	0.831	0.772 – 0.880
Ear-related [f]	156	0.814	0.744 – 0.872
Wound/trauma [g]	102	0.765	0.670 – 0.843
Other [h]	172	0.703	0.629 – 0.771

[a] ‘diarrhoea’, ‘vomiting’, ‘diarrhoea and vomiting’;

[b] ‘mass/swelling – skin (cutaneous)’, ‘pruritus’, ‘skin (cutaneous) abnormality – eruptions/hives/rash’, ‘skin (cutaneous) abnormality – other’;

[c] ‘gait abnormality – lameness’, ‘musculoskeletal injury’;

[d] ‘coughing’, ‘coughing and vomiting’;

[e] ‘ophthalmic (eye) abnormality’, ‘discharge – ocular (eye)’;

[f] ‘ear (aural) abnormality’;

[g] ‘wound’, ‘traumatic episode’;

[h] ‘anal irritation’, ‘mass/swelling – other’, ‘urination abnormal – other’, ‘presenting complaint not listed’

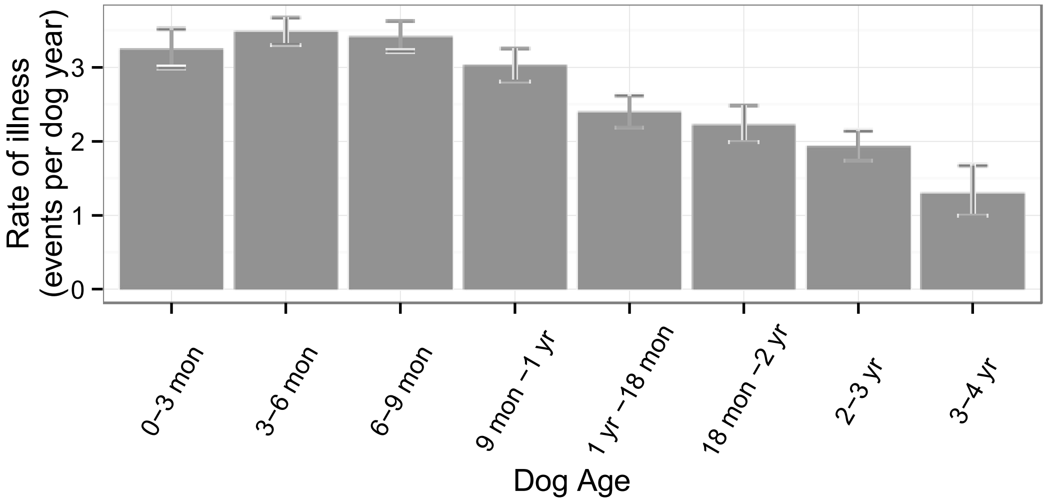


Fig. 2 Illness incidence rates split by dog age. A dog of precisely three months of age would be included in the 3-6 months category

Considering only illness events that occurred in a window of 40 days prior to each completed questionnaire reduced the number of events from 6,115 to 5,081 and the time at risk to 1,733 dog years. Incidence rates with 95% confidence intervals are shown in Fig. 2. The rates of reported illnesses steadily declined after six months. Figure 3 shows how these incidence rates split between the different types of event. It is apparent that musculoskeletal reports did not peak until 6-9 months and the wound/trauma category peaked even later at between 9 months and one year.

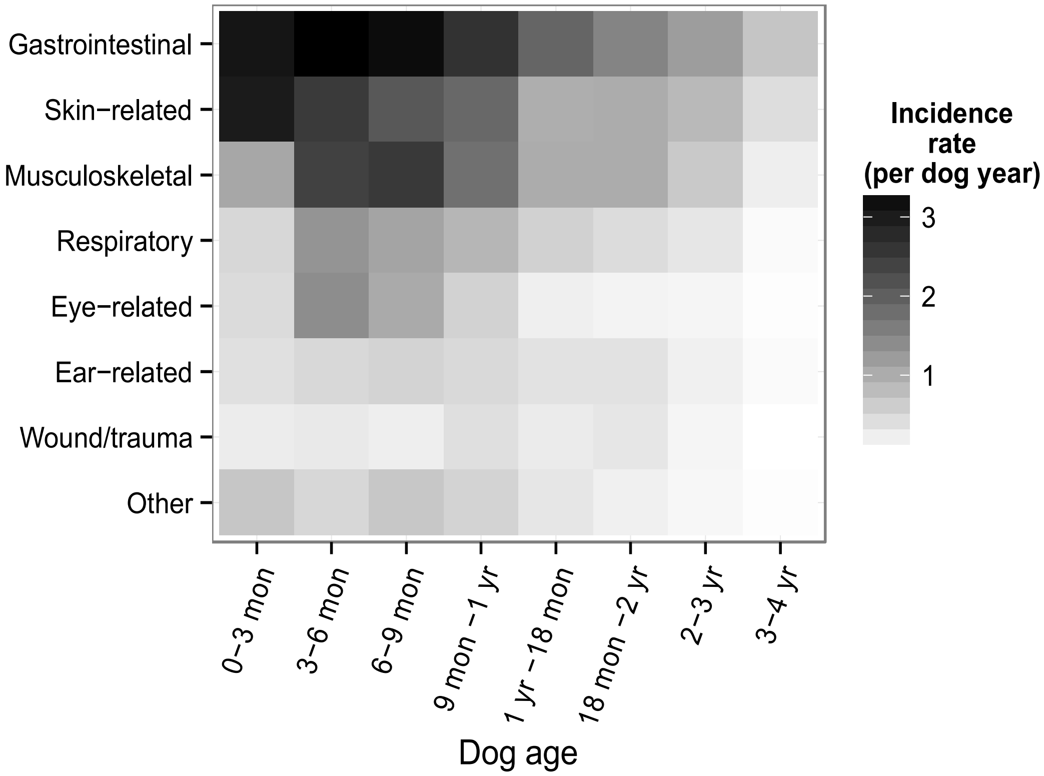


Fig. 3 Illness incidence rates for different illness types. A dog of precisely three months of age would be included in the 3-6 months category

DISCUSSION

Engaging thousands of dog owners in Dogslife has yielded a wealth of data regarding LR in the UK and has highlighted the diversity of LR morphology. In 2008, Sutter et al. collected measurements for 1,155 dogs including 14 LR and assessed the percentage of those measured that met the American KC (AKC) breed standards (American Kennel Club, 2014). It was concluded that the AKC breed standards were a good proxy for height at the shoulder. There is greater allowance for variation in the AKC standard for LR (5.08 cm for each sex in the USA compared to 1 cm for each sex in the UK) but there was also potential for bias in their study. The majority of their sample comprised dogs that had been entered in conformational competitions whereas few of the Dogslife cohort were show dogs. The issue of incorrect measurement or reporting must be considered with all Dogslife data (the height unit error being an obvious example) but visits to a sample of the cohort found no systematic bias to owner height measurements (data not shown). Therefore whilst individual measurements might be treated with caution, the model parameters should be a good guide to the heights of the population.

Breed standard heights have been used as group phenotypes in studies as proxies for dog size. It is undoubtedly convenient and minimises the time and expense of data collection from individual dogs. However, the Dogslife results suggest two things: firstly that the breed standard is not necessarily the average height for a breed and secondly, if it does represent the average, the variability of morphologies might mean that this average poorly reflects many individuals. Under these circumstances, using the breed standard may not be appropriate and might limit the ability of investigators to find true effects. Studies, such as that by Frischknecht et al., (2013), that use individual dog measurements to characterise a phenotype, should have more scope to identify complex patterns. In this instance, it was possible to find potentially causative mutations associated with dwarfism in LR.

Nearly 30 years ago, LR were identified as the most likely breed to be overweight in the UK vet visiting dog population (Edney & Smith, 1986). The mean weight of a two year old Dogslife LR was 26.8 kg for females and 31.6 kg for males but there was considerable variation between individuals. Both averages fit within the suggested weight range for adults of the breed of 25-34 kg (Alderton & Morgan, 1993). Of concern however is the fact that the average weight of the cohort continued to increase with age. If this observed increase continues, an expanding proportion of the cohort will become subject to the health consequences of obesity. For example, it has been demonstrated in Elkhounds that there is an association between dogs that were overweight throughout their lives and diabetes mellitus (Wejdmark et al., 2011) and in LR, an association between higher body weight and increased prevalence and severity of hip dysplasia (Smith et al., 2006).

In the wealth of data collected regarding signs of illness, the bulk of signs were either gastrointestinal or skin-related. The illnesses were presumably self-limiting in the majority of these cases and owners did not take their dog to see a vet. In contrast to a recent study of 3,884 UK vet-visiting dogs that found otitis externa to be the most prevalent condition (O'Neill et al., 2014), ear-related complaints were only the sixth most numerous of the twenty event types most frequently reported to Dogslife. This might simply be due to breed susceptibility or the younger age of the Dogslife cohort, which was under four years, compared to a median age of 4.8 years for a variety of breeds in the O'Neill et al. study. However, it also seems likely that there is a difference between illnesses that do, and do not, precipitate vet visits; presumably influenced by perceived severity in the eyes of the pet owner. As a general trend, the illness rates decreased as the dogs aged which reflects similar findings from insured, vet-visiting dogs in Sweden (Egenvall et al., 2000).

In conclusion, the Dogslife study has revealed important information relating to LR in the UK. The cohort have diverse morphologies and were subject to ongoing weight gain up to four years of age. There was also a high level of illness in young dogs not reported to veterinarians. These findings set a baseline for further analysis of the relationship between dog morphology, lifestyle and health.

ACKNOWLEDGEMENTS

The Dogslife team are grateful to the many Dogslife owners. Dogslife was set up with funding from the Kennel Club Charitable Trust and has ongoing financial support from the Roslin Foundation. The first author is funded by the BBSRC.

REFERENCES

Adams, V.J., Evans, K.M., Sampson, J., and Wood, J.L.N. (2010). Methods and mortality results of a health survey of purebred dogs in the UK. J. Small Anim. Pract. 51, 512–524

Alderton, D., and Morgan, T. (1993). Dogs (London: Dorling Kindersley)

American Kennel Club (2014). [https://www.akc.org/breeds/labrador_retriever/breed_-standard.cfm]

Bartoń, K. (2014). MuMIn: Multi-model inference version 1.10.5. http://cran.r-project.org/package=MuMIn

Clements, D.N., Handel, I.G., Rose, E., Querry, D., Pugh, C.A., Ollier, W.E., Morgan, K.L., Kennedy, L.J., Sampson, J., Summers, K.M., et al. (2013). Dogslife: a web-based longitudinal study of Labrador Retriever health in the UK. BMC Vet. Res. 9, 13

Doll, R., and Hill, A. (1950). Smoking and carcinoma of the lung. Br. Med. J. 2, 739–748

Edney, A.T., and Smith, P.M. (1986). Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet. Rec. 118, 391–396

Egenvall, A., Bonnett, B., Olson, P., and Hedhammar, A. (2000). Gender, age and breed pattern of diagnoses for veterinary care in insured dogs in Sweden during 1996. Vet. Rec. 146, 551–557

Frischknecht, M., Niehof-Oellers, H., Jagannathan, V., Owczarek-Lipska, M., Drögemüller, C., Dietschi, E., Dolf, G., Tellhelm, B., Lang, J., Tiira, K., et al. (2013). A COL11A2 mutation in Labrador retrievers with mild disproportionate dwarfism. PLoS One 8, e60149

Greer, K.A., Canterberry, S.C., and Murphy, K.E. (2007). Statistical analysis regarding the effects of height and weight on life span of the domestic dog. Res. Vet. Sci. 82, 208–214

Irwin, M.L., McTiernan, A., Manson, J.E., Thomson, C.A., Sternfeld, B., Stefanick, M.L., Wactawski-Wende, J., Craft, L., Lane, D., Martin, L.W., et al. (2011). Physical activity and survival in postmenopausal women with breast cancer: results from the women’s health initiative. Cancer Prev. Res. 4, 522–529

James, D., and DebRoy, S. (2012). RMySQL: R interface to the MySQL database. R package version 0.9–3. http://cran.r-project.org/package= RMySQL

Li, Y., Deeb, B., Pendergrass, W., and Wolf, N. (1996). Cellular proliferative capacity and life span in small and large dogs. J. Gerontol. A. Biol. Sci. Med. Sci. 51, B403–B408

McGreevy, P.D., Georgevsky, D., Carrasco, J., Valenzuela, M., Duffy, D.L., and Serpell, J.A. (2013). Dog behavior co-varies with height, bodyweight and skull shape. PLoS One 8, e80529

O’Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C., and Brodbelt, D.C. (2014). Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England. PLoS One 9, e90501

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., and Team, R.D.C. (2013). nlme: Linear and Nonlinear Mixed Effects Models version 3.1-111. http://cran.r-project.org/package=nlme

Plummer, M., and Stukalov, A. (2014). rjags: Bayesian graphical models using MCMC version 3-13. http://mcmc-jags.sourceforge.net

Plummer, M., Best, N., Cowles, K., and Vines, K. (2006). CODA: Convergence Diagnosis and Output Analysis for MCMC. R News 6, 7–11

R Core Team (2013). R: A language and environment for statistical computing version 3.0.2. http://www.r-project.org/

SAVSNET (2014a). [http://www.savsnet.co.uk/]

SAVSNET (2014b). [http://www.savsnet.co.uk/savsnet-reports/]

Smith, G.K., Paster, E.R., Powers, M.Y., Lawler, D.F., Biery, D.N., Shofer, F.S., McKelvie, P.J., and Kealy, R.D. (2006). Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. J. Am. Vet. Med. Assoc. 229, 690–693

Sutter, N.B., Mosher, D.S., Gray, M.M., and Ostrander, E.A. (2008). Morphometrics within dog breeds are highly reproducible and dispute Rensch's rule. Mamm. Genome 19, 713–723

The Kennel Club (2014). [http://www.thekennelclub.org.uk/services/public/breed/standard.aspx?id=2048]

Therneau, T.M. (2014). A Package for Survival Analysis in S version 2.37-7. http://cran.r-project.org/package=survival

VeNom Coding Group (2014). [http://www.venomcoding.org/VeNom/Terms_of_use.html]

VetCompass (2014). [http://www.rvc.ac.uk/VetCompass/Index.cfm]

Wejdmark, A.-K., Bonnett, B., Hedhammar, A., and Fall, T. (2011). Lifestyle risk factors for progesterone-related diabetes mellitus in elkhounds - a case-control study. J. Small Anim. Pract. 52, 240–245

PIG HEALTH AND PRODUCTION

DISEASE PRIORITISATION USING POINT OF TRUTH CALIBRATION

V.J. BROOKES[*], M. HERNÁNDEZ-JOVER, S.C. BARRY AND M.P. WARD

SUMMARY

A regression-based method, Point of Truth Calibration (POTCal), was used to prioritise exotic diseases for the Australian pig industry. Advantages of this method include allowing flexibility in model selection (an extension of previous disease prioritisation methods), as well as enabling validation of results. Vesicular diseases were the highest priority diseases, followed by swine fevers and zoonotic encephalitides. Results were most sensitive to the criterion "attack rate in pigs" in the ranges used to fit the model. Model selection using the POTCal method provided insight into decision-makers' heuristics.

INTRODUCTION

Disease prioritisation is a decision-making process used to identify those diseases for which allocation of resources would achieve the most benefit to human or animal health. There are a variety of methods that can be used for disease prioritisation; generally objective measures of disease impact are integrated with subjective values that describe the importance of these impacts to decision-makers to score or rank diseases. This information is used as a decision-aid to achieve consensus about resource allocation.

The method used for disease prioritisation should be transparent and reproducible (and so, defensible), and the results should accurately reflect the priorities of the decision-makers. Previous studies have used a range of methods including rapid risk analysis (McKenzie et al., 2007), qualitative decision trees (Palmer et al., 2005), qualitative consensus techniques (Weinberg et al., 1999) and semi-quantitative scoring techniques (Carter & National Advisory Committee on Epidemiology Subcommittee, 1991; Rushdy & O'Mahony, 1998; Weinberg et al., 1999; Doherty, 2000; Valenciano & Working Grp., 2001; Krause & Prioritization Working Grp, 2008; Balabanova et al., 2011). However, driven by the requirement to produce valid, defensible results, disease prioritisation has gradually conformed to methods from the discipline of decision science. These methods include multi-criteria decision analysis (MCDA) using traditional methods or probabilistic inversion, and conjoint analysis (Havelaar et al., 2010; Ng & Sargeant, 2012; Del Rio Vilas et al., 2013; Ng & Sargeant, 2013; Brookes et al., 2014b; Kadohira et al., 2014). To derive a model to predict decision-makers' disease priority, a series of standard steps is followed (von Winterfeldt, 1980; Keeney, 1982). Although the process is transparent, it does not always accurately reflect decision-makers' priorities (Havelaar et al., 2010; Teck et al., 2010; Flari et al., 2011; Neslo & Cooke, 2011; Humblet et al., 2012; Brookes et al., 2014c). There is a need to understand the reasons for this suboptimal validity to improve the accuracy of disease prioritisation, to ensure that resource allocation reflects decision-makers priorities (Neslo & Cooke, 2011).

---

[*] Victoria Brookes, Faculty of Veterinary Science, The University of Sydney, Private Bag 4003, Camden, NSW, Australia. Email: viki.brookes@bigpond.com

Currently, methods for decision analysis are selected on an empirical basis, often dependent on the decision analyst's familiarity with techniques, the time available and the perceived complexity of the decision problem (Guitouni & Martel, 1998). In the context of disease prioritisation, the weighted sum model is commonly used as the underlying model structure (Havelaar et al., 2010; Humblet et al., 2012; Ng & Sargeant, 2012; Del Rio Vilas et al., 2013; Ng & Sargeant, 2013; Brookes et al., 2014b). It is straightforward to implement and transparent due to its simplicity (Dodgson et al., 2009). However, the weighted sum model might not always reflect decision-makers heuristics, contributing to the limited validation of prioritisation results in previous studies (Brookes et al., 2014c). Development of methods or guidelines is required to select models that accurately describe decision-makers' heuristics, improve understanding of the most appropriate models for disease prioritisation, and improve validity of results.

Point of truth calibration (POTCal), has been advocated as a method to calibrate criterion weights using expert judgement on constructed risk scenarios (Barry & Xunguo, 2010). POTCal has not previously been used for disease prioritisation, but can be extended for use in this context by describing decision-makers' estimate of overall disease importance as a function of the criteria, to produce a predictive model for disease prioritisation. Analysis uses standard statistical techniques based on regression, and validation can be used to assess the accuracy of model predictions. Implementation of expert elicitation for POTCal is similar to that used for probabilistic inversion and conjoint analysis. However, for analysis of preferences and disease priority prediction, the underlying form of the model is not assumed.

The aim of the current study was to prioritise exotic diseases for the pig industry in Australia to direct future research into biosecurity requirements for this industry. POTCal was used to select the most appropriate model to describe decision-makers' priorities regarding exotic disease impacts. The use of POTCal was evaluated in the context of exotic disease prioritisation in this study.

MATERIALS AND METHODS

The procedures used in this study were approved by the Human Research Ethics Committee of The University of Sydney (protocol number 12–2011/14384).

Study structure

The study was structured according to recommendations by Keeney (1982), and followed steps for MCDA in disease prioritisation (Fig. 1). The decision-makers in this study were pig producers in Australia. Exotic pathogens and disease syndromes, criteria that describe disease impact and objective disease measurements for each criterion were identified for a concurrent study, as described by Brookes et al. (2014b).

Evaluation of stakeholder preferences

A survey was designed and distributed (SurveyMonkey.com) to 430 pig producers who had registered an email address with Australian Pork Limited (www.australianpork.com.au, accessed 04/12/14). Responses were collected between 8 December 2011 and 22 March 2012. The first part of the survey collected information about participants' demographics and pig production systems. In the second part of the survey participants were asked to score constructed disease scenarios.

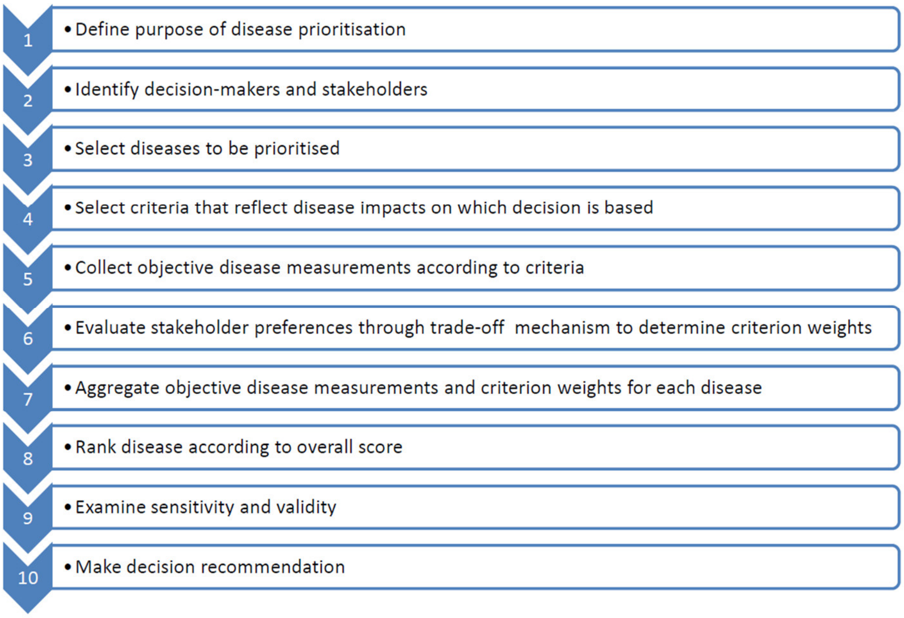


Fig. 1 Flowchart of steps for disease prioritisation using multi-criteria decision analysis (Brookes et al., 2014a)

This survey was also used for preference elicitation using probabilistic inversion in a concurrent study, and details of scenario construction are presented in Brookes et al. (2014c). Briefly, the constructed disease scenarios comprised nine quantifiable disease criteria that reflected disease impacts across the pig industry, ruminant industry and human health (Table 1). Sixteen test scenarios were constructed to ensure trade-offs between impact areas. An additional fifth group of scenarios constructed using criterion measurements based on real diseases. These scenarios were used to validate expert opinion derived from responses to groups 1–4.

Table 1. Criteria (by area of concern) used to describe disease importance in a survey to elicit expert opinion for disease prioritisation from pig producers in Australia

Area of concern	Criteria	Range
Pig Industry	Government contribution to industry to compensate for losses	0-100%
	Attack rate in pigs	0-100%
	Length of clinical disease in pigs	0-42days
	Case fatality rate in pigs	0–100%
	Pork market loss	0-100%
Ruminant Industry	Ruminant market loss	0-100%
Human Health	Incidence in humans	0-100%
	Disability weight in humans	0-1
	Case fatality rate in humans	0-100%

To collect preference data for analysis using POTCal, participants were asked to score each scenario on a scale from 0–100 ("I'm not bothered about this disease in any way at all" – "this disease is the worst possible scenario that I can imagine"). The scenarios were presented in both a table and a newspaper-style story format to encourage participation in the survey. A copy of the survey is available on request from the corresponding author.

Data analysis

Demographic and production system data were initially described, and compared with available industry data.

In accordance with the POTCal method, participants' estimates of disease importance ($\hat{I}$) were modelled as a function of the criteria (X). The authors' starting hypothesis was that all criteria (X) were necessary to describe the response variable $\hat{I}$. A generalised additive mixed model (gamm function in the mcgv package (Wood, 2006), R version 3.0.0 (R Core Team, 2013)) was used to define this relationship; Eq. (1). The estimated score for the ith scenario ($\hat{I}_i$) is modelled as a quasi-binomial distribution with a logit link function, $X_i\beta$ represents fixed effects of the set of covariates (criteria), f_n are random effect smooth functions of each or two-way combinations of covariates, the distribution of survey participant effects is included as a random effect, Z_ib, and ϵ represents the error term associated with the model.

$$log\frac{\hat{I}}{1-\hat{I}_i} = X_i\beta + f_1(x_{1i}) + f_2(x_{2i}, x_{3i}) + \cdots + Z_ib + \epsilon_i \qquad (1)$$

This model allowed maximum flexibility in describing producers' priorities, and provided a starting point from which a potentially simpler model could be selected based on minimising AIC (Akaike information criterion (Burnham et al., 2011)). Using partial regression plots as a guide to the linearity of the relationship between the response variable and the covariates, smooth functions were removed from the full model then successive models to simplify the model (as far as AIC could be minimised). Interactions between covariates were introduced based on the authors' industry and disease process knowledge, and retained or rejected from the model, again based on minimising AIC. Model fit was assessed by examining the distribution of residuals using a normal quantile-quantile (Q-Q) plot, and the relationship between scaled and raw residuals against fitted outcome values. Model validation was assessed externally to the data used to fit the model by comparing model predictions to actual scores of validation scenarios. Variation between predicted and actual scores was assessed visually by overlaying the predicted and actual mean scores for each scenario, and using the Bland-Altman method of agreement to assess agreement between predicted and actual scores of validation scenarios (Bland & Altman, 2010).

It was also investigated whether separating participant groups according to their primary concerns (the impacts of disease on human health versus livestock) would lead to differences in model definition and whether validation would be improved. After definition of a model that best described preferences for the whole group, subsets of participants were selected by dividing participants based on their responses for different scenarios (some scenarios had mainly impacts on human health, whilst others had mainly impacts on livestock health). The POTCal method was used to define models for these subsets, and validation was performed as described above.

Disease prioritisation

The final model for disease prioritisation was selected based on validation, and used to predict scores for diseases that are exotic to the pig industry in Australia to produce a list of exotic diseases prioritised by mean score – a higher score indicating greater disease importance.

Sensitivity of disease score to criterion measurements was assessed by using the final model to predict the score for scenarios in which each criterion in turn was included with the highest value used to fit the model, whilst all other criterion measurements were set to zero.

RESULTS

Eighty-one producers (19%) responded to the survey, and 51 scored at least one test or validation scenario. Of these participants, 80% were male and 66% were between 40 and 59 years old (range 21 years – > 60 years). Participants had a mean of 15.3 years of experience working in the pig industry. Most participants operated in Victoria and supplied the domestic market. There was no significant difference (Fisher's exact test (two-sided), P = 0.278) between the producer distribution by state and production unit by state recorded in the Australian Pig Annual 2011–12 (Australian Pork Limited, 2012). Nearly all participants worked on farrow to finish units, using conventional or a combination of conventional and deep litter housing. Industry statistics were not available for comparison.

Table 2 summarises the scores for each scenario by all participants. Test scenarios F and H, and validation scenarios R and S had the widest interquartile ranges, with correspondingly large standard errors of their mean. Scenarios F, H and R were all zoonotic disease scenarios, and scenario S had livestock impacts only. Examination of the data demonstrated that participants who scored F highly, generally scored H highly, with lower scores for scenarios E and G (disease with livestock impacts only). This pattern was reversed for those who gave F and H low scores. Participants who scored R highly subsequently gave scenario S a lower score, and vice versa. This indicated that there were at least two groups of participants with preferences divided between the importance of diseases with zoonotic impacts or livestock impacts.

Model selection for all participants

Plots of partial regression functions from the initial model which included all criteria and used responses from all participants, showed that non-linear covariates were "market loss in pigs", "market loss in ruminants" and "case fatality rate in humans". The level of government compensation had no effect on the estimate of importance ($\hat{I}$) and longer clinical disease in pigs reduced $\hat{I}$. The other covariates all had increasing linear relationships with $\hat{I}$. The most parsimonious model with lowest AIC was achieved by removing the covariates "length of clinical disease in pigs" and "government compensation", removing smooth functions (including "market loss in pigs" and "market loss in ruminants"), and putting an interaction term between case fatality rate and disability weight in humans. The final model (model 1) is described in Table 3.

Model fit and validation: The Q-Q plot indicated that the residuals were approximately normally distributed. Scaled (Pearson) residuals against fitted values were approximately evenly distributed around the mean, except at extremes of fitted values. This was consistent with the pattern demonstrated by the plot of raw residuals against fitted values, which were generally within two standard deviations of the residual mean except at extreme values of fitted values. Although these plots indicated reasonable model fit, it is likely that the model is less predictive at outcome values approaching either 0 or 100. External validation of this model demonstrated that predicted scores were visually close to actual scores for scenarios used to fit the model (scenarios A–P), as well as group 5 validation scenarios Q–T (Fig. 2). Mean predicted and actual scores for validation scenarios differed by a mean of 1.01, with standard deviation 1.22 (Table 3).

Table 2. Summary of all participants' (n = 51) scores for constructed test (A–P) and validation (Q–T) scenarios used in a survey to elicit expert opinion for disease prioritisation from pig producers in Australia

Scenario	Number of Participants	Interquartile range	Median	Mean	SE mean
A	51	14	90	84.25	2.62
B	51	25	70	69.53	2.98
C	51	30	70	63.37	3.54
D	51	30	40	39.33	3.32
E	45	20	95	87.18	2.75
F	45	45	50	53.2	4.1
G	45	35	55	56.4	3.76
H	45	40	75	66.29	4.29
I	39	25.5	65	60.92	3.48
J	40	20	42.5	44.12	3.47
K	40	24.25	80	79.12	3.22
L	40	30	80	74.47	4.05
M	40	31.25	50	55.9	3.69
N	40	30	75	67.65	3.56
O	40	34.25	90	81.67	3.47
P	40	25	70	68.8	3.51
Q	40	20	90	86.62	2.7
R	40	38	82.5	73.95	4.23
S	40	40	70	66.92	3.82
T	40	35	82.5	77.9	3.28

Model selection for subsets of participants

Subsets of participants were selected by differentiating groups of participants with diverse preferences based on their scores for scenarios F and H, with the aim of comparing model definition and improving model fit and external validation. Participants were divided by the median score for these scenarios. Final models using responses from participants who scored ≤ median score (indicating their lesser concern for human than livestock impacts of disease) for each of these scenarios were simpler, generally including only attack rate in pigs, market loss in pigs and either incidence or disability weight in humans (Table 3). External validation was poorer for all subsets of participants, both visually (Fig. 3) and on calculation of agreement (Table 3).

Table 3. Final model definition for all and subsets of participants in a survey to elicit expert opinion for disease prioritisation from pig producers in Australia

Model	Number of partici-pants	Median cut-off	Final model structure	Validation[a]	
				Mean difference	Standard deviation
1	51	None	_~ MLPig + ARPig + CFRPig +MLRum + IncHum + (DisWtH * CFRHum)_	1.01	1.22
2, F High	22	> 50	_~ MLPig + ARPig + CFRPig + MLRum + IncHum + DisWtH_	0.43	9.1
3, F low	23	≤ 50	_~ s(MLPig) + ARPig + IncHum_	0.45	17.97
4, H high	23	> 75	_~ MLPig + ARPig + CFRPig + MLRum + IncHum + (DisWtH * CFRHum)_	4.82	6.82
5, H low	21	≤ 75	_~ MLPig + ARPig + DisWtH_	2.31	13.82

[a] actual versus predicted scores of validation scenarios, using Bland-Altman method of agreement (Bland and Altman, 2010)

_s_ = smooth function, MLPig = market loss to pig industry, ARPig = attack rate in pigs, CFRPig = case fatality rate in pigs, MLRum = market loss to ruminant industry, PrevHum = Incidence in humans, DisWtH = disability weight in humans, CFRHum = case fatality rate in humans.

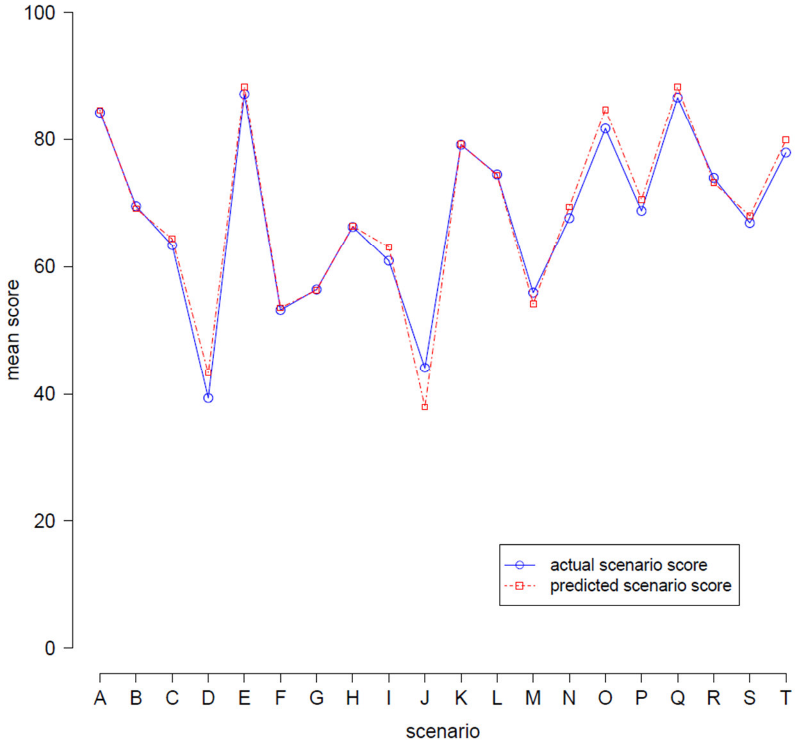


Fig. 2 Plot of actual and predicted mean scores for all scenarios using the final model with responses from all participants (n = 51) from a survey to elicit expert opinion for disease prioritisation from pig producers in Australia

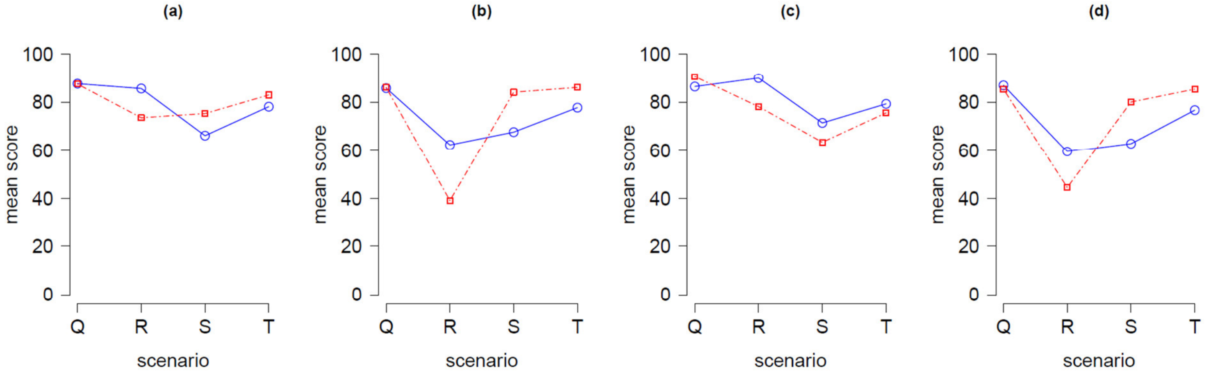


Fig. 3 Plot of actual and predicted mean scores for validation scenarios using models with responses from subsets of participants from a survey to elicit expert opinion for disease prioritisation from pig industry producers in Australia. Solid line= actual scenario score, dotted line = predicted scenario score. Subsets: a) 2, F High; b) 3, F Low; c) 4, H High; d) 5, H Low

<u>Disease prioritisation</u>

The final model using responses from all participants was selected for disease prioritisation due to better validation than the models from subsets of participants (model 1, Table 3). Figure 4 shows a centipede plot prioritising diseases by mean score, predicted using this final model. The highest priority diseases were the vesicular diseases, although the priority of swine vesicular disease and vesicular stomatitis diminished once they were differentiated from foot and mouth disease (FMD). Classical and African swine fevers were the next highest priority, followed by diseases with both severe zoonotic and livestock impacts (Nipah, Japanese encephalitis, Eastern equine encephalitis and swine influenza). Rabies, the other zoonosis with high impact in humans, had smaller livestock impact and was lower in priority, indicating that overall, livestock disease impacts were more important to these participants than zoonotic disease impacts.

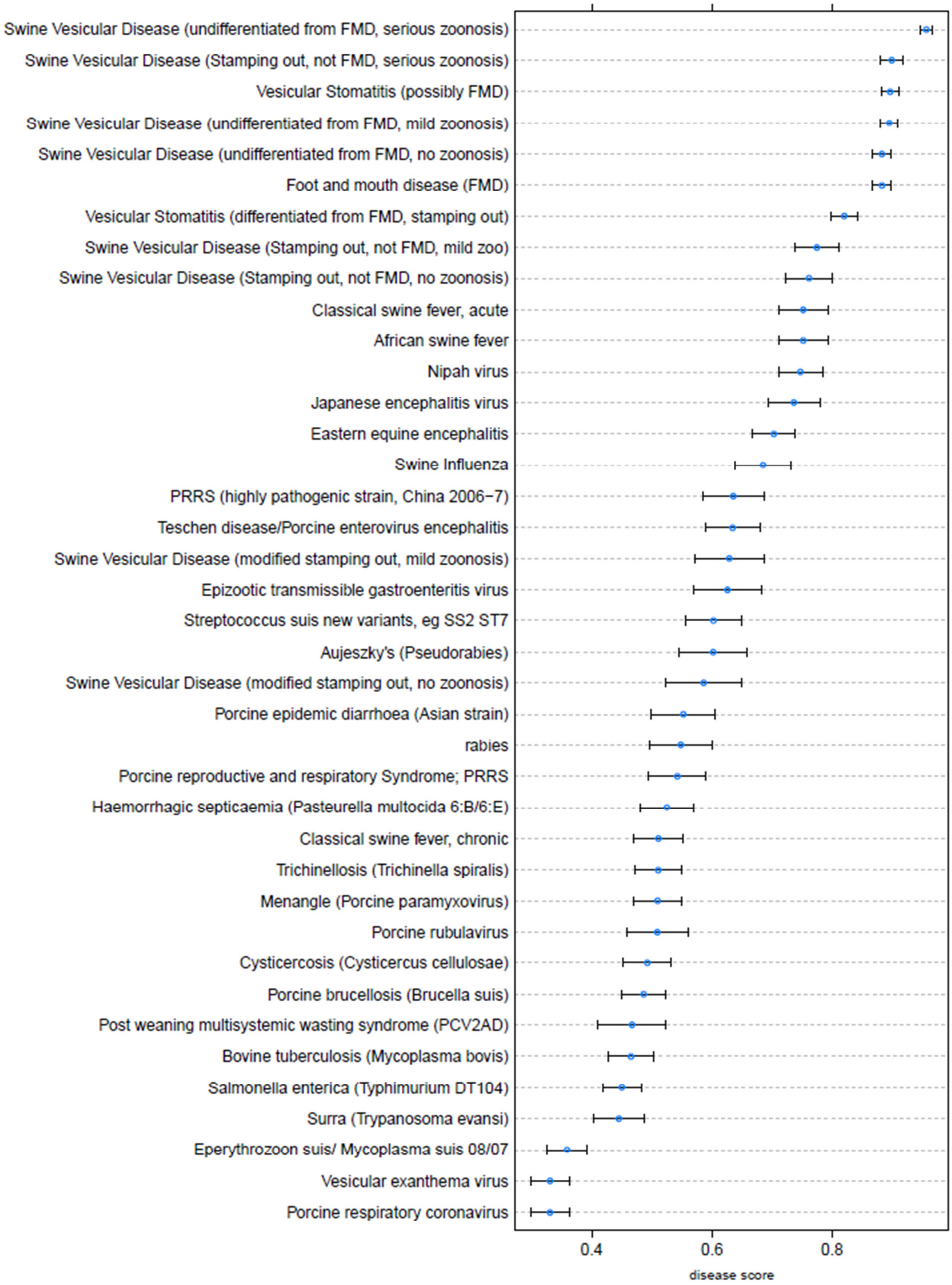


Fig. 4 Plot of scores of importance for exotic diseases, ordered by mean score (bars = standard error), using responses from all participants (n = 51) from a survey to elicit expert opinion for disease prioritisation from pig producers in Australia

Sensitivity of score to criteria

Figure 5 shows the disease score with maximum measurements for each criterion whilst other criterion measurements are zero, in the ranges used to fit the final model using responses from all participants (n = 51) (model 1, Table 3), and an increased range for "incidence in humans". The overall disease score was most sensitive to changes in the criterion "attack rate in pigs", which gave a proportionally larger change to the overall score for a disease compared to equivalent changes in other criteria. Disease score was moderately sensitive to "market loss in pigs", "market loss in ruminants", "case fatality rate in pigs" and "incidence in humans", and least sensitive to "disability weight" and "case fatality rate in humans". If the range of the criterion "incidence in humans" was increased to 0.0001 (approximately 2,350 people affected in Australia; Australian Bureau of Statistics, http://www.abs.gov.au/ausstats/abs@.nsf/mf/3101.0, accessed 14/01/15), this criterion was the most influential to disease score.

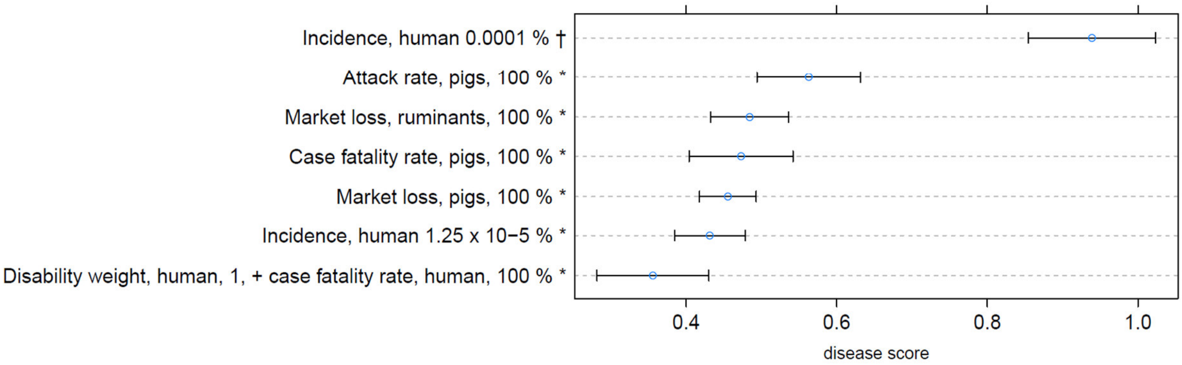


Fig. 5 Plot of scores of importance for each criterion ([*]at maximum range used in scenarios and to fit model, [†]above range used in scenarios and to fit model) whilst other criteria are held at zero, to assess sensitivity to criteria in a study of disease prioritisation for pig producers in Australia (bars = standard error)

DISCUSSION

This study used Point of Truth Calibration (POTCal; Barry & Xunguo, 2010) to derive a predictive model for prioritisation of exotic diseases based on the preferences of pig producers in Australia. A survey elicited expert opinion from a sample of pig producers about the importance of the potential impacts of constructed disease scenarios – the *point of truth*. Statistical modelling was used to characterise the relationship between the importance of disease impacts and disease criteria, i.e. *calibration*. Thus this method makes use of opinions from non-traditional experts within a statistical framework.

The final model used responses from all participants and predicted that the highest priority diseases were the vesicular diseases and swine fevers. This indicated that, overall, livestock impacts of disease were important to this group. Sensitivity analysis confirmed that within the ranges used to elicit expert opinion and fit the model, the criteria with the most influence on disease importance were industry criteria: attack rate and case fatality rate in pigs, and market loss to both the pig and ruminant industries. Consequently, rabies – a disease with high impact on individual humans but low impact on livestock industries – had lower priority to these producers in this study. These results are not surprising: pig producers operate commercial businesses with a focus on profit. However, the results of the sensitivity analysis might potentially be misleading. The maximum value used to assess sensitivity to "incidence in humans" was the maximum value used to elicit expert opinion and fit the model. This value reflected the range that would be expected for exotic zoonoses currently known to affect pigs. An advantage of deriving predictive models for disease prioritisation is that they can be used to update prioritisation lists as new diseases emerge, and it is not unreasonable to suggest that a disease with a greater incidence in humans could emerge. When the maximum value for incidence in humans was increased to 0.0001% (approximately 2000 people in Australia) this criterion had the greatest influence on disease importance. This indicates that there is a potential for a disease with high incidence in humans to be higher priority than livestock diseases to this group of producers. Care should be taken in interpreting the output of regression models using parameters that are beyond the ranges used to fit the model. Also, in this study residual plots indicated that the model is likely to be less accurate when disease importance approaches either 0 or 100. Future studies should consider increasing the range of incidence in humans in the constructed disease scenarios so that the model has greater predictive range and the influence of criteria can be more comprehensively assessed.

Examination of responses indicated that some participants valued the importance of diseases with impacts on humans more than diseases with impacts only on livestock, but validation of models could not be improved by separating participants into subsets based on disease scores for the test scenarios. There are a number of potential reasons for this. Firstly, subsets were based on participants' scores for only two scenarios, which might not be the most appropriate method of differentiating subsets – further investigation of the best way to differentiate participants' preferences is needed. Also, considerable amounts of data are required to fit mixed models with non-linear functions. Subset sizes ranged from only 17–23 participants and, given the number of criteria, this is likely to have limited accuracy of model fit leading to poorer validation for the subset models versus the model using responses from all participants. It is likely that more accurate model fit, and hence better validation, could be achieved by increasing the number of participants in this study. However, the pattern of criteria included in the subset models gave an indication of differences in participants' decision-making heuristics. Models generally included more criteria and were more complex for subsets of participants who placed more value on the human impacts of disease rather than livestock impacts. In contrast, participants who prioritised livestock impacts of diseases appeared to simplify the decision choice to three criteria: market loss to the pig industry, attack rate in pigs, and either incidence or disability weight in humans. It is known that decision makers can simplify decisions by targeting selected criteria rather than considering all criteria, dependent on decision context (Einhorn, 1971), and this study demonstrated the potential use of POTCal to derive models that reflect decision-makers' heuristics for disease prioritisation in this context.

Apart from sample size, other limitations of this study included response bias (low number of completed surveys) and selection bias. The source population was producers registered with the industry organisation, Australian Pork Limited; therefore, they were more likely to be farm managers. This is supported by the demographic results which showed that participants were generally experienced in the pig industry. This selection bias reduces the external validity of the study to the general population of people working on pig farms in Australia. However, it could be considered that the participants in this study were more able to assess disease impact due to their experience in the pig industry; therefore, they were a suitable group for expert opinion for disease prioritisation.

Choosing the most appropriate model to describe decision-makers' preferences is challenging when decision-makers heuristics are unknown (Guitouni & Martel, 1998). In previous studies in which the form of the model to describe heuristics was assumed, validation demonstrated sub-optimal ability to predict disease priority (Havelaar et al., 2010; Brookes et al., 2014c). This study demonstrated the potential value of the POTCal method in deriving models that accurately reflect decision-maker heuristics for disease prioritisation in this context. As well as ensuring adequate sample size, further development of methods to characterise groups of participants with diverse preferences prior to model fitting is required.

ACKNOWLEDGEMENTS

The first author was funded as a PhD student by Australian Pork Limited (project number 2010/1000.381).

REFERENCES

Australian Pork Limited (2012). Australian pig annual 2011-2012

Balabanova, Y., Gilsdorf, A., Buda, S., Burger, R., Eckmanns, T., Gaertner, B., Gross, U., Haas, W., Hamouda, O., Huebner, J., Jaenisch, T., Kist, M., Kramer, M.H., Ledig, T., Mielke, M., Pulz, M., Stark, K., Suttorp, N., Ulbrich, U., Wichmann, O. and Krause, G. (2011). Communicable diseases prioritized for surveillance and epidemiological research: Results of a standardized prioritization procedure in germany, 2011. PLoS ONE 6

Barry, S. and Xunguo, L. (2010). Point of truth calibration: Putting science into scoring systems. Australian Centre of Excellence for Risk Analysis (ACERA)

Bland, J.M. and Altman, D.G. (2010). Statistical methods for assessing agreement between two methods of clinical measurement. Int. J. Nurs. Stud. 47, 931-936

Brookes, V.J., Hernández-Jover, M., Black, P.F. and Ward, M.P. (2014a). Preparedness for emerging infectious disease: pathways from anticipation to action. Epidemiol. Infect. DOI:10.1017/S095026881400315X

Brookes, V.J., Hernández-Jover, M., Cowled, B., Holyoake, P.K. and Ward, M.P. (2014b). Building a picture: Prioritisation of exotic diseases for the pig industry in australia using multi-criteria decision analysis. Prev. Vet. Med. 113, 103-117

Brookes, V.J., Hernández-Jover, M., Neslo, R., Cowled, B., Holyoake, P. and Ward, M.P. (2014c). Identifying and measuring stakeholder preferences for disease prioritisation: A case study of the pig industry in australia. Prev. Vet. Med. 113, 118-131

Burnham, K.P., Anderson, D.R. and Huyvaert, K.P. (2011). Aic model selection and multimodel inference in behavioral ecology: Some background, observations, and comparisons. Behav. Ecol. Sociobiol. 65, 23-35

Carter, A. and National Advisory Committee on Epidemiology Subcommittee (1991). Establishing goals, techniques and priorities for national communicable disease surveillance. Can. J. Infect. Dis. 2, 37-40

Del Rio Vilas, V.J., Burgeno, A., Montibeller, G., Clavijo, A., Vigilato, M.A., Cosivi, O. and (2013). Prioritization of capacities for the elimination of dog-mediated human rabies in the americas: Building the framework. Pathog. Glob. Health 107, 340-345

Dodgson, J., Spackman, M., Pearman, A. and Phillips, L. (2009). Multi-criteria analysis: A manual. Department for Communities and Local Government: London

Doherty, J.A. (2000). Establishing priorities for national communicable disease surveillance. Can. J. Infect. Dis. 11, 21-24

Einhorn, H.J. (1971). Use of nonlinear, noncompensatory models as a function of task and amount of information. Organ. Behav. Hum. Perform. 6, 1-27

Flari, V., Chaudhry, Q., Neslo, R. and Cooke, R. (2011). Expert judgment based multi-criteria decision model to address uncertainties in risk assessment of nanotechnology-enabled food products. J. Nanopart. Res. 13, 1813-1831

Guitouni, A. and Martel, J.-M. (1998). Tentative guidelines to help choosing an appropriate mcda method. Eur. J. Oper. Res. 109, 501-521

Havelaar, A.H., van Rosse, F., Bucura, C., Toetenel, M.A., Haagsma, J.A., Kurowicka, D., Heesterbeek, J.H.A.P., Speybroeck, N., Langelaar, M.F.M., van der Giessen, J.W.B., Cooke, R.M. and Braks, M.A.H. (2010). Prioritizing emerging zoonoses in the netherlands. PLoS ONE 5, e13965

Humblet, M.-F., Vandeputte, S., Albert, A., Gosset, C., Kirschvink, N., Haubruge, E., Fecher-Bourgeois, F., Pastoret, P.-P. and Saegerman, C. (2012). Multidisciplinary and evidence-based method for prioritizing diseases of food-producing animals and zoonoses. Emerg. Infect. Dis. 18

Kadohira, M., Hill, G., Yoshizaki, R., Ota, S. and Yoshikawa, Y. (2014). Stakeholder prioritization of zoonoses in japan with analytic hierarchy process method. Epidemiol. Infect. FirstView, 1-9

Keeney, R.L. (1982). Decision-analysis - an overview. Oper. Res. 30, 803-838

Krause, G. and Prioritization Working Grp (2008). How can infectious diseases be prioritized in public health? A standardized prioritization scheme for discussion. EMBO Rep. 9, S22-S27

McKenzie, J., Simpson, H. and Langstaff, I. (2007). Development of methodology to prioritise wildlife pathogens for surveillance. Prev. Vet. Med. 81, 194-210

Neslo, R.E.J. and Cooke, R.M. (2011). Modeling and validating stakeholder preferences with probabilistic inversion. Applied Stochastic Models in Business and Industry 27, 115-130

Ng, V. and Sargeant, J.M. (2012). A quantitative and novel approach to the prioritization of zoonotic diseases in north america: A public perspective. PLoS ONE 7, e48519

Ng, V. and Sargeant, J.M. (2013). A quantitative approach to the prioritization of zoonotic diseases in north america: A health professionals' perspective. PLoS ONE 8, e72172

Palmer, S., Brown, D. and Morgan, D. (2005). Early qualitative risk assessment of the emerging zoonotic potential of animal diseases. BMJ 331, 1256-1260

R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing Vienna, Austria

Rushdy, A. and O'Mahony, M. (1998). Phls overview of communicable diseases 1997: Results of a priority setting exercise. Commun. Dis. Rep. CDR Wkly. 8 Suppl 5, S1-12

Teck, S.J., Halpern, B.S., Kappel, C.V., Micheli, F., Selkoe, K.A., Crain, C.M., Martone, R., Shearer, C., Arvai, J., Fischhoff, B., Murray, G., Neslo, R. and Cooke, R. (2010). Using expert judgment to estimate marine ecosystem vulnerability in the california current. Ecol. Appl. 20, 1402-1416

Valenciano, M. and Working Grp. (2001). Setting priorities for non-foodborne zoonoses. Med. Maladies Infect. 31, 302S-304S

von Winterfeldt, D. (1980). Structuring decision problems for decision analysis. Acta Psychol. (Amst.) 45, 71-93

Weinberg, J., Grimaud, O. and Newton, L. (1999) Establishing priorities for European collaboration in communicable disease surveillance. Eur. J. Public Health 9, 236-240

Wood, S.N. (2006). Generalized additive models: An introduction with r. Boca Raton, Fl.: Chapman and Hall/CRC Press

PREDICTION OF PIG TRADE MOVEMENTS IN DIFFERENT PRODUCTION SYSTEMS WITH EXPONENTIAL RANDOM GRAPH MODELS

A. RELUN*, V. GROSBOIS, E. ETTER, A. WARET-SZKUTA, T. ALEXANDROV, J.M. SANCHEZ-VIZCAINO, S. MOLIA AND B. MARTINEZ-LOPEZ

SUMMARY

For several major infectious diseases, the structure of contact patterns between herds trough live animal trade will determine the dynamic of their spread. However, complete data on trade movements can be difficult to include in epidemic models, either because they are not available on time, too time-consuming or computationally challenging. The aim of this paper was to use exponential random graph models (ERGMs) to reproduce and understand pig trade networks in different European production systems, including small-scale, extensive and intensive pig production systems. ERGM was found to be a useful method to examine and represent pig trade networks. The results highlight the need to include network statistics to explain pig trade networks topology, premises characteristics being necessary but not sufficient to represent the observed networks, whichever production system considered.

INTRODUCTION

Movements of animals play a key role in the spread of several major infectious diseases, like foot-and-mouth disease, and classical and African swine fevers (Fritzemeier et al., 2000; Shirley & Rushton, 2005; Costard et al., 2013). Therefore detailed data on livestock movements may help to better simulate transmission dynamics and identify areas, periods and farms that are more likely to spread the diseases and could be targeted to improve surveillance and control strategies (Dube et al., 2009; Martinez-Lopez et al., 2009). However, one of the challenges of using livestock movement data to support decision-making in preventive veterinary medicine is the limited availability of timely and updated records on animal movements and the massive amount of data that have to be processed. This is particularly challenging when considering diverse and, sometimes, epidemiologically complex, production systems such as backyard or extensive, where the information may not be frequently collected and accessible. Models of livestock movement networks based on holding characteristics and past-temporal observed networks could be useful to simplify real-world networks and to predict disease spread even in backyard or extensive environments.

Pig trade movements can be represented as a network, consisting of a set of nodes (here the pig premises) connected by links (also called edges) representing movements of pigs between them. These networks are not strictly identical from one year to the following, but their structural properties, which impact disease dynamics (Bigras-Poulin et al., 2007; Dorjee et al., 2013), are likely to be stable over time. These properties emerge from pig trading behaviours. For example, some premises may be more likely to trade with each other due to

---

* Anne Relun, CIRAD, UPR AGIRs, Campus international de Baillarguet, 34398 Montpellier Cedex 5, France; and CADMS, University of California, Davis, US. Email: anne.relun@cirad.fr

geographical proximity, or because they belong to the same pig company (selective mixing or homophily). Some types of premises may also be more likely to trade with more premises (attributes that influence degree). Finally, if a trading partner B of premises A trades with a third premises C, this might encourage A to trade with C (structural balance effect).

The first statistical models developed to evaluate which processes lead to observed network structures, were quite simple. They only addressed relational reciprocation (mutuality; see Holland & Leinhardt, 1981) or assortative mixing (Morris, 1991). The recent developments of exponential random graph models (ERGMs), also known as p^* models (Wasserman & Pattison, 1996), offer possibilities to better capture the complexity of real-life networks (Goodreau, 2007). This family of models assume that the observed network is only one realisation among many potential networks with similar characteristics and that the probability that a link exists is a logit-linear function of predictors that reflect node characteristics, link characteristics and network structural properties (Wasserman & Pattison, 1996; Snijders et al., 2006; Robins et al., 2007). Although they were developed to handle the inherent non-independence of network data, the results of ERGMs are interpreted in similar ways to logistic regression, making this a very useful method for examining social networks in the context of epidemiology.

The aims of this paper were to use ERGMs to 1) develop models that reproduce observed pig trade networks; 2) understand the mechanisms that underlie the organisation of pig trade networks; and 3) highlight the key differences between European pig production systems. Results of this study are intended to inform policies to better prevent and control swine diseases such as African swine fever or classical swine fever under diverse epidemiological scenarios and pig productions systems in Europe.

MATERIALS AND METHODS

Data collection and network construction

Three areas were selected to represent different European pig production systems: Bulgaria, were most premises raise pigs for own consumption; the autonomous community of Extremadura, which is the cradle of extensive Iberian pig production; and the department of Côtes-d'Armor, which is the French department with the highest concentration of industrial pig premises.

Data on pig movements and premises characteristics were obtained from national databases, through BFSA, BDPORC and MAGRAMA, in Bulgaria, France and Spain respectively. The year 2011, which was common in all databases, was retained for analysis. The premises characteristics available were the type of production, the size of premises, the type of housing system, the geographical coordinates and the pig company number (only for France). In Bulgaria, pig farms were classified as backyard (pigs kept for own consumption), Type B (medium-size, low biosecurity level), Type A (medium-size, high biosecurity level) or industrial farms (large size, high biosecurity level) (Martinez-Lopez et al., 2013). For Spain and France, pig farms were classified as multipliers (premises that produce breeding stocks and semen), farrowing farms, farrow-to-finish farms, finishing farms or small producers (Spain only). Traders, collection centers, markets, fairs and stop points were considered as trade operators. Because of the dead-end characteristics of slaughterhouses, these premises were excluded from analysis.

For each area, yearly networks were built, the nodes being all pig premises of the study areas, even those that were not trading pigs during the study period. Movement data were aggregated over the study period and a direct link was drawn whenever a displacement of pigs occurred between the corresponding premises.

The ERGMs

ERGMs specify the probability of any random network **Y** given a set of n nodes and their attributes as in Eq. (1).

$$P_\theta(\boldsymbol{Y} = y \mid n \text{ nodes}) = \left(\frac{1}{\mathrm{C}}\right) \exp\left(\sum_{\mathrm{k=1}}^{\mathrm{K}} \theta_k z_k(y)\right) \tag{1}$$

The $z_k(y)$ terms represent model covariates, any set of K network statistics calculated on the y observed network and hypothesised to affect the probability of this network forming. The model covariates can include network parameters that account for the frequency of occurrence of certain network configurations (e.g. two-path, triangles), as well as node or edge-wise covariates like the pig company to which a premises belongs or the distance between two premises, respectively. The θ coefficients estimate the strength of the effect of each. The denominator C represents the normalising constant, the sum of $\exp\left(\sum_{\mathrm{k=1}}^{\mathrm{K}} \theta_k z_k(y)\right)$ over all possible networks with n nodes.

Model specification

First, an exploration of network data was undertaken, with the computation of several local topological measures (number of isolates, triangles, degree distribution etc.) and of mixing matrices for premises' attributes (Goodreau et al., 2008). Network graphs were plotted, with the nodes coloured according to nodes' attributes, to better visualise the selective mixing patterns.

Based on this exploration, few key network statistics were chosen to represent hypothetic rules for trade movements (Table 1). $L(y)$ captures the density of the network. $M_{i,y,a}(y)$, $M_{o,y,a}(y)$, $H_{v,a}(y)$, $U_{v,a}(y)$, $S_{v,a}(y)$ and $E_a(y)$ are attribute-specific terms that capture the way in which premises attribute structure trading patterns. The main effects, $M_{i,y,a}(y)$ and $M_{o,y,a}(y)$, allow variation in the propensity of a premises to form in- and outgoing edges according to the level of an attribute characterising this premise. $H_{v,a}(y)$ models a tendency of edges to occur between premises belonging to the same attribute level that varies among attribute levels (hereafter referred to as differential homophily), while $U_{v,a}(y)$ models a uniform tendency of edges to occur between premises belonging to the same attribute level (hereafter referred to as uniform homophily). $S_{v,a}(y)$ accounts for variation in the occurrence of edges according to the levels of an attribute characterising each of two premises (hereafter referred to as selective mixing). $E_a(y)$ captures variation in the propensity of premises to form links according to the Euclidian distance in km to other premises.

$A(y)$ and $I(y)$ model the tendency of premises to form unidirectional links or no links, respectively. $gwdsp(y, \alpha)$, $gwesp(y, \alpha)$, $gwid(y, \alpha)$ and $gwod(y, \alpha)$ are terms related to local structures and represent the parametric forms of the alternating two-paths, clustering (alternating k-triangles), in- and out-degree distributions, respectively. A fixed value of 0.5 was adopted for the α term (Goodreau, 2007).

The Markov Chain Monte Carlo (MCMC) algorithm was used to estimate the maximum likelihood for the parameters included in models. A chain burn-in of 10^5 toggles, an MCMC sample size of 10^4 and an interval between successive samples of 10^3 was fixed for these models.

Table 1. Network statistics used to fit the ERGMs of pig trade networks

Network statistics $z_k(y)$	Abbreviation used[a]
# of edges	$L(y)$
# of in- and out-going edges for each type of production, housing system, pig company	$M_{i,y,a}(y)$, $M_{o,y,a}(y)$
# of edges that are within housing systems, within pig companies, within regions, with differential homophily	$H_{v,a}(y)$
# of edges that are within housing systems, within pig companies, within regions, with uniform homophily	$U_{v,a}(y)$
# of edges that are within and between housing systems, within and between type of productions , within and between regions	$S_{v,a}(y)$
Euclidian distance between pairs of premises	$E_a(y)$
# of isolates	$I(y)$
# of asymmetric links	$A(y)$
Geometrically weighted dyadwise shared partners	$gwdsp(y, \alpha)$
Geometrically weighted edgewise shared partners	$gwesp(y, \alpha)$
Geometrically weighted in- and out-degree distribution	$gwid(y, \alpha)$, $gwod(y, \alpha)$

[a] Some statistics used attribute-specific terms where *a* and *v* represent the attribute and the level, respectively

Model selection and goodness of fit

For each area, four models were built: 1) a simple Bernoulli model that only includes the number of edges; 2) a model with edges and statistics based on nodal attributes (hereafter called ‘edge + attribute’ model); 3) a model with edges and structure-related statistics (‘edge + network statistics’ model); and 4) a model with edges, nodal attributes and structure-related statistics (‘edge + attributes + network statistics’ model).

For the ‘edge + attribute’ and ‘edge + network statistics’ models, univariable analyses were performed first. The terms were then added one by one, until the best model fit was obtained. The third model was based on the final ‘attribute’ model. ‘Network statistics’ terms were added one by one until the best model fit was obtained.

Three approaches were used to examine goodness of fit of the models: 1) check for model convergence and degeneracy; 2) comparison of Akaike information criteria (AIC); and 3) comparison of goodness of fit plotting for higher order statistics (Goodreau, 2007). For this purpose, four sets of statistics were used: the in- and out- degree distributions, the geodesic distance distribution, and the edgewise shared partner distribution, which reflects the clustering of the network (Hunter & Handcock, 2006). These statistics were chosen because of their impact on disease spread dynamics (for more details, see Hunter et al., 2008). Finally, plots of simulated networks were visually compared to the plot of the observed networks.

All analyses were conducted in R (R Core Team, 2014) using the "statnet" suite of packages (Handcock et al., 2008; Handcock et al., 2014).

RESULTS

Calculation time dramatically increased with the increase of network size. It was thus decided to exclude isolates, i.e. pig premises that did not trade with other premises, from the small producer system (Bulgaria, initially 28,729 premises, of which 95.3% were isolated premises). The observed pig trade networks exhibited different topological characteristics (Table 2).

Table 2. Topological statistics of the pig trade networks in 2011

Production system (area)	Topological statistics[a]					
	# of nodes	Density	% of isolates	Clustering coefficient	Mean k_{in} (range)	Mean k_{out} (range)
Small producers (Bulgaria)	1,349	$6.7 * 10^{-4}$	0.0	0.049	0.9 (0 – 7)	0.9 (0 – 35)
Extensive (Spain – Extremadura)	14,097	$2.1 * 10^{-5}$	67.7	0.038	0.3 (0 – 70)	0.3 (0 – 27)
Intensive (France – Côtes d'Armor)	2,396	$5.4 * 10^{-4}$	20.4	0.066	1.3 (0 – 236)	1.3 (0 – 83)

[a] k_{in}: in-degree; k_{out}: out-degree

The inclusion of nodal attributes and network configurations statistics provided the best fit to the data (Table 3-5, Fig. 3 & 2). Selective mixing between premises according to their type of production appeared to be an important mechanism of pig organisation, whichever system considered (Table 3-5). In addition to this mechanism, the other mechanisms related to premises characteristics that impacted the most on trade organisation were belonging to the same pig company, the tendency of outdoors premise to trade with outdoor premises and the geographical location of pig premises, in the intensive, extensive and small-scale production systems, respectively (Table 3-5. Computational problems occurred when trying to include the distance between premises as a covariate in the largest networks (extensive production - Spain), preventing a conclusion to be drawn on the impact of this covariate in this production system. Network statistics on dyadwise and edgewise shared partner distributions, as well as on in- or out-degree distributions were needed to fit the models (Table 3-5). These statistics better reflected the clustering of the observed networks (Fig. 3).

Table 3. Parameter coefficients and fit for the four final models of pig trade in a small-scale production system (Bulgaria)

Covariates	Final models coefficients (Standard error)[a]			
	Bernoulli (edges)	Edges + attributes	Edges + network statistics	Edges + attributes + network statistics
$L(y)$	- 7.30 (0.03) ***		- 10.18 (0.30) ***	- 9.62 (0.67) ***
$A(y)$			NS	1.31 (0.40) **
$gwdsp(y, 0.5)$			- 2.72 (0.07) ***	- 2.52 (0.09) ***
$gwesp(y, 0.5)$			4.59 (0.29) ***	2.28 (0.36) ***
$gwid(y, 0.5)$			10.18 (0.30) ***	10.44 (0.35) ***
$E_{dist}(y)$		- 0.07 (0.00) ***		- 0.07 (0.00) ***
$S_{Region, E-E}(y)$		0.02 (0.16)		- 0.88 (0.53)
$S_{Region, NW-E}(y)$		0.08 (0.48)		- 0.36 (1.02)
$S_{Region, S-E}(y)$		0.92 (1.02)		1.85 (1.60)
$S_{Region, SW-E}(y)$		NA		NA
$S_{Region, E-NW}(y)$		0.57 (0.38)		- 0.51 (0.74)
$S_{Region, NW-NW}(y)$		- 1.29 (0.13) ***		- 0.82 (0.44)
$S_{Region, S-NW}(y)$		NA		NA
$S_{Region, SW-NW}(y)$		- 1.43 (1.01)		3.10 (1.66)
$S_{Region, E-S}(y)$		3.50 (0.32) ***		3.89 (0.68) ***
$S_{Region, NW-S}(y)$		1.61 (0.37) ***		1.75 (0.62) **
$S_{Region, S-S}(y)$		Reference		Reference
$S_{Region, SW-S}(y)$		NA		NA
$S_{Region, E-SW}(y)$		15.91 (0.49) ***		20.78 (0.99) ***
$S_{Region, NW-SW}(y)$		2.55 (0.31) ***		6.49 (0.68) ***
$S_{Region, S-SW}(y)$		3.77 (0.45) ***		5.68 (1.06) ***
$S_{Region, SW-SW}(y)$		0.39 (0.36)		1.75 (0.93)
$S_{ProdS, BY-BY}(y)$		Reference		Reference
$S_{ProdS, IN-BY}(y)$		2.37 (0.17) ***		0.75 (0.24) **
$S_{ProdS, TA-BY}(y)$		2.20 (0.12) ***		0.92 (0.17) ***
$S_{ProdS, TB-BY}(y)$		1.98 (0.08) ***		0.82 (0.10) ***
$S_{ProdS, BY-IN}(y)$		- 1.45 (1.00)		- 1.08 (1.33)
$S_{ProdS, IN-IN}(y)$		3.33 (0.28) ***		2.31 (0.93) *
$S_{ProdS, TA-IN}(y)$		1.19 (0.52) *		1.43 (1.16)
$S_{ProdS, TB-IN}(y)$		0.58 (1.01)		0.14 (1.74)
$S_{ProdS, BY-TA}(y)$		- 0.81 (0.45)		0.09 (0.68)
$S_{ProdS, IN-TA}(y)$		2.95 (0.25) ***		2.22 (0.78) **
$S_{ProdS, TA-TA}(y)$		1.26 (0.37) ***		1.24 (0.83)
$S_{ProdS, TB-TA}(y)$		2.26 (0.32) ***		2.16 (0.69) **
$S_{ProdS, BY-TB}(y)$		- 1.03 (0.26) ***		0.73 (0.44)
$S_{ProdS, IN-TB}(y)$		3.08 (0.29) ***		3.32 (0.71) ***
$S_{ProdS, TA-TB}(y)$		2.72 (0.24) ***		3.22 (0.55) ***
$S_{ProdS, TB-TB}(y)$		1.92 (0.22) ***		2.49 (0.59) ***
AIC	20372	14940	17394	12397

[a] *** : <0.001; ** <0.01; * <0.05

Table 4. Parameter coefficients and fit for the four final models of pig trade in an extensive production system (Spain – Extremadura)

Covariates	Final models coefficients (Standard error)[a]			
	Bernoulli (edges)	Edges + attributes	Edges + network statistics	Edges + attributes + network statistics
$L(y)$	- 10.77 (0.02) ***	- 9.34 (0.04) ***	- 5.87 (0.26) ***	- 4.87 (0.55) ***
$I(y)$			1.08 (0.04) ***	0.90 (0.06) ***
$A(y)$			- 1.99 (0.27) ***	- 2.28 (0.54) ***
$gwdsp(y, 0.5)$			- 0.24 (0.02) ***	- 0.26 (0.03) ***
$gwesp(y, 0.5)$			3.63 (0.27) ***	4.34 (0.24) ***
$gwod(y, 0.5)$			- 2.59 (0.06) ***	- 2.55 (0.08) ***
$S_{ProdS, Ind-Ind}(y)$		- 1.23 (0.05) ***		- 0.74 (0.06) ***
$S_{ProdS, Ind-Out}(y)$		- 0.68 (0.04) ***		- 0.30 (0.05) ***
$S_{ProdS, Out-Ind}(y)$		- 0.68 (0.04) ***		- 0.56 (0.05) ***
$S_{ProdS,Out-Out}(y)$		Reference		Reference
$S_{ProdS, MU-MU}(y)$		2.44 (1.00) *		2.09 (2.47)
$S_{ProdS, MU-FA}(y)$		1.79 (0.58) **		1.84 (0.88) *
$S_{ProdS, MU-FF}(y)$		- 0.26 (0.27)		- 0.34 (0.28)
$S_{ProdS, MU-FI}(y)$		- 0.23 (0.38)		- 0.41(0.46)
$S_{ProdS, MU-SP}(y)$		NA		NA
$S_{ProdS, FA-MU}(y)$		1.38 (0.71)		0.83 (1.17)
$S_{ProdS, FA-FA}(y)$		0.07 (0.58)		- 0.09 (0.82)
$S_{ProdS, FA-FF}(y)$		- 0.39 (0.13) **		- 0.45 (0.16) **
$S_{ProdS, FA-FI}(y)$		0.18 (0.13)		0.06 (0.18)
$S_{ProdS, FA-SP}(y)$		- 0.89 (0.71)		- 0.67 (0.87)
$S_{ProdS, FF-MU}(y)$		0.20 (0.22)		0.36 (0.32)
$S_{ProdS, FF-FA}(y)$		- 0.67 (0.14) ***		- 0.28 (0.18)
$S_{ProdS, FF-FF}(y)$		- 1.25 (0.05) ***		- 0.75 (0.06) ***
$S_{ProdS, FF-FI}(y)$		- 0.72 (0.05) ***		- 0.33 (0.06) ***
$S_{ProdS, FF-SP}(y)$		- 2.46 (0.26) ***		- 1.83 (0.28) ***
$S_{ProdS, FI-MU}(y)$		0.47 (0.27)		0.28 (0.36)
$S_{ProdS, FI-FA}(y)$		- 0.02 (0.15)		- 0.05 (0.21)
$S_{ProdS, FI--FF}(y)$		- 0.59 (0.05) ***		- 0.50 (0.06) ***
$S_{ProdS, FI--FI}(y)$		Reference		Reference
$S_{ProdS, FI--SP}(y)$		- 1.79 (0.27) ***		- 1.52 (0.31) ***
$S_{ProdS, SP-MU}(y)$		0.15 (1.00)		0.96 (1.27)
$S_{ProdS, SP-FA}(y)$		NA		NA
$S_{ProdS, SP-FF}(y)$		- 2.46 (0.26) ***		- 1.37 (0.29) ***
$S_{ProdS, SP-FI}(y)$		- 1.95 (0.29) ***		- 1.00 (0.30) ***
$S_{ProdS, SP-SP}(y)$		- 2.12 (1.00) *		- 0.86 (1.39)
AIC	96949	94851	91182	89952

[a] *** : <0.001; ** <0.01; * <0.05

Table 5. Parameter coefficients and fit for the four final models of pig trade in an intensive production system (France – Côtes d’Armor)

Covariates[b]	Final models coefficients (Standard error)[a]			
	Bernoulli (edges)	Edges + attributes	Edges + network statistics	Edges + attributes + network statistics
$L(y)$	-7.52 (0.02) ***	- 10.87 (0.40) ***	- 3.47 (0.10) ***	- 5.66 (0.43) ***
$I(y)$			0.98 (0.07) ***	0.33 (0.08) ***
$A(y)$			- 2.28 (0.09) ***	- 2.39 (0.18) ***
$gwdsp(y, 0.5)$			- 0.24 (0.01) ***	- 0.13 (0.02) ***
$gwod(y, 0.5)$			- 2.88 (0.06) ***	- 1.83 (0.10) ***
$M_{i, ProdS, Ind}(y)$		- 0.44 (0.10) ***		- 0.45 (0.15) **
$M_{i, ProdS, Out}(y)$		Reference		Reference
$M_{o, ProdS, Ind}(y)$		1.48 (0.39) ***		0.82 (0.36) *
$M_{o, ProdS, Out}(y)$		Reference		Reference
$H_{Comp,1}(y)$		2.13 (0.11) ***		2.14 (0.13) ***
$H_{Comp,2}(y)$		3.42 (0.25) ***		3.38 (0.31) ***
$H_{Comp,None}(y)$		Reference		Reference
$S_{ProdS, MU\text{-}MU}(y)$		3.69 (0.27) ***		1.80 (0.41) ***
$S_{ProdS, MU\text{-}FA}(y)$		4.10 (0.22) ***		2.53 (0.34) ***
$S_{ProdS, MU\text{-}FF}(y)$		4.61 (0.10) ***		3.03 (0.14) ***
$S_{ProdS, MU\text{-}FI}(y)$		2.14 (0.17) ***		0.54 (0.19) **
$S_{ProdS, MU\text{-}TR}(y)$		6.69 (0.30) ***		4.61 (0.14) ***
$S_{ProdS, FA\text{-}MU}(y)$		0.91 (1.00)		- 2.05 (1.82)
$S_{ProdS, FA\text{-}FA}(y)$		0.81 (1.00)		- 0.66 (0.43)
$S_{ProdS, FA\text{-}FF}(y)$		2.02 (0.17) ***		0.60 (0.20) **
$S_{ProdS, FA\text{-}FI}(y)$		3.38 (0.12) ***		2.01 (0.16) ***
$S_{ProdS, FA\text{-}TR}(y)$		6.38 (0.32) ***		5.08 (0.76) ***
$S_{ProdS, FF\text{-}MU}(y)$		- 1.17 (0.71)		-3.69 (0.96) ***
$S_{ProdS, FF\text{-}FA}(y)$		- 0.24 (0.42)		-1.58 (0.50) **
$S_{ProdS, FF\text{-}FF}(y)$		0.85 (0.12) ***		- 0.21 (0.14)
$S_{ProdS, FF\text{-}FI}(y)$		2.57 (0.10) ***		1.57 (0.12) ***
$S_{ProdS, FF\text{-}TR}(y)$		6.80 (0.14) ***		5.81 (0.19) ***
$S_{ProdS, FI\text{-}MU}(y)$		- 0.64 (0.59)		-1.10 (0.76)
$S_{ProdS, FI\text{-}FA}(y)$		- 0.82 (0.59)		- 1.40 (0.73)
$S_{ProdS, FI\text{--}FF}(y)$		- 1.33 (0.22) ***		-1.73 (0.25) ***
$S_{ProdS, FI\text{--}FI}(y)$		Reference		Reference
$S_{ProdS, FI\text{--}TR}(y)$		3.55 (0.31) ***		3.41 (0.40) ***
$S_{ProdS, TR\text{-}MU}(y)$		NA		NA
$S_{ProdS, TR\text{-}FA}(y)$		NA		NA
$S_{ProdS, TR\text{-}FF}(y)$		2.71 (0.72) ***		1.23 (1.33)
$S_{ProdS, TR\text{-}FI}(y)$		3.43 (0.51) ***		1.87 (0.70) **
$S_{ProdS, TR\text{-}TR}(y)$		NA		NA
AIC	53087	40600	49312	39845

[a] *** : <0.001; ** <0.01; * <0.05; [b] for readability, values for main effects for the pig companies are not shown but are significant for the ‘edges + attributes’ and the ‘edge + attributes + network statistics’ models

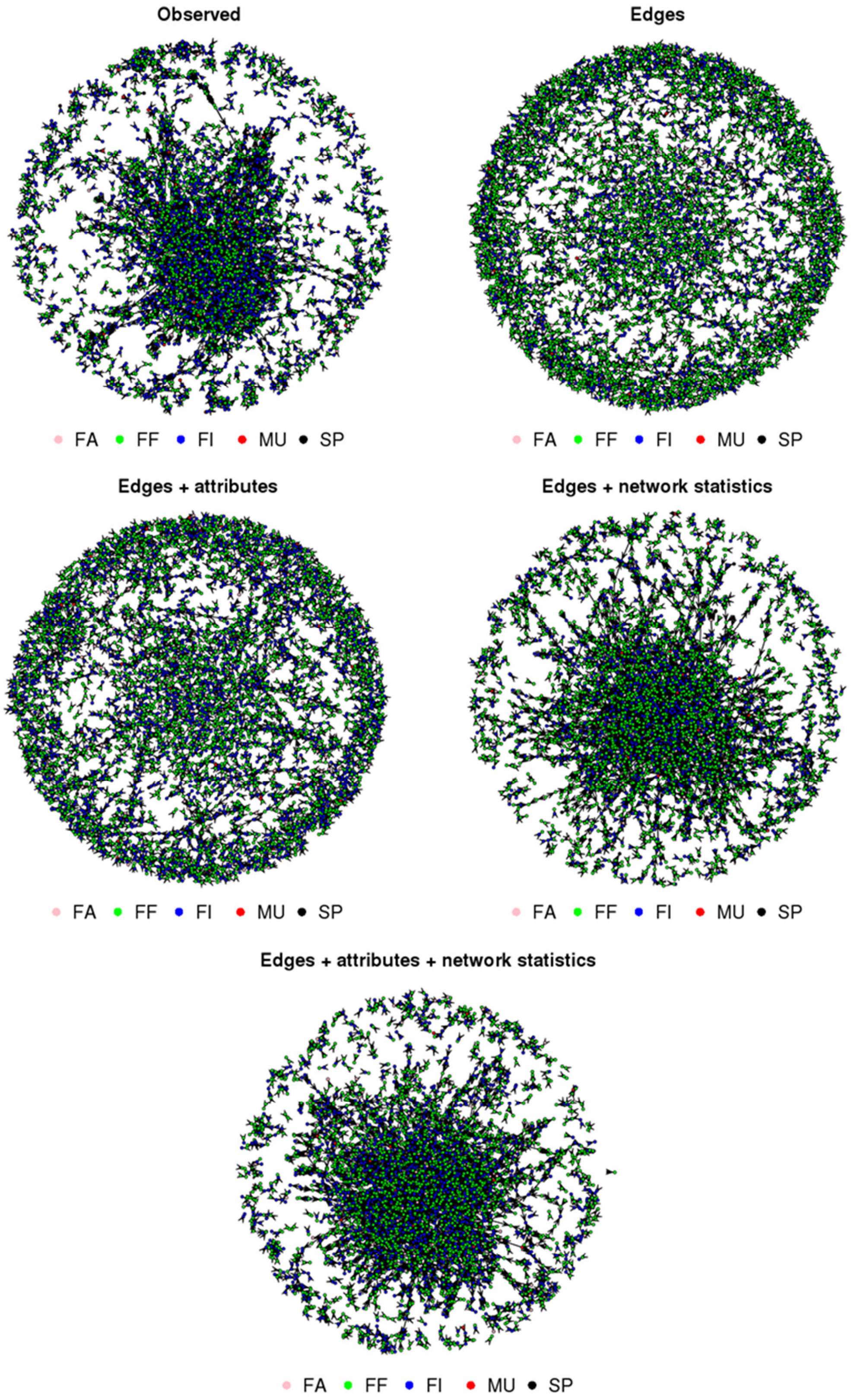


Fig. 3 Observed and simulated trade networks based on the final models in an extensive pig production system (Spain – Extremadura – 2011; nodes coloured according to their type of production: MU = multipliers; FA = farrowers; FF = farrow-to-finishers; FI = finishers; SP = small producers)

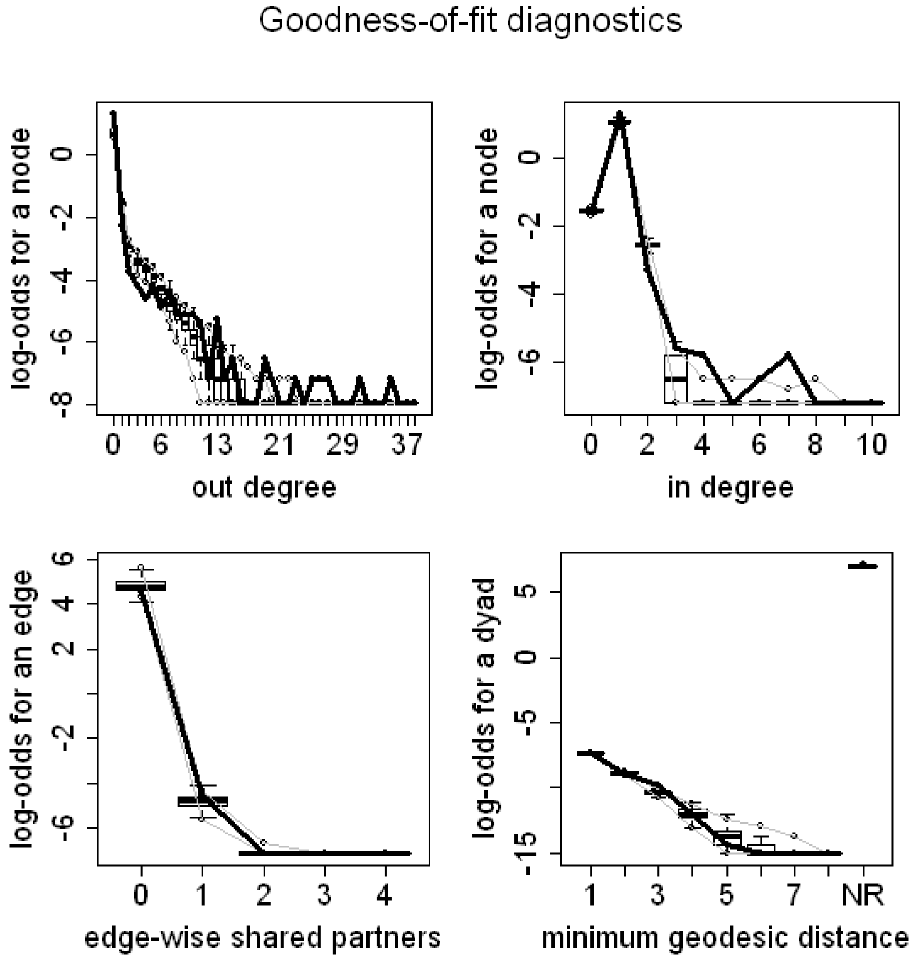


Fig. 4 Goodness-of-fit diagnosis for the final model "Edges + attributes + network statistics" in the small-scale production system (Bulgaria – 2011)

DISCUSSION

ERGMs were used to represent, understand and predict pig trade networks structures from different European production systems, with predominantly small-scale, extensive or intensive pig producers. Such information improved our understanding of the processes that govern the organisation of pig trade and can further be used to better inform European policy makers on prevention and control measures against swine diseases such as African or classical swine fevers through infectious disease modelling.

Until recently, problems of degeneracy and computational intractability for large network sizes limited the use of ERGMs in epidemiological modelling (Goodreau, 2007; Danon et al., 2011). Indeed, ERGMs have been mainly used on small networks to understand the factors driving human social behaviours (Goodreau et al., 2009; Cheadle & Schwadel, 2012), and have sometimes been applied to disease transmission modelling (Potter et al., 2012). Ortiz-Pelaez et al. (2012) were the first to introduce ERGMs in preventive veterinary medicine, using this method to understand the factors driving livestock trade in a small network of villages in Ethiopia.

In this study, the use of new parameters that limit degeneracy problems (Snijders et al., 2006) allowed us to obtain statistical models with a good fit to the large-size observed networks. These models confirmed the impact of management factors, such as the pyramidal organisation of pig production or the tendency of premises of the same pig companies to trade with each other in industrial production systems. If including nodal attributes was necessary to represent the mixing patterns, it was not sufficient to reproduce the great clustering observed in the trade networks, which could only be represented when adding additional statistics on local network configurations. These statistics reveal some features of these networks such as the propensity of trade to have a short path length (negative coefficient for the degree distribution terms). Some social behaviour or unobserved covariates may also have driven the choices of farmers for trading partners, which increased clustering as represented by the positive coefficient for the *gwesp* term.

Since implementation of Regulation (EC) n° 1760/2000 of the European parliament, recording of livestock movements between premises is mandatory, making data on pig trade movements available, at least in the main producing countries in the EU. However, there are no standards of referencing premises characteristics information. The scales of the networks considered in this study were also different, being at national level for Bulgaria and at regional level for France and Spain. Therefore mechanisms and rules that govern trade organisation in the different production systems are not fully comparable.

This study still highlighted some similarities and key differences among production systems in the mechanisms driving live pig trade. For all systems, flow of live pigs is governed by the specialisation and organisation of pig production. The housing system and belonging to a pig company were key parameters in extensive and intensive production systems, respectively, whereas regional flows strongly structured pig trade organisation in the small-scale production system.

Results of this study can be useful to simplify epidemic models. Their final validation should be made by comparing their performances between epidemic models built on these network models and on raw movements' data, in terms of computational time and epidemic parameters (epidemic size, spatio-temporal repartition of the outbreaks etc.).

ACKNOWLEDGEMENTS

The research leading to these results received funding from the European Union, Seventh Framework Programme [*FP7/2007-2013*] under *grant agreement* n° 311931 (ASFORCE). The authors are very grateful to BFSA, BDPORC and MAGRAMA for providing the data.

REFERENCES

Bigras-Poulin, M., Barfod, K., Mortensen, S. and Greiner, M. (2007). Relationship of trade patterns of the Danish swine industry animal movements network to potential disease spread. Prev. Vet. Med. 80, 143-165

Cheadle, J.E. and Schwadel, P. (2012). The 'friendship dynamics of religion,' or the 'religious dynamics of friendship' A social network analysis of adolescents who attend small schools. Soc. Sci. Res. 41, 1198-1212

Costard, S., Mur, L., Lubroth, J., Sanchez-Vizcaino, J.M. and Pfeiffer, D.U. (2013). Epidemiology of African swine fever virus. Virus Res. 173, 191-197

Danon, L., Ford, A.P., House, T., Jewell, C.P., Keeling, M.J., Roberts, G.O., Ross, J.V. and Vernon, M.C. (2011). Networks and the Epidemiology of Infectious Disease. Interdiscip. Perspect. Infect. Dis. 2011, 1-28

Dorjee, S., Revie, C.W., Poljak, Z., McNab, W.B. and Sanchez, J. (2013). Network analysis of swine shipments in Ontario, Canada, to support disease spread modelling and risk-based disease management. Prev. Vet. Med. 112, 118-127

Dube, C., Ribble, C., Kelton, D. and McNab, B. (2009). A review of network analysis terminology and its application to foot-and-mouth disease modelling and policy development. Transbound. Emerg. Dis. 56, 73-85

Fritzemeier, J., Teuffert, J., Greiser-Wilke, I., Staubach, C., Schlüter, H. and Moennig, V. (2000). Epidemiology of classical swine fever in Germany in the 1990s. Vet. Microbiol. 77, 29-41

Goodreau, S.M. (2007). Advances in exponential random graph (p*) models applied to a large social network. Soc. Netw. 29, 231-248

Goodreau, S.M., Handcock, M.S., Hunter, D.R., Butts, C.T. and Morris, M. (2008). A statnet Tutorial. J. Stat. Softw. 24, 1-25

Goodreau, S.M., Kitts, J.A. and Morris, M. (2009). Birds of a Feather, or Friend of a Friend? Using Exponential Random Graph Models to Investigate Adolescent Social Networks. Demogr. 46, 103-125

Handcock, M.S., Hunter, D.R., Butts, C.T., Goodreau, S.M., Krivitsky, P., Bender-deMoll, S. and Morris, M. (2014). statnet: Software tools for the Statistical Analysis of Network Data. The Statnet Project, http://www.statnet.org

Handcock, M.S., Hunter, D.R., Butts, C.T., Goodreau, S.M. and Morris, M. (2008). statnet: Software Tools for the Representation, Visualization, Analysis and Simulation of Network Data. J. Stat. Softw. 24, 1-11

Holland, P.W. and Leinhardt, S. (1981). An exponential family of probability distributions for directed graphs. J. Amer. Stat. Assoc. 76, 33-50

Hunter, D.R., Goodreau, S.M. and Handcock, M.S. (2008). Goodness of Fit of Social Network Models. J. Amer. Stat. Assoc. 103, 248-258

Hunter, D.R. and Handcock, M.S. (2006). Inference in Curved Exponential Family Models for Networks. J. Comput. Gr. Stat. 15, 565-583

Martinez-Lopez, B., Ivorra, B., Ramos, A.M., Fernandez-Carrion, E., Alexandrov, T. and Sanchez-Vizcaino, J.M. (2013). Evaluation of the risk of classical swine fever (CSF) spread from backyard pigs to other domestic pigs by using the spatial stochastic disease spread model Be-FAST: The example of Bulgaria. Vet. Microbiol. 165, 79-85

Martinez-Lopez, B., Perez, A.M. and Sanchez-Vizcaino, J.M. (2009). Social network analysis. Review of general concepts and use in preventive veterinary medicine. Transbound. Emerg. Dis. 56, 109-120

Morris, M. (1991). A log-linear modeling framework for selective mixing. Math. Biosci. 107, 349-377

Ortiz-Pelaez, A., Ashenafi, G., Roger, F. and Waret-Szkuta, A. (2012). Can Geographical Factors Determine the Choices of Farmers in the Ethiopian Highlands to Trade in Livestock Markets? PLOS ONE 7, e30710

Potter, G.E., Handcock, M.S., Longini Jr, I.M. and Halloran, M.E. (2012). Estimating within-school contact networks to understand influenza transmission. Ann. Appl. Stat. 6, 1-26

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/

Robins, G., Pattison, P., Kalish, Y. and Lusher, D. (2007). An introduction to exponential random graph (p*) models for social networks. Soc. Netw. 29, 173-191

Shirley, M.D.F. and Rushton, S.P. (2005). Where diseases and networks collide: lessons to be learnt from a study of the 2001 foot-and-mouth disease epidemic. Epid. Infect. 133, 1023-1032

Snijders, T.A.B., Pattison, P.E., Robins, G.L. and Handcock, M.S. (2006). New specifications for exponential random graph models. Soc. Methodol. 36, 99-153

Wasserman, S. and Pattison, P. (1996). Logit models and logistic regressions for social networks: I. An introduction to Markov graphs and p*. Psychom. 61, 401-425

ECONOMICS APPLIED TO ANIMAL HEALTH

BENEFIT-COST MAPPING OF INTERVENTIONS TO COMBAT BOVINE TRYPANOSOMOSIS IN EASTERN AFRICA

A.P.M. SHAW*, G.R.W. WINT, G. CECCHI, S.J. TORR, R.C. MATTIOLI AND T.P. ROBINSON

SUMMARY

This study builds on earlier work analysing the costs of a range of interventions to combat bovine trypanosomosis and mapping potential benefits to livestock keepers in eastern Africa. Updated intervention costs reflect price changes and recent field studies. A series of benefit-cost ratio maps illustrates the potential profitability of control using trypanocides, targets, aerial spraying or insecticide-treated cattle and of elimination using the latter three techniques and the sterile insect technique. For all approaches, returns vary substantially but areas such as the mixed farming, high oxen use areas of western Ethiopia, the crescent north of Lake Victoria and the dairy production areas in western and central Kenya stand out as offering the highest returns. The assumptions and uncertainties underpinning these variations are discussed.

INTRODUCTION

Tsetse-transmitted trypanosomosis is confined to the African continent, where it affects people and animals across a swathe including all or parts of 39 countries, commonly referred to as the ‘tsetse belt’ within which tsetse populations are often fragmented or discontinuous, especially on the fringes of their distribution. The direct impact of the disease on the health of the human and animal populations living alongside tsetse also varies, as do the indirect constraints on more intensive, improved or diversified livestock production and, to a lesser extent, on other forms of land use from cropping to tourism. Differences in habitats and tsetse species composition compound the spatial heterogeneity in the impact of trypanosomosis. This has important implications for decision-making that are difficult to capture through individual location-specific studies.

The last two decades have seen the growing application of geographic information systems (GIS) to the study of the tsetse/trypanosomosis problem, mapping tsetse and host distributions, foci of human African trypanosomosis (HAT), disease risk, (e.g. Robinson, 1998; Wint & Rogers, 2000; de La Rocque et al., 2005; Wint & Robinson, 2007; Simarro et al., 2012; Cecchi et al., 2014). The potential benefits to cattle keepers from animal trypanosomosis control in western and eastern Africa were mapped by Shaw et al. (2006) and Shaw et al. (2014). On the cost side, the interest in evidence-based decision-making and prioritisation has been supported by analyses of recent interventions (Adam et al., 2013; Bouyer et al., 2014). The range of applicability and cost of different interventions also have

---

* Alexandra Shaw, AP Consultants, 22 Walworth Enterprise Centre, Duke Close, Andover, SP10 5AP, United Kingdom. Email: alex@apconsultants.co.uk

marked spatial characteristics which could be captured by mapping costs and then comparing them to mapped benefits.

MATERIALS AND METHODS

This work builds on the benefit maps produced for six countries of eastern Africa (Shaw et al., 2014) and the cost calculations and approach of Shaw et al. (2013a). The former mapped potential benefits of the removal of trypanosomosis in cattle, based on herd models for twelve cattle production systems. It has now been possible to refine and update the costs by incorporating new knowledge on cost levels or applying an appropriate inflation rate. As before, the costs used applied to Uganda, validated against those of other countries studied. The inflation rates were derived using the Uganda Consumer Price Index for non-food items and converting from Ugandan Shillings to US dollars (USD) using the historical rates given by FX Oanda (http://www.oanda.com/currency/historical-rates-classic). On this basis, by 2013, prices had increased by 27.1% since 2006 and 11.2% since 2009.

The twenty-year time horizon was retained for both benefits and costs, with a preparatory year 0 added to the costs, with benefits starting in year 1. This long period made it possible to compare the two main strategic options for dealing with African trypanosomosis – sustained control operations (continuous control) or the creation of permanent tsetse free zones (elimination). A discount rate of 10% was applied to all benefits and costs. Five interventions were analysed.

Interventions

Trypanocides are regularly used by cattle keepers, both curatively and prophylactically. One option for continuous control is to administer isometamidium chloride, which is primarily prophylactic, and is effective for about 3 months, depending on the cattle breed and level of tsetse challenge. Its current rural price is estimated at USD 1.93 for a 300 kg adult dose or USD 1.35 for the average bovine (210 kg) (personal communication, Dennis Muhanguzi, 2014). At current prices, delivery costs are USD 0.65 (updated from Shaw et al., 2014), bringing the cost per dose to USD 2.00 or USD 8.00/year if administered every 3 months.

Insecticide-treated traps and targets act as stationary baits against tsetse for both control and elimination. Here, costs were estimated for two target-based control options. The first uses standard 1 m^2 targets with odour baits, suitable for use against both savanna and riverine tsetse species. For savanna tsetse, 4 targets km^{-2} were costed. Where riverine species were present this number was increased to 10 km^{-2} (Shaw et al., 2013a). This overall density resulted in much higher effective densities as traps are deployed only in riparian vegetation where riverine tsetse species are found. Target costs were adapted from Shaw et al. (2013a) by applying inflation and replacing trap with target costs, yielding USD 252 and 629 km^{-2} for densities of 4 and 10 km^{-2}, respectively.

However, where only riverine tsetse are present, odour baits are not required and much smaller 0.5 x 0.25 m 'tiny targets' can be highly effective (Esterhuizen et al., 2011). These can be transported by bicycle or motorcycle, leading to much lower logistics costs than for installing and servicing conventional targets. The costs of these were calculated from information supplied by the research team (Kovacic et al., 2013) for their target deployment project in Arua District of Uganda where 6 targets were deployed km^{-2}. Logistics costs were increased by 50% to allow for more isolated areas and 10 rather than 6 targets km^{-2} were allowed for. This yielded a cost for control of USD 142 km^{-2}. For elimination scenarios, target operations were extended to 18 months, but the same densities km^{-2} were used as for control.

Insecticide-treated cattle (ITC) act as mobile baits from which both tsetse and ticks pick up a lethal dose of insecticide. This can be highly effective for controlling tsetse and reducing the prevalence and impact of AAT (e.g. Rowlands et al., 1999; Muhanguzi et al., 2014). The insecticide can be applied as a pour-on or by spraying. The approach costed here assumes the restricted application protocol (Muhanguzi et al., 2014) whereby insecticide is only applied to the preferred feeding sites of tsetse and ticks: the legs, belly and ears. The cost of insecticide and delivery is USD 0.60 per bovine (personal communication: Dennis Muhanguzi and Walter Okello, 2014). Within cattle herds, tsetse prefer feeding on larger animals, so treating 4 large bovines monthly km^{-2} would be sufficient for control or elimination of all tsetse species (Vale and Torr, 2004). To add a safety margin, the number was increased to 5. As about 50% of cattle in the region are adults, this technique can only be used where there are at least 10 cattle km^{-2}. Also, at least 10% of the flies' bloodmeals must be taken from treated hosts (as discussed in Shaw et al., 2013a). Thus, at cattle population densities greater than 50 km^{-2}, where cattle are likely to be the predominant source of bloodmeals, costs were based on treating 10% of the herd.

Though unproven in field conditions, modelling indicates that ITC applied on a sufficiently large scale could be effective in eliminating tsetse (Hargrove, 2003), if isolated from tsetse reinvasion. Accordingly, in this analysis, for the elimination scenario, twice as many annual treatments were costed – thus either doubling the number or the frequency of cattle treated. As with targets, where ITC could be used as a barrier to reinvasion, these numbers were again doubled, so that a minimum threshold of 20 cattle km^{-2} was set.

Aerial spraying, using the Sequential Aerosol Technique (SAT**)**, involves 5 cycles of spraying insecticide from fixed wing aircraft. It has been shown to be effective in eliminating tsetse (Kgori et al., 2006) although difficulties have been encountered with riverine tsetse species in areas of dense vegetation (Adam et al., 2013). Adjusting the Shaw et al. (2013a) SAT estimates for inflation gives USD 483 km^{-2} which is very close to the cost figure of USD 492 km^{-2} derived from Adam et al. (2013) if 9.7% is added for permanent staff salaries and depreciation (Shaw et al., 2013a). SAT has also been used for sporadic control interventions to deal with increased incidences of HAT or AAT. Accordingly, as well as costing for elimination, a cost deploying SAT at 3-year intervals was included for control. SAT is not suitable for rugged terrain.

The use of the Sterile Insect Technique (SIT) is exclusively recommended where the strategic objective is elimination following tsetse suppression using other tsetse control methods (Feldmann, 2004). Sterile male tsetse flies are released from fixed wing aircraft in sufficient numbers to outcompete wild males in mating with the females, rendering them sterile. The costs of this technique were estimated by Shaw et al. (2013a) at USD 758 km^{-2}, for an area of 10,000 km^2, based on information from ADB et al. (2004) and Feldmann (2004). Bouyer et al. (2014) indicate field costs of the SIT component to be USD 4,900 (EUR 3,800) km^{-2} for a project covering 1,000 km^2 in Senegal. This relatively high cost is similar to the inflation-adjusted USD 5100 km^{-2} reported by Msangi et al. (2000) for a similarly small (1,600 km^2) operation on Unguja Island. Operations involving aircraft are very sensitive to scale: aerial survey costs per unit area for 10,000 km^2 surveys in west Africa are 38% and 59% of that estimated for 1,000 and 2,000 km^2 operations respectively (Resource and

Inventory Management, unpublished information). The elimination options costed here follow Shaw et al. (2013a) and are based on an area of 10,000 km^2. Accordingly, these estimates are based on Bouyer et al. (2014), but apply a scale deflator of 40% to the sum of flying time, the cost of sterile males and other field costs for SIT. This yielded a figure of USD 1,458 km^{-2} for adding an SIT component for one species. Where more than one tsetse species is present, economies of scale should allow a further 20% reduction in the cost of sterile males, and increase flying costs by only 15% (personal communication, U. Feldmann, 2011). Assuming an increase of 20% in overheads, the cost for each additional tsetse species present would reach USD 838 km^{-2}.

Overheads

Overheads are defined here as administrative/office costs of control and elimination programmes, plus any added research costs involved in entomological and parasitological studies for elimination as detailed in Shaw et al. (2013a) and adjusted for inflation and rounded up to avoid spurious accuracy. Projects often include significant research components – thus Bouyer et al. (2014) report the cost of studies and preparation at over USD 2,000 km^{-2}. For the control strategies, aerial spraying would require significant preparation and oversight, so 20% was added to costs. For targets and ITC the 10% overheads figure was confirmed by field data from the work reported on in Kovacic et al. (2013) and Muhanguzi et al. (2014). As trypanocide use is well established in the region a 5% overhead is used.

Barriers to reinvasion

To achieve and sustain elimination when the targeted tsetse populations are not isolated a ‘barrier’ around the cleared area is needed to prevent reinvasion by tsetse. These barriers may be permanent or, if the cleared area is to be expanded, temporary. Barrier maintenance using either targets or ITC was costed at twice the densities used for elimination, lasting for five years following elimination, and barriers were deployed in 10% of the cleared areas (Shaw et al., 2013a). Rather than trying to precisely locate barriers, the cost of the barrier was ‘spread’ over the whole intervention area, by adding a barrier cost to 10% of every km^2 cleared.

Mapping benefit-cost ratios

As a first step to mapping benefit cost ratios (BCRs), the costs were mapped. This involved combining costs that were incurred per bovine (trypanocides, ITC) with those that were calculated per km^2 (targets, SAT and SIT). The suitability criteria for each technique was then applied to map the costs (minimum cattle densities for ITC, presence of riverine, savanna or mixed tsetse infestations for targets, exclusion of rugged terrain for SAT and SIT and number of fly species for SIT). For the elimination scenarios, these criteria also applied to the barriers, with the cheaper option of ITC selected where cattle densities were sufficient.

To obtain the final BCRs, the mapped benefits derived in Shaw et al. (2014) were divided by the mapped costs. First, the costs were converted to 2009 values to match the benefits, reflecting the 11.2% inflation rate. Secondly, assumptions had to be made regarding the proportion of potential benefits that could be ‘harvested’ by each technique. Subsequent to elimination, it was assumed that all losses due to the disease within the cleared area would be avoided, except in barrier areas, where only half would be avoided. This implies that overall 95% of losses (90% plus half of 10%) would be avoided. For the three ‘full time’ control strategies the percentage was set at 75%. This is a relatively low, conservative figure: good levels of control remove almost all losses due to the disease (Rowlands et al., 1999, Muhanguzi et al., 2014). For the 3-yearly applications of SAT a lower figure of 60% was applied. This reflects evidence (Hargrove, 2000) that a tsetse population reinvasion front can move at 6 km per year where reinvasion occurs from one direction, but where reinvasion occurs from all directions, an area of 10,000 km^2 could be reinvaded within two years.

Lastly, some of the benefits of improved cattle health would be transferred to areas outside the tsetse-infested zones, as cattle populations expand and migrate to new areas (Shaw et al., 2014). Because these benefits occur outside the intervention areas, they could not be mapped as BCRs, as they have no spatially associated costs.

RESULTS

The costs obtained are summarised in Tables 1 (control) and 2 (elimination). Costs per bovine increase in line with projected average annual cattle population growth (2.9%) over the period analysed and are discounted to their present value in the first year and expressed as a value/bovine present at the start of the analysis. Present values are over 21 years, including year zero, discounted at 10%. Trypanocides are the cheapest control option, at cattle densities below those that would sustain ITC. Otherwise, ITC is the most cost-effective option. The 'tiny target' technology allows for low cost control in areas where only riverine tsetse are present. Used only every 3 years, SAT is relatively cheap – but should be balanced against the risk of tsetse reinvasion that could be expected between applications. If SAT were applied every second year, the discounted cost over the whole time period would increase to USD 4,142 and, if every year, to USD 5,515.

Table 1. Estimated costs of tsetse and trypanosomosis control using different techniques

Technique and applicability	Annual Field Cost USD	Administrative overheads %	Total discounted cost over 21 years USD
Trypanocide prophylaxis			
4 doses per bovine per year	8.0 per bovine	5%	98 per bovine
ITC (insecticide-treated cattle)			
< 10 cattle km^{-2}		Technique not feasible	
10-50 cattle km^{-2}	36 km^{-2}	5%	441 km^{-2}
>50 cattle km^{-2}	0.07 per bovine	5%	8.8 per bovine
Targets			
Savanna (4 targets km^{-2})	252 km^{-2}	10%	2,634 km^{-2}
Riverine (10 tiny targets km^{-2})	142 km^{-2}	10%	1,484 km^{-2}
Riverine + savanna (10 km^{-2})	629 km^{-2}	10%	6,585 km^{-2}
SAT (aerial spraying)			
Applied every 3 years (non rugged areas only); total of 7 applications	483 every 3 years	20% every 3 years	3,104 km^{-2}

Building up the costs of elimination (Table 2) was far more complex, because of the need to factor in the applicability criteria for barriers and, for SIT, for the initial suppression preceding its deployment. This created 8 SIT options, with extra costs for additional sterile male releases if several fly species were present. Elimination strategies fall roughly into three cost bands: under USD 500 for ITC, over USD 2,000 for SIT and between USD 800 and 2,000 for SAT and targets, depending on fly species and cattle population densities.

Table 2. Estimated costs of 'large scale' tsetse elimination using different techniques

Technique and applicability[a]	Overheads USD km^{-2}	Initial tsetse suppression USD km^{-2}	Field cost of main technique USD km^{-2}	Cost of Barriers USD km^{-2}	Total discounted cost USD km^{-2}
ITC (insecticide-treated cattle)					
< 20 cattle km^{-2}					Not feasible
20-50 cattle km^{-2}	250	0	105	76	430
>50 cattle km^{-2}	250	0	2.10 / bovine	1.52 / bovine	250 plus 3.62 / bovine
SAT (aerial spraying)					
< 20 cattle km^{-2} savanna tsetse only	250	0	483	290	1,023
< 20 cattle km^{-2} riverine tsetse only	250	0	483	163	896
< 20 cattle km^{-2} sav. + riv. tsetse	250	0	483	724	1,457
20-50 cattle km^{-2}	250	0	483	88	821
>50 cattle km^{-2}	250	0	483	1.77/bovine	733 plus 1.77/bovine
Targets					
Savanna (4 targets km^{-2})	250	0	352	246	848
Riverine (10 tiny targets km^{-2})	250		288	138	676
Riverine + savanna (10 km^{-2})	250	0	881	614	1,745
SIT for one tsetse species					
< 20 cattle savanna, not rugged	350	483	1,458	339	2,630
< 20 cattle riverine only, not rugged	350	483	1,458	191	2,482
< 20 cattle sav. and riv., not rugged	350	483	1,458	848	3,139
< 20 cattle savanna, rugged	350	352	1,458	339	2,499
< 20 cattle riverine only, rugged	350	288	1,458	191	2,287
< 20 cattle sav. and riv., rugged	350	881	1,458	847	3,536
20-50 cattle km^{-2}	350	105	1,458	93	2,006
>50 cattle km^{-2}	350	2.10/bovine	1,458	1.85/bovine	1,808 plus 3.95/bovine
SIT more than one tsetse species	Add USD 838 km^{-2} per additional species.				

[a] Costs are USD km^{-2} unless otherwise indicated.

The BCRs are illustrated in Fig. 1 (control) and Fig. 2 (elimination). The areas which are either unsuitable for cattle production or do not contain tsetse are shown in white as "0". The areas where the techniques' benefits do not cover costs are those with BCRs of less than one. The areas where a modest return is achieved are those with BCRs between 1 and 2, those with a good return, 2 to 5. Areas with higher BCRs than this offer a very attractive return on investment.

The maps show that, for all control and elimination interventions, certain areas offer high returns. These 'high return areas' are parts of western Ethiopia, with its high work oxen numbers, intensive dairying areas of central and western Kenya and the area bordering the north of Lake Victoria. BCRs are also relatively high for the Somalia and Kenya coasts, north-eastern Uganda, neighbouring South Sudan, and the southernmost part of Sudan.

Of the control scenarios, trypanocides consistently achieve BCRs > 1, and exceed 2 in the core 'high return areas'. In contrast, for SAT and targets, BCRs are <1 over much of the area, although targets do achieve BCRs >10 in parts of western Ethiopia, the Kenya/Somalia coast and the Lake Victoria crescent, especially where only riverine flies are present. SAT, as a control technique, seldom achieves BCRs over 2. Lastly, as ITC is restricted to areas with over 10 cattle km^2, and is linked to the distribution of cattle, the unit of benefit, it is both relatively cheap and mostly yields BCRs of >5, achieving >10 in much of the area. The maps also show that where ITC cannot be used, the BCRs of targets and SAT are also < 1. In these regions, trypanocides are the only option which yields a return, which has to be weighed against the risk of emerging drug resistance at high levels of use (Geerts et al., 2001).

Turning to elimination, the BCRs are similarly distributed, but generally higher. For ITC, the increase in the stipulated minimum cattle density from 10 to 20 cattle km-2 reduces the areas of its applicability, but BCRs remain high: almost all over 10, a high proportion over 15. The maps for aerial spraying and targets are similar, with some areas accessible to targets not being suitable for SAT. SIT yields high returns in the core of the 'high return areas'.

DISCUSSION

Thus, despite the many assumptions made and inevitable uncertainties in the modelling, these maps paint a very diverse picture and point to some clear patterns. Nevertheless, in order to interpret these, some of the key discussion points must be revisited.

Scale is an important factor in this interpretation. Whereas the control scenarios (with the exception of SAT) can mostly be applied at smaller scales, the elimination scenarios are predicated on large scale interventions (10,000 km^2 as in Shaw et al., 2013a).

The choice of BCR to quantify economic returns makes the results independent of a particular time period and set of prices. It enables the decision-maker to choose a BCR threshold to meet expectations or even implicitly adjust the assumptions made in the analysis. Thus, if, for example, it proves possible to deliver odour-baited targets or traps for controlling savanna fly populations more cheaply, the benefit cost ratios for these would increase, and could be readily visualised. Furthermore, where foci of HAT exist, interventions to control or eliminate tsetse would deliver sizeable further benefits.

These maps aim to identify where interventions other than trypanocide use are profitable and thence to help inform the choice between interventions and strategies. Most field interventions integrate several approaches – for example using traps or targets alongside ITC where there are specific areas with no cattle. Mapping BCRs for combinations of techniques was not addressed in this study as it would involve a huge range of options with outcomes that would be difficult to evaluate. The single method approach provides a baseline from which to assess combinations of the costs given in Tables 1 and 2 and to compare relative costs.

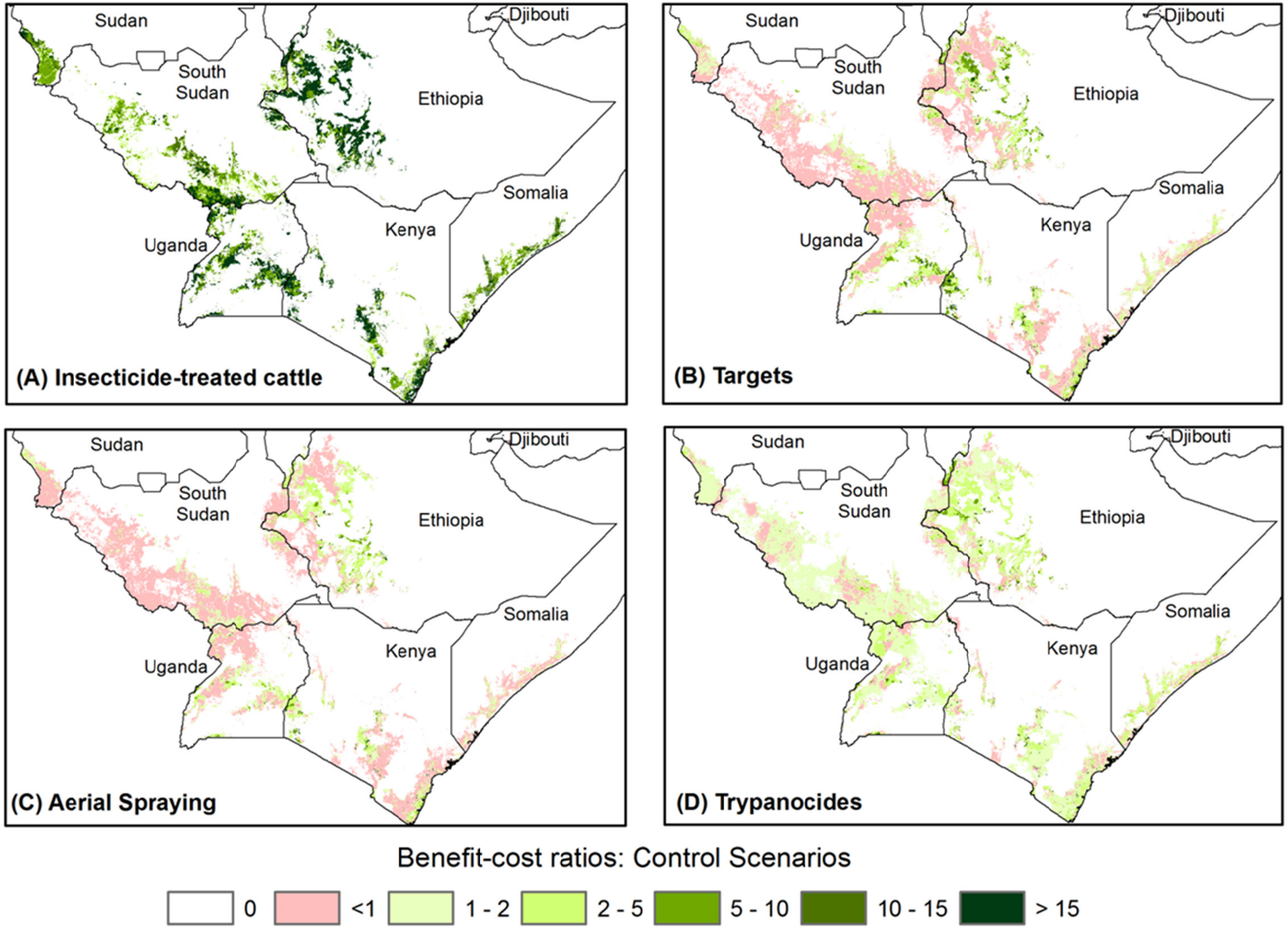


Fig. 1 Estimated benefit-cost ratios for four options for long term bovine trypanosomosis control

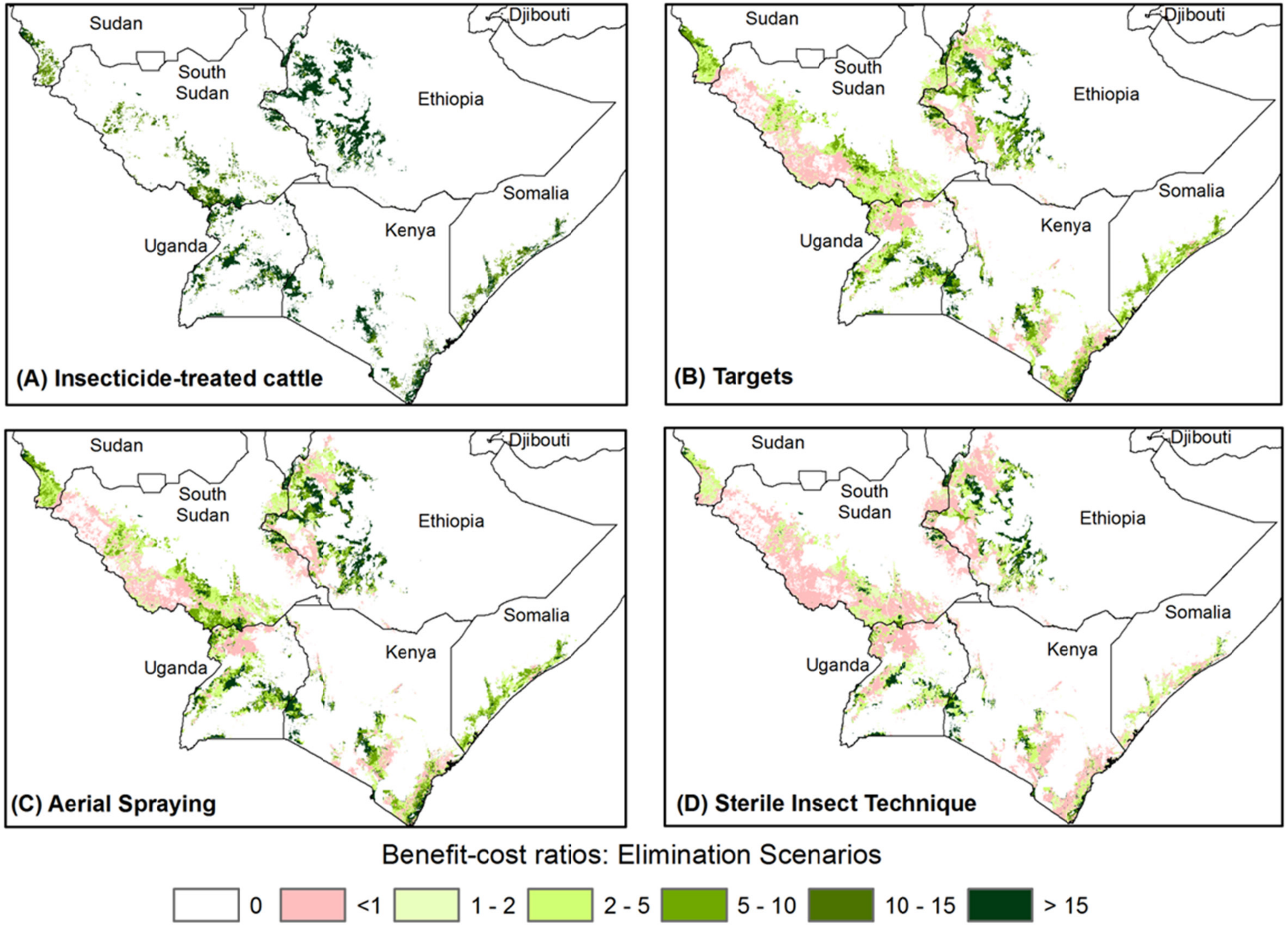


Fig. 2 Estimated benefit-cost ratios for four options for large scale tsetse elimination

The issues around the feasibility and sustainability of elimination have been frequently debated (e.g. Hargrove, 2003), most recently in the context of costing interventions (Bouyer et al., 2013, Shaw et al., 2013b). The issue is ultimately an entomological one and beyond the scope of this paper. In this analysis, the assumptions relating to elimination are very favourable – i.e. techniques are assumed to be implemented in an ideal manner, to follow the predictions of available entomological models, and to be free from disruptions. Barriers are always costed, but in only 10% of the area and only for 5 years following elimination while for SIT a relatively modest cost is used. Conversely, the use of a relatively high, 10%, discount rate is less advantageous to elimination than a lower rate would be. For the control strategies, very conservative assumptions about impact (preventing 60 – 75% of disease losses) have been made. Although presenting elimination in a relatively favourable light, the mapped BCRs for elimination do not always show overwhelmingly higher returns than for control. The feasibility, success and economic return of control operations are well documented, whereas elimination is subject to far greater uncertainties. The maps reinforce the view that, in many contexts, control scenarios should be pursued independently as a highly economically viable strategy, using current low cost options that can be applied by livestock keepers and/or appropriate local government departments, ideally supporting each other.

Despite the operational and technical uncertainties involved in analysing interventions against African trypanosomosis, this analysis does demonstrate that a spatial visualisation of the potential economic returns provides substantial information and insights for decision-making. While maps have been extensively used in epidemiology and some monetary human health indicators have been mapped, it is only in the fields of transport economics and environment that monetary maps seem to have been adopted (e.g. Naidoo & Rickets, 2006). The approach used here to map the BCRs of interventions could be of wider applicability in the field of vector-borne and/or endemic livestock diseases as well as other agricultural contexts, such as crop pests.

ACKNOWLEDGEMENTS

This work was jointly funded by FAO's Pro-poor Livestock Policy Initiative, under a grant from the UK's DfID and The Programme Against African Trypanosomosis, in particular by the Government of Italy through the FAO Trust Fund for Food Security and Food Safety (Project "Improving food security in sub-Saharan Africa by supporting the progressive reduction of tsetse-transmitted trypanosomosis in the framework of the NEPAD" - GTFS/RAF/474/ITA). The authors are grateful to Udo Feldmann for comments and suggestions. Dennis Muhanguzi, Walter Okello, Anne Holm Rannaleet, John David Kabasa, Charles Waiswa and Sue Welburn of the Stamp out Sleeping Sickness project in Uganda and the Integrated Control of Neglected Zoonoses in Africa project are thanked for providing information on the field costs of using insecticide-treated cattle and trypanocides in Uganda. Vanja Kovacic, Mike Lehane, Inaki Tirados, Johan Esterhuizen and Clement Mangwiro are thanked for information on the costs of deploying tiny targets, undertaken as part of the project "Targeting tsetse: use of targets to eliminate African sleeping sickness" BGMF /LSTM 1017770.

REFERENCES

Adam,Y., Cecchi, G., Kgori, P.M., Marcotty, T., Mahama, C.I., Abavana, M., Anderson, B., Paone, M., Mattioli, R. and Bouyer, J. (2103). The sequential aerosol technique: a major component in an integrated strategy of intervention against Riverine Tsetse in Ghana. PLoS Negl Trop Dis. 7, e2135

ADB, IAEA and PATTEC (2004). Integrated area-wide programme for trypanosomiasis-free zones in Uganda. African Development Bank, International Atomic Energy Authority, Pan African Tsetse and Trypanosomosis Eradication Campaign, Uganda, 111p

Bouyer J, Seck, M.T. and Sall B (2013). Misleading guidance for decision making on tsetse eradication: Response to Shaw et al. (2013). Prev. Vet. Med. 1122013: 443–446

Bouyer, F., Seck, M.T., Dicko, A.H., Sall, B., Lo, M., Vreysen, M.J.B., Chia, E., Bouyer, J. and Wane, A. (2014). Ex-ante Benefit-Cost Analysis of the Elimination of a *Glossina palpalis gambiensis* Population in the Niayes of Senegal. PLoS Negl Trop Dis. e3112

Cecchi, G., Paone, M., Feldmann, U., Vreysen, M.J., Diall, O. and Mattioli, R,C. (2014). Assembling a geospatial database of tsetse-transmitted animal trypanosomosis for Africa Parasit. Vectors 7, 39

de La Rocque, S., Michel, M.F., Bouyer, J., De Wispelaere, G. and Cuisance D. (2005). Geographical Information Systems in parasitology: a review of potential applications using the example of animal trypanosomosis in West Africa. Parrasitologia 47, 97-104

Esterhuizen, J., Rayaisse, J.B., Tirados, I., Mpiana, S., Solano, P., Vale, G.A., Lehane, M.J. and Torr, S.J. (2011). Improving the Cost-Effectiveness of Visual Devices for the Control of Riverine Tsetse Flies, the Major Vectors of Human African Trypanosomiasis. PLoS Negl. Trop. Dis. 5, e1257

Feldmann, U. (2004). The sterile insect technique as a component of area-wide integrated pest management of tsetse. In: Maudlin, I., Holmes, P. and Miles, M. (Eds.) The Trypanosomiases. CABI Publishing, Wallingford, 565-582

Geerts, S., Holmes, P.H., Diall. O. and Eisler, M.C. (2001). African bovine trypanosomiasis: the problem of drug resistance. Trends Parasitol. 17, 25-28

Hargrove, J.W. (2000). A theoretical study of the invasion of cleared areas by tsetse flies. B. Entomol. Res. 90, 201-209

Hargrove, J.W. (2003). Tsetse eradication: sufficiency, necessity and desirability. Edinburgh: DFID Animal Health Programme. 133p

Kgori, P.M., Modo, S. and Torr, S.J. (2006). The use of aerial spraying to eliminate tsetse from the Okavango Delta of Botswana. Acta Trop. 99, 184–199

Kovacic, V., Tirados, I., Esterhuizen, J., Mangwiro, C.T.N., Torr, S.J., Lehane, M.J. and Smith, H. (2013). Community acceptance of tsetse control baits: a qualitative study in Arua District, North West Uganda. PLoS Negl Trop Dis 7, e2579

Msangi, A.R. Saleh, K.M., Kiwia, N., Malele, I.I., Mussa, W.A., Mramba F., Juma, K.G., Dyck, V.A., Vreysen, M.J.B., Parker, A.G., Feldmann, U., Zhu, Z.R. and Pan, H. (2000). Success in Zanzibar: eradication of tsetse. In: Keng-Hong, T. (Ed.) Area-wide control of Fruit Flies and Other Insect Pests. Penerbit Universiti Sains, Penang, Malaysia, 57-66

Muhanguzi, D, Picozzi, K., Hattendorf, J., Thrusfield, M., Welburn, S.C., Kabasa, J.D. and Waiswa, C. (2014). Improvements on Resticted Insecticide Applicaton Protocol for Control of Human and Animal African Trypanosomiasis in Eastern Uganda. PLoS Negl. Trop. Dis. 8, e3284

Naidoo, R.. and Rickets, T.H (2006). Mapping the Economic Costs and Benefits of Conservation. PLoS Biol. 4:e360

Robinson, T.P. (1998). Geographic information systems and the selection of priority areas for control of tsetse-transmitted trypanosomiasis in Africa. Parasitol. Today 14, 457-461

Rowlands, G.J., Woudyalew M., Leak, S.G.A., Nagda, S.M. and d'Ieteren, G.D.M. (1999). Estimating the Effects of Tsetse Control on Livestock Productivity – A Case Study in Southwest Ethiopia. Trop. Animal Health Prod. 31, 279-294

Shaw, A., Hendrickx, G., Gilbert, M., Mattioli, R., Codjia, V., Dao, B., Diall, O., Mahama, C., Sidibé, I. and Wint, W., (2006). Mapping the benefits: a new decision tool for tsetse and trypanosomiasis interventions. Research report DFID Animal Health Programme, Centre for Tropical Veterinary Medicine, University of Edinburgh and FAO Programme Against African Trypanosomiasis, Rome. 154p

Shaw, A.P.M., Torr, S.J., Waiswa, C., Cecchi, G. Wint, W., Mattioli, R.C. and Robinson, T P. (2013a). Estimating the costs of tsetse control options: an example for Uganda. Prev. Vet. Med. 110: 290-303

Shaw A.P.M., Torr S.J., Waiswa, C, Cecchi, G., Wint, G.R.W., Mattioli, R.C. and Robinson, T.P. (2013b). Reply to the letter to the Editor by Bouyer et al. (2013). Prev. Vet. Med. 112: 447–449

Shaw A.P., Cecchi, G., Wint, G.R.W., Mattioli, R.C. and Robinson, T.P. (2014). Mapping the economic benefits to livestock keepers from intervening against bovine trypanosomosis in Eastern Africa. Prev. Vet. Med. 113:197-210

Simarro, P.P., Cecchi, G., Franco, J.R, Paone, M., Diarra, A., Ruiz-Postigo, J.A, Fèvre, E.M., Mattioli, R.C. and Jannin, J.G. (2012). Estimating and mapping the population at risk of sleeping sickness. PLoS neglected tropical diseases 6, e1859

Vale, G. and Torr, S. (2004). Development of bait technology to control tsetse. In: Maudlin, I., Holmes, P. and Miles, M. (Eds.) The Trypanosomiases, CABI Publishing, Wallingford, 509-523

Wint, G.R.W. and Rogers, D. (2000). Predicted distributions of tsetse in Africa. Consultancy report and database prepared by Environmental Research Group Oxford Ltd and TALA Research Group, Department of Zoology, University of Oxford, for the Animal Health Service of the Animal Production and Health Division of the FAO. FAO, Rome

Wint, W. and Robinson, T. (2007). Gridded Livestock of the World. FAO, Rome. 131p

ECONOMIC IMPACT OF SUBCLINICAL KETOSIS AT FARM LEVEL: TACKLING THE CHALLENGE OF ACCOUNTING FOR MULTIPLE INTERACTIONS

D. RABOISSON*, M. MOUNIE AND E. MAIGNE

SUMMARY

To evaluate the total cost of subclinical ketosis (SCK) in dairy cows, a two-step approach was developed. First, all the production and reproduction changes and all the health disorders associated with SCK were quantified using meta-analysis. Secondly, the total cost of SCK was determined. The mean total cost of SCK was €257 per calving cow with SCK (95% prediction interval (PI): €72-442). The price of milk influenced results slightly. If parameters of the model were not modified to account for the meta-analysis conclusions, the mean cost of SCK was largely overestimated, reaching €434 (95%PI: €192-676). The proposed method took uncertainty and variability in input parameters into account by using distributions rather than point estimates. The five main scenarios and the PIs provide good insight into the economic consequences of this complex disease. The results can be used by decision makers in the field.

INTRODUCTION

Subclinical ketosis (SCK) is a major dairy cow metabolic disorder caused by strong dietary negative energy balance around calving. Its prevalence in Europe is estimated to 25% of all lactations (Philippe & Raboisson, 2012). Accurately determining its costs at farm level is necessary to help decision making. This implies clarification of SCK epidemiological consequences, in particular taking into account the multiple interactions that exist among the production, reproduction and health changes in case of SCK.

Many studies have shown that increased blood concentrations of betahydroxybutyrate (BHBA) or non-esterified fatty acids (NEFA) are associated with an increased risk of developing various diseases, reproductive disorders and changes in milk production (Duffield et al., 2009; McArt et al., 2013, for instance). These studies have determined the objective cow-level NEFA and BHBA thresholds that are associated with increased risks of disorders. Using such results directly for an economic evaluation remains difficult, since (i) data regarding certain outcomes have been scarce, (ii) the covariates included in the models have differed among and within studies, and the estimation of the relevant risk has often depended on these covariates, and (iii) the BHBA and NEFA threshold used to define SCK has differed between papers. Altogether, this suggests the need for meta-analysis so as to clearly quantify the links of SCK and associated disorders. This step would allow quantifying the direct association between disorders and SCK while tackling interactions among these disorders.

For the results to be easily applicable in the field it is also necessary to include biological and livestock system variability in the model. Most of the economic evaluations of the costs

---

* Didier Raboisson, Toulouse Veterinary School, 23 Chemin des Capelles, Toulouse, 31076 Cedex, France. Email: d.raboisson@envt.fr

of animal diseases provided up until now have been based on determinist methods. The mean total cost has been reported and the impact of key input parameters has been described through sensitivity analysis. Such a presentation remains difficult to use in the field, since practitioners have reduced time to make a decision, and need precise information on the total costs as well as a good idea of the limits of this data at a glance.

MATERIALS AND METHODS

The two-step method proposed here was based on first a meta-analysis to provide parameters as precise as possible for the second step, which was the economic evaluation per se.

Meta-analysis

The study included 23 peer reviewed papers and 131 different results, since most of the papers included association between SCK and more than one outcome. Papers were selected from a literature search on the PubMed, CAB and Goggle Scholar. Only papers in epidemiology and linking SCK and diseases, reproduction performances or milk production were included. All variables and results of models from peer-reviewed papers were implemented in a database: herd size, milk production level, way risk was expressed (relative risk (RR) or odd ratio (OR)), thresholds of BHBA and NEFA used to define SCK, week after or before calving of the sampling, the value of the risk and its standard error or confidence interval, and all the co-variables included in the raw data models. The thresholds and the co-variables were codified so as to obtain class variables. A random variable was also created, considering results from the same papers. The meta-regressions were built for each outcome variable. Mixed or fixed-effect models were included. The package Metafor in R was used (Raboisson et al., 2014).

Economic model

Each disease, the reproduction performance and the milk production represent the different components in the economic analysis. The total cost of SCK was estimated by the sum of the cost ($Cost_i$) of each component i. The calculations were made for an average 100 cow herd.

For each component, $Cost_i$ was calculated as the difference between the cost of SCK at the studied prevalence ($Cost_{i\_SCK}$) and the cost of SCK of a control herd ($Cost_{i\_CT}$) (Eq. (1)).

$$Cost_i = Cost_{i\_SCK} - Cost_{i\_CT} \tag{1}$$

The total cost of one component for a given herd is the cost of one case multiplied by the number of cases that come from (i) the baseline risk of this component for cows without SCK and (ii) the cows with SCK and consequently with the increased risk for this component (Eq. (2)).

$$\begin{gathered} Cost_i = \\ C_i \times (\left[\left(1 - Prev_{HERD\_SCK}\right) \times Prev_{COMPi\_NoSCK} + \left(Prev_{HERD\_SCK}\right) \times Prev_{COMPi\_SCK}\right] - \\ \left[\left(1 - Prev_{HERD_{CT}}\right) \times Prev_{COMPi\_NoSCK} + Prev_{HERD\_CT} \times Prev_{COMPi\_SCK}\right]) \end{gathered} \tag{2}$$

where

C_i = unit cost of component *i* for one animal

$Prev_{HERD\_SCK}$ = Prevalence of SCK in the study herd

$Prev_{HERD\_CT}$ = Prevalence of SCK in the control herd

$Prev_{COMPi\_NoSCK}$ = Prevalence of component *i* in cows without SCK

$Prev_{COMPi\_SCK}$ = Prevalence of component *i* in cows with SCK

RR_i = Relative risk of component *i* in cows with SCK compared to cows without SCK

$Prev_{COMPi\_SCK}$ and $Prev_{COMPi\_NoSCK}$ are linked by the RR (Eq. (3.))

$$Prev_{COMPi\_SCK} = Prev_{COMPi\_NoSCK} \times RR_i \tag{3}$$

Combining Eq. (2) and Eq. (3) leads to Eq. (4).

$$Cost_i = C_i \times \left(Prev_{HERD\_SCK} - Prev_{HERD\_CT}\right) \times Prev_{COMPi\_NoSCK}\left(RR_i - 1\right) \tag{4}$$

The costs of the component "milk losses" were calculated according to Eq. (5), using the milk production losses of a cow with SCK compared to a cow without SCK, and the margin over feeding for the milk price.

$$Cost_{MILK} = \left(Prev_{HERD\_SCK} - Prev_{HERD\_CT}\right) \times Milk\ losses\ per\ cow \times milk\ margin\ over\ feed \tag{5}$$

The costs of the component "increase of calving to conception interval" ($Cost_{Increased\ Calv\_Conc}$) was calculated according to Eq. (6), using the cost of extra open days per cow.

$$Cost_{Increased\ Calv\_Conc} = C_{extra\ open\ day\ per\ cow} \times (Prev_{HERD\_SCK} - Prev_{HERD\_CT}) \tag{6}$$

Because the relative risk must apply to the prevalence of diseases in the population not at risk for SCK, and because literature mostly referred to the prevalence within the overall population, a correction was made (Eq. (7)).

$$Prev_{COMPi\_NoSCK} = 100 * Prev_{COMPi\_AllPop} / (Prev_{SCK} * \mathrm{RR} + 100 - Prev_{SCK}) \tag{7}$$

where

$Prev_{COMPi\_AllPop}$ = Prevalence of component *i* in the whole population (with or without SCK) as often reported in literature.

$Prev_{SCK}$ = Prevalence of SCK from the study reporting the RR and $Prev_{COMPi\_AllPop}$

The model was run using the open source software 'Scilab' (www.scilab.org), with 10,000 iterations, and 95% prediction (PI) and confidence intervals (CI) were calculated. Data for the economic evaluation are presented in Table 1 with $Prev_{HERD\_CT}$ established at 10%. They originate from the 23 above mentioned papers and other sources.

Table 1. Data used for the main scenario

	Prevalence (%)			Costs (€)		
	Law of distribution	Mean	Standard error	Law of distribution	Mean	Standard error
Left abomasal displacement	Normal	2%	1	Normal	235	50
Right abomasal displacement	Normal	0.7%	0.33	Normal	294	63
Clinical ketosis	Normal	1.6%	0.4	Normal	23	5,8
Early culling	Normal	7%	5	Normal	1,188	300
Puerperal metritis	Normal	8%	8	Normal	105	10
Placental retention	Normal	8%	3	Normal	105	10
Milk production losses (kg)				Margin over diet costs		
First insemination calving rate	Normal	42%	5	Normal	20	5
Subclinical endometritis	Normal	15%	6.5	Normal	15	4.2
Purulent vaginal discharge	Normal	5.8%	3.3	Normal	15	4.2
Calving conception interval	One extra cycle if SCK			Normal	30	6.2
Clinical mastitis	Normal	11%	6	Normal	333	101
Twice increased in somatic cell counts	Normal	24%	10	Depends on price of milk		
Lame	Normal	26%	25	Lognormal	4.4	0.4

RESULTS

Meta-analysis

An overview of the results of the meta-analysis is provided in Table 2. Compared to the raw mean of values, the meta-regression allows an important correction of the effect size, by accounting for the precision of each raw data (through standard error or confidence interval).

Moreover, the results show that two main categories of moderators had a significant effect on the adjusted risk. First, the adjustment made by defining SCK as (i) BHBA> 1.4 m*M*, (ii) NEFA> 0.4 m*M* prepartum or (iii) NEFA>1.0 m*M* postpartum corrected the underestimated risk (despite low significance). This is because several trials reported the relevant risks using lower BHBA or NEFA thresholds. Using a low threshold leads to lower risk of disease compared with using a high threshold. Secondly, the correction produced using the polyfactorial terms corrected the overestimation of risk because many papers reported only univariable models. The confidence within the meta-regression results remained low for udder health indicators and lameness (Table 2).

Table 2. Quantification of the association between SCK and changes in health and production parameters

	Unit	Raw mean (sd)	Adjusted value, without moderator [95% CI]	Final adjusted value, with moderator [95% CI] (sd)
Left abomasal displacement	RR	5.2 (3.5)	3.9 [3.3-4.6]	3.3 [2.6-4.3][a]
Clinical ketosis	RR	8.9 (7.5)	6.9 [4.9-9.9]	5.4 [3.3-8.8][a]
Early culling	RR	2.4 (1.0)	1.9 [1.6-2.3]	
Puerperal metritis	RR	3.4 (4.3)	1.9 [1.7-2.1]	1.8 [1.5-2.0][a]
Placental retention	RR	1.6 (0.3)	1.5 [1.2-1.9]	
Clinical mastitis	RR	1.64 (0.2)	1.61 [1.24-2.09]	
Twice increase in somatic cell counts	RR	1.46 (0.2)	1.42 [1.26-1.60]	
Lame	RR	2.0 (0.4)	2.0 [1.6-2.5]	
Milk production	Litres			-251 (73)/-112 (89)[b]
Subclinical endometritis	RR		1.4 [1.1-2.0]	
Purulent vaginal discharge	RR		2.3[1.4-3.7]	
First insemination calving rate	RR	0.6 (0.16)	0.67 [0.53-0.83]	
Calving- conception interval	Days		+ 21	
Calving-first insemination interval	Days		+ 8	

[a] corrected by the moderator "mono or poly-variable".

[b] 251 litres after adjustment on abomasum displacement, clinical ketosis, puerperal metritis and placental retention; 112 litres after adjustment on lame, increased somatic cell count and clinical mastitis in addition to abomasum displacement, clinical ketosis, puerperal metritis and placental retention

RR = relative risk ; sd = standard deviation

Economic model

The following results were obtained for a cow producing 10,000 kg of milk a year, and for a margin over feeding cost of €0.12 per L of milk. The total cost of SCK was €257 (95%PI: €72-442) per cow with SCK (Table 3), in the estimation with the most probable input parameters (BASE). The alternative scenario proposed (ALTERNATIVE) took into account input parameters that remained plausible. The total cost estimated was then €301.

When relative risks were not corrected by the meta-analysis, when mean prevalence was used instead of the prevalence of components in cows without SCK, and when the highest costs for each components were retained, the estimation result was increased by almost 70% (Scenario BASE_max, Table 3).

Excluding the labour costs led to a 10% decrease in the total cost of SCK. Excluding the components with low confidence in the epidemiological data led to a 20% decrease in the total cost of SCK (Table 2). When both exclusions were combined, then the mean total cost of SCK was estimated to be €177 (95%PI: €16-338) per cow with SCK. This was the lowest mean total cost of SCK.

Table 3. Total costs of SCK under several scenarios

	Costs (€) per cow with SCK	Variation	95%CI (€)	95% PI (€)
BASE	257		255-259	72-442
ALTERNATIVE	301	+17%	299-303	109-492
BASE_max	434	+68%	432-436	192-676
BASE_no labour	225	-12%	223-226	96-441
BASE_no mastitis no lame	210	-18%	209-212	31-391
BASE_no mastitis no lame no labour	177	-31%	175-179	16-338

The estimation was not very sensitive to the total milk production (2-4% of changes of the total costs) and to the margin over feed costs (3-4% of changes of the total costs for the most probable margins over feed costs).

Contribution of all components to the total costs of SCK is shown in Fig. 1. The weight of each component depended more on the prevalence of cows without SCK and on the risk for cows with SCK than on the cost of one case of the component. The ranking of the components did not vary between scenarios, and the magnitude of changes of the percentage of each component was only slightly affected.

DISCUSSION

In the dairy industry, many animal health decisions are made without accounting for economics. Estimations of the cost of multiple diseases considered to be occurring simultaneously, where losses or extra costs are difficult to attribute to one or the other, are particularly lacking.

The proposed two-step approach allowed estimating costs of diseases with multiple interactions accurately. First, the correction brought by the meta-analysis allowed reducing the risk of economic misestimating due to overestimated or underestimated relative risks. In particular the overestimation due to estimated risk coming from univariable models was accounted for. Secondly, the prevalence of diseases in the population non-at-risk was used instead of the overall population prevalence. These two types of adjustment of input parameters allowed proposing an accurate estimation. The present study showed a 70% overestimation of the total costs of the disease if calibration only took into account the mean values from the literature, and not adjusted values. Unfortunately, much prior economic estimation has been based on raw mean values for input parameters.

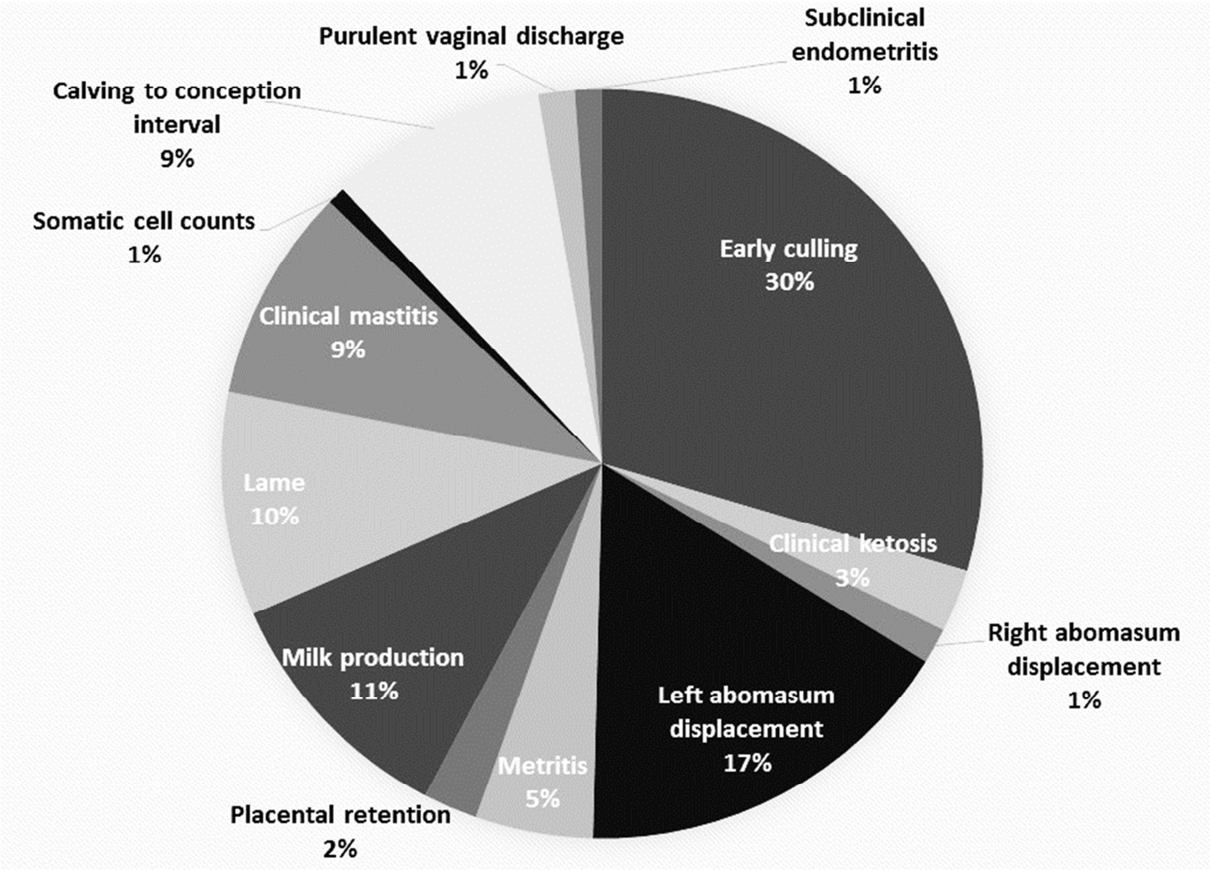


Fig 1. Part of each component in the total costs of SCK

The proposed method was based on the herd level to allow for different calibrations of low or high prevalence of diseases. Indeed, this allowed accounting for infectious pressure that increases in case of high prevalence. In the present study, SCK was not an infectious disease, but extra-culling was considered for high prevalence of SCK (data not reported) since literature reports decreased "sexual active group" dynamism in herds with deteriorated reproduction performances. Yet, the result can be presented at the herd level (mean cost per 100 cows for a given prevalence), or per cow with SCK, as done here.

The results reported here represent the total costs of one case of SCK and not the avoidable costs. Because SCK is mostly a herd issue, and because the reasoning at herd level is based on differences in SCK prevalence between two situations, the obtained difference represents avoidable costs.

The presentations of the results aim at facilitating their use for the daily activity of the farmer's advisors. Because data were implemented through laws of distribution, results were presented with their 95%CI or PI. This allowed an overview of the results at a glance. Moreover, because practitioners want to know the expected total cost of SCK in the current herd he is visiting, the 95%PI is more suitable than the 95%CI. Thanks to the mean value and its 95%PI, farm advisors know they are likely to have a total cost of SCK around €257 per cow with SCK, with possibility of decrease up to €72 and of increase up to €472 per cow with SCK, if the 5% extreme cases were excluded. Farm advisors are more interested in the farm they arrive in than in the 95% farms they have planned to visit for a given period, suggesting the use of the PI instead of the CI.

Because the characteristics of farms differ, several scenarios were proposed. For instance, in farms where the opportunity costs are considered as low or null, the scenario without labour cost is more suitable.

The present results should help farm advisors consider economics in their daily activity. For instance, they can easily compare the total cost of the current situation, when current prevalence of SCK in the herd is known, to the expected new situation, i.e. a new SCK prevalence, after measures are adopted. This may help them to justify their advices from an economic point of view. Because of the biological variability, the use of the mean values, but also the ranges of the 95%PI, is recommended to make robust economic-oriented decisions.

REFERENCES

Duffield, T.F., Lissemore, K.D., McBride, B.W. and Leslie, K.E. (2009). Impact of hyperketonemia in early lactation dairy cows on health and production. J. Dairy Sci. 92, 571-580

McArt, J.A., Nydam, D.V. and Oetzel, G.R. (2013). Dry period and parturient predictors of early lactation hyperketonemia in dairy cattle. J. Dairy Sci. 96, 198-209

Philippe P. and Raboisson D. (2012). Subclinical ketosis prevalence in bovine dairy herds in western France. Rencontres Recherche Ruminants. Paris, 19, p 137

Raboisson, D., Mounié, M. and Maigné, E. (2014). Diseases, reproductive performance, and changes in milk production associated with subclinical ketosis in dairy cows: A meta-analysis and review. J. Dairy Sci. 97, 7547-7563

THE USE OF INCREMENTAL COST-EFFECTIVENESS RATIOS TO EXPLORE ALTERNATIVE STRATEGIES FOR SURVEILLANCE OF BSE AND CLASSICAL SCRAPIE IN GREAT BRITAIN

B.A. WALL*, M.E. ARNOLD, A. ORTIZ-PELAEZ, W. GILBERT, D. RADIA, E. VAN KLINK, K. STAERK AND J. GUITIAN

SUMMARY

Due to the recent decline in prevalence of bovine spongiform encephalopathy and classical scrapie in Great Britain, cost-effective strategies are sought for the compulsory active surveillance of these diseases. Following consultation with policy makers, various alternative strategies for surveillance were modelled. Reducing the proportion of fallen cattle tested for BSE by 25% proved to be the most cost-effective option. Halving the number of sheep tested and removing testing of healthy slaughtered sheep are cost-effective alternative strategies for scrapie surveillance. The cost-effectiveness of alternative strategies can be interpreted and communicated to policy makers through use of incremental cost-effectiveness ratios (ICERs), which are well established in human healthcare but less commonly used in animal health. The ICER was adapted into a 'reduction-acceptability' ratio (RA-ICER) which considers potential cost savings and reduction in surveillance effectiveness. This research was undertaken with consultation from policy experts, to ensure that outcomes were aligned with policy requirements.

INTRODUCTION

The prevalence of both bovine spongiform encephalopathy (BSE) and scrapie has fallen consistently in Great Britain in recent years (Department for Environment Food and Rural Affairs, 2014). A number of measures aimed at the eradication of these transmissible spongiform encephalopathies (TSEs) have contributed to this decrease. Currently, in order to determine the trend of BSE prevalence over time in EU member states, active surveillance involving the testing of healthy slaughter, emergency slaughter and fallen stock is carried out, in addition to passive surveillance based on reporting of suspect clinical cases. For classical scrapie, active surveillance in the form of annual surveys was added in 2002 to the compulsory notification of suspect clinical cases. This serves to monitor the occurrence of the disease in the sheep population.

Back calculation methods using surveillance data have been developed in recent years to estimate the prevalence of BSE and classical scrapie in Great Britain (Arnold & Wilesmith, 2003; Arnold & Ortiz-Pelaez, 2014). Estimates of the prevalence of infection are essential for assessing the efficacy of risk mitigation and control strategies. Given the declining prevalence of TSEs, and the low ratio of detected positives to the number of animals tested, there are economic incentives to reduce the number of animals tested. Simultaneously, it is

---

* Ben Wall, Veterinary Epidemiology, Economics and Public Health Group, Royal Veterinary College, Hawkshead Lane, Hertfordshire AL9 7TA, UK. Email: bwall@rvc.ac.uk

important that the UK continues to have robust evidence to respond in a timely way to threats from new or re-emerging TSEs. Therefore it is crucial that the most cost-effective strategy for surveillance is adopted.

This paper discusses the economic analysis of various hypothetical surveillance strategies for the detection of BSE positive cattle and scrapie positive sheep, with explicit consideration of policy requirements.

Historically, animal health scientists have tended to focus on technical aspects of disease without consideration of the economic and socio-political impacts of their research (Boqvist et al., 2014). It is imperative that science and policy are linked, especially when dealing with diseases such as BSE and classical scrapie, as the potential human health impact and resulting political concern are important considerations in the formulation of surveillance strategies. In addition, in situations where state or EU legislation applies, the research must be framed within this context. More widely, the lack of connectivity between technical analysis and policy has been well documented in the context of global warming research and natural resource policy (Brunner et al., 2006), but equally in veterinary sciences there is a need to bridge the gaps between science, policy and legislation.

The purpose of this research was to provide scientific evidence for decision-making in relation to the future of BSE and classical scrapie surveillance within Great Britain. In order for policy makers to achieve the maximum benefit, a workshop was held between policy makers and researchers to determine how to align proposed modelling work with current policy objectives and to ensure the evaluation methods meet the needs of stakeholders. During the initial workshop, policy makers proposed hypothetical surveillance scenarios which should be modelled and defined measures of technical outcomes which would be most relevant to future policy decisions. The output of modelling was therefore aligned with policy objectives at each stage in the process, as depicted in Fig. 1.

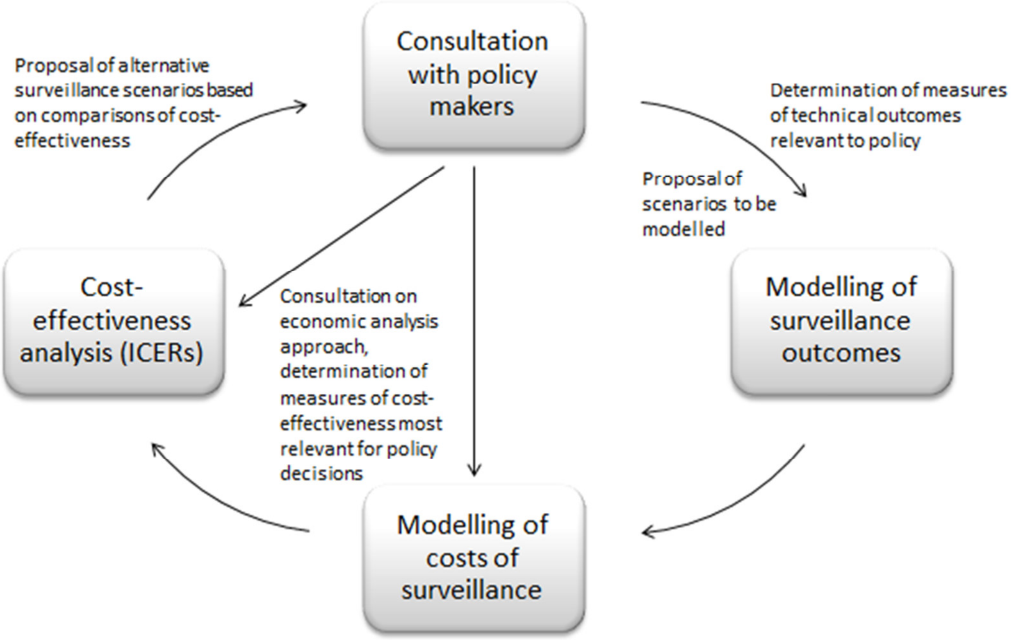


Fig. 1 Conceptual flow of project cycle

An additional aim of this study was to determine an appropriate method for the economic analysis which would produce outcomes highly relevant to the policy question and easily interpretable by decision makers. During the initial workshop, researchers and policy experts agreed that the most suitable approach would be a cost-effectiveness analysis with outcomes expressed as incremental cost-effectiveness ratios (ICERs). A cost-benefit analysis was precluded as the purpose of the economic modelling in this case is to assess the relationship between the cost of surveillance and technical outcomes, rather than analyse the economic or societal benefit of surveillance.

ICERs are calculated as per Eq. (1):

$$(C_P - C_B) / (O_P - O_B) \qquad (1)$$

Where C=cost; O=outcome; p=proposed scenario and b=baseline.

A number of technical indicators (i.e. measures of the effectiveness of surveillance, such as the time taken for an increase in prevalence to be detected) could be used as the denominator for the ICER, and these were pre-defined by policy makers in order to aid interpretation and ensure relevance of the results (see Fig. 1). The ICER allows direct comparison between the baseline of the current surveillance strategy and alternative scenarios.

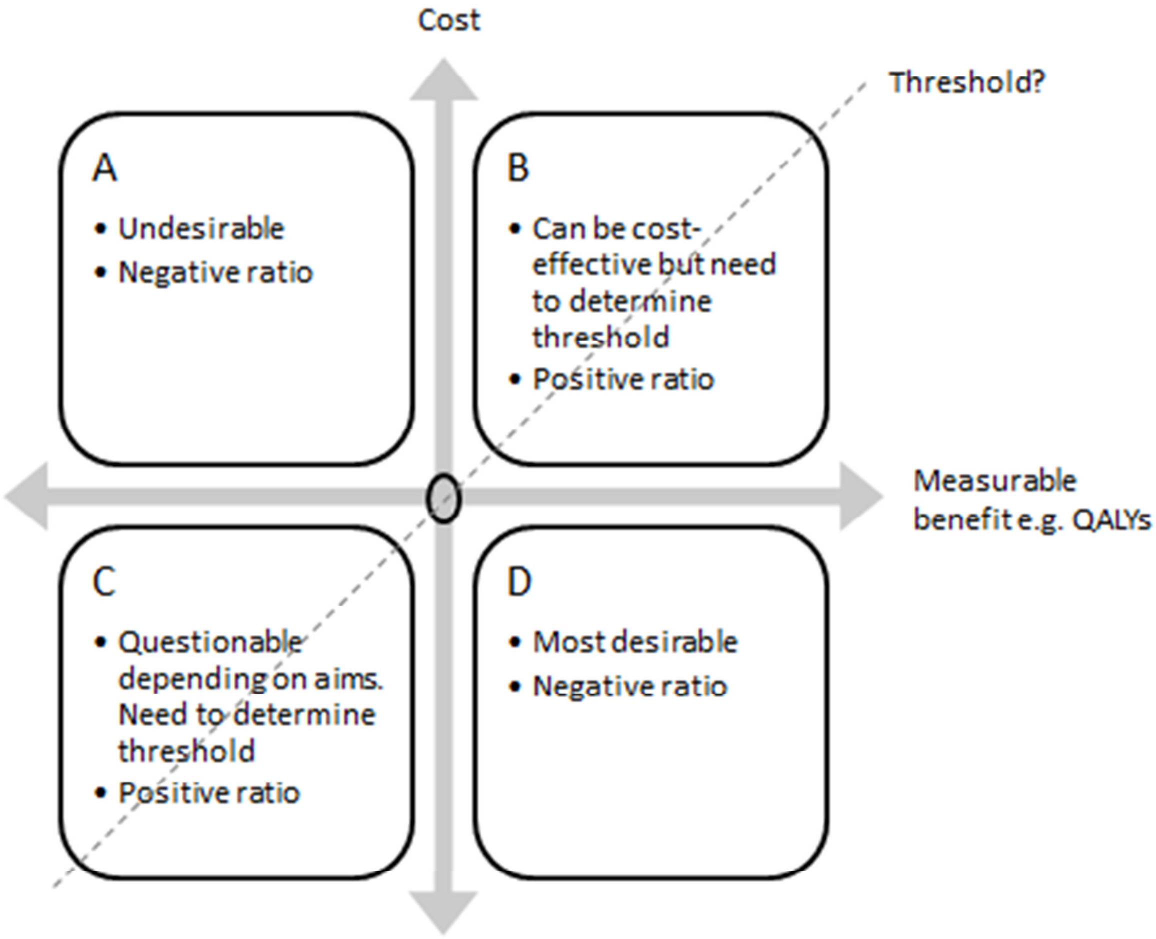


Fig. 2 Incremental cost-effectiveness ratios schematic plot. 0 = baseline scenario

ICERs are widely used in human healthcare, but less commonly in animal health. ICERs are typically used to evaluate the cost-effectiveness of a proposed healthcare intervention using costs as the numerator and some measure of benefit as the denominator, such as additional years of life expectancy, typically measured in quality-adjusted life years (QALYs) (Garber, 1997; National Institute for Clinical Excellence, 2004). Usually these are employed to measure the cost-effectiveness of a proposed intervention that would require increased spending but is expected to produce a desirable outcome such as an increase in QALYs. ICERs can be interpreted by the plot shown in Fig. 2.

Scenarios that fall into area ‘B’ may be cost-effective, but policy makers must determine an appropriate threshold. Scenarios with a lower ratio (shallower gradient) will be more cost-effective than those with a higher ratio (steeper plot gradient). Those with high ICERs - above the hypothetical threshold line - may not be acceptable to policy makers as they will require large financial investments for minimal benefits. Care must be taken in interpreting ICERs, as a positive ratio may fall into area ‘C’, whereby costs are saved but the benefit is reduced. This may or may not fit within the policy aims for the particular scenario being tested. Care should also be taken in interpreting a negative ICER value (areas ‘A’ or ‘D’), as this can indicate either a totally undesirable scenario (increased cost and reduced life expectancy), or a highly desirable scenario (reduced costs and increased life expectancy).

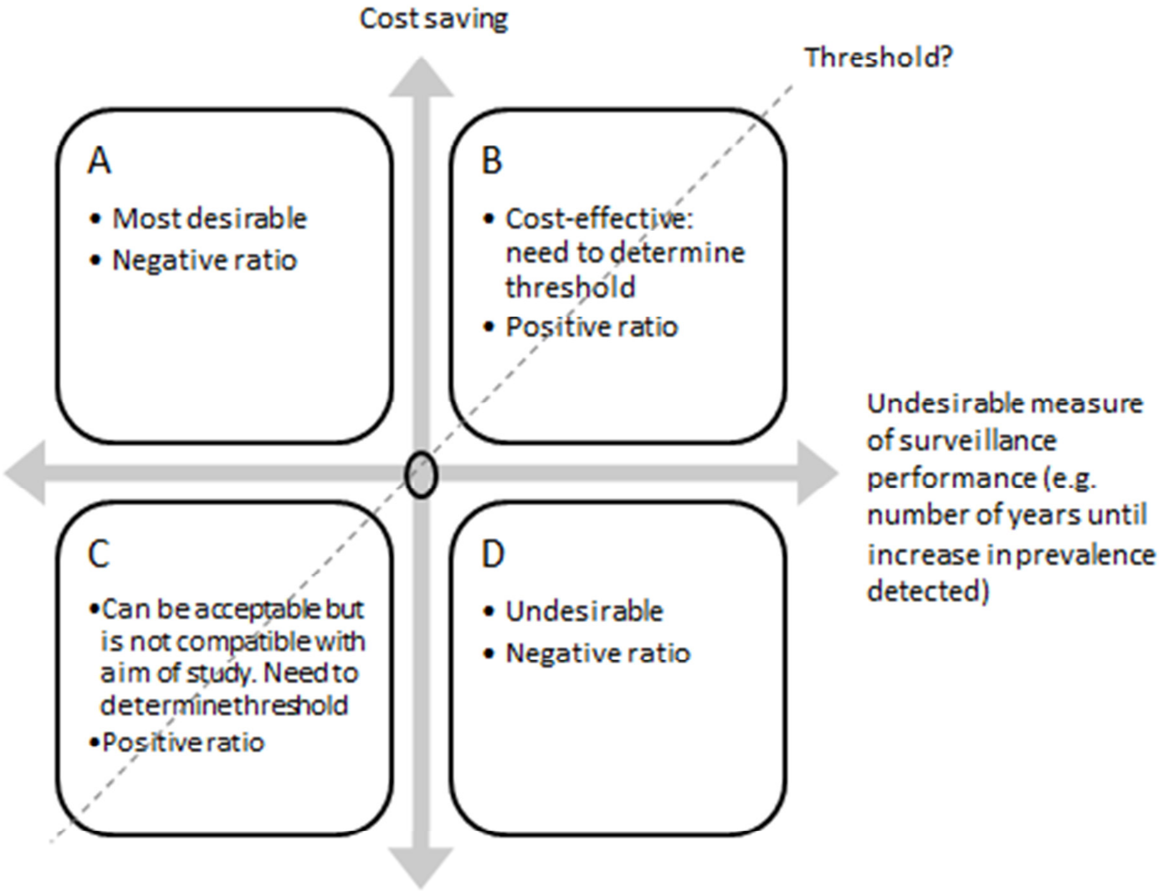


Fig. 3 Reduction-acceptability ratio schematic plot for alternative surveillance scenarios for BSE and classical scrapie in Great Britain. 0 = baseline scenario

MATERIALS AND METHODS

For the purposes of this study, in contrast to the typical application of ICERs as described above, a proposed *reduction* in spending is compared with an increase in an *undesirable* outcome, such as the number of years until detection of an increase in prevalence. Therefore this approach can instead be described as a 'reduction-acceptability' ratio (henceforth referred to as RA-ICER). This can be used to determine to what extent costs can be saved with regards to the acceptability of the denominator variable.

The RA-ICER is calculated as per Eq. (2):

$$- (C_P - C_B) / (O_P - O_B) \tag{2}$$

The numerator is therefore the *cost saving* rather than the cost. This RA-ICER compares the amount of money saved (desirable) with increased risk (undesirable), which is the opposing concept of a typical ICER and therefore must be interpreted accordingly. The RA-ICER plot is shown in Fig. 3 and is identical in concept but a mirror image of Fig. 2 above.

In general, a higher positive ratio indicates a steeper gradient on the graph and greater cost-effectiveness, which in this case means greater cost savings for less compromise on technical performance. Less desirable scenarios would lie below the hypothetical threshold line. Similarly to Fig. 2 above, it should be noted that a positive ratio could also fall within area 'C', which indicates an increase in spend for an improvement in technical efficacy of surveillance. This outcome is not relevant to this particular policy agenda and research question. Hypothetical scenarios were selected in advance for their potential to meet the policy agenda (i.e. to save costs while compromising technical efficacy); and as a result the majority of modelled scenarios are likely to fall within area 'B'. Given the likely clustering of scenarios in area 'B', plotting RA-ICERs on the axes enables comparison of the relative cost-effectiveness of different scenarios. Additionally it is useful to define a threshold of acceptability below which scenarios will not be considered.

The major difference between this RA-ICER approach and the standard use of ICERs is that the threshold needs to be determined by policy makers based on the acceptability of a reduction in surveillance efficacy; whereas ICERs in human healthcare have been extensively used, and standard thresholds have been long established by policy makers (Gafni & Birch, 2006). These reflect how much stakeholders are willing to pay for the benefit of, for example, increased quality-adjusted life years.

Results of economic modelling were presented to policy makers, as shown in Fig. 1, enabling the explicit comparison of alternative policy options for surveillance of BSE and classical scrapie in Great Britain.

RESULTS

Economic modelling and RA-ICERs showed that BSE surveillance could be more cost-effective than the current strategy if the proportion of fallen cattle tested was modestly reduced. A further reduction could enable even greater cost savings, but with considerably reduced cost-effectiveness. Therefore it would be a matter for policy makers to decide which strategies are acceptable. Increasing the age of cattle tested would be a poorly cost-effective strategy, and this can be attributed to the considerably reduced effectiveness of surveillance and only moderate cost savings. These observations were true for all measures of surveillance effectiveness which were modelled.

In terms of classical scrapie surveillance, the most cost-effective alternative strategy involved removing the testing of healthy slaughtered animals and testing only fallen stock. This would produce a relatively minor cost saving although technical outcomes would be unaffected. By reducing the number of fallen stock tested each year by half, a greater cost saving could be achieved, but with some reduced technical effectiveness, and this would also be a cost-effective strategy. Testing even fewer animals per year would result in considerable cost savings but would be a much less cost-effective strategy, which may fall below a policy-driven cost-effectiveness threshold.

DISCUSSION

Interpreting a cost-effectiveness model in terms of 'reduction-acceptability' using RA-ICERs can provide robust evidence to policy makers when it is necessary to justify a reduction in surveillance to a legislating body such as the EU. This method was developed following consultation with stakeholders in response to the need to downscale surveillance while accepting some reduction in effectiveness, and enables the clear and explicit comparison of alternative policy options for the consideration of decision-makers.

This approach provides policy makers with the means to define a threshold of cost-effectiveness acceptability for the performance of surveillance systems, which would be a novel application for animal health policy and could be adaptable to other animal diseases and settings. In order to determine the threshold, policy makers can refer to approaches already established in human healthcare policy (Fenwick et al., 2006; Gafni & Birch, 2006; Weintraub & Cohen, 2009), although it may be additionally necessary to consult with stakeholders such as consumers, producers, processors, industry bodies and EU legislators. This is because the value of effective surveillance may be subjective and perhaps more challenging to define than the value of a QALY.

ACKNOWLEDGEMENTS

The authors would like to thank all of the policy experts who took part in the consultations, the project team at Defra who supported this research, and Amie Adkin of APHA for providing information on costings.

REFERENCES

Arnold, M. and Ortiz-Pelaez, A. (2014). The evolution of the prevalence of classical scrapie in sheep in Great Britain using surveillance data between 2005 and 2012. Prev. Vet. Med. 117, 242-250

Arnold, M. and Wilesmith, J.W. (2003). Modelling studies on bovine spongiform encephalopathy occurrence to assist in the review of the over thirty months rule in Great Britain. Proc. R. Soc. Lond. B. 270, 2141-2145

Boqvist, S., Dekker, A., Depner, K., Grace, D., Hueston, W., Staerk, K.D.C. and Sternberg Lewerin, S. (2014). Contagious animal diseases: the science behind trade policies and standards. Vet. J. 202**,** 7-10

Brunner, R.D., Steelman, T.A., Coe-Juell, L., Cromley, C., Edwards, C.M. and Tucker, D.W. (2006). Adaptive Governance: Integrating Science, Policy, and Decision Making. Gov. 19**,** 673-675

Department for Environment Food and Rural Affairs (2014). TSE disease surveillance statistics. Available at https://www.gov.uk/government/collections/tse-disease-surveillance-statistics. Accessed 10th December 2014

Fenwick, E., Marshall, D.A., Levy, A.R. and Nichol, G. (2006). Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. BMC H. Serv. Res. 6**,** 52

Gafni, A. and Birch, S. (2006). Incremental cost-effectiveness ratios (ICERs): the silence of the lambda. Soc. Sci. and Med. 62**,** 2091-2100

Garber, A.M. and Phelps, C.E. (1997). Economic foundations of cost-effectiveness analysis. J. of H. Econ. 16**,** 1-31

National Institute for Clinical Excellence (2004). Guide to the Methods of Technology Appraisal. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/191504/NICE_guide_to_the_methods_of_technology_appraisal.pdf. Accessed 10th December 2014

Weintraub, W.S. and Cohen, D.J. (2009). The limits of cost-effectiveness analysis. Circ. Cardio. Qual. and Outc. 2**,** 55-58

DISEASE MODELLING

CONTROLLING THE SPREAD OF *MYCOBACTERIUM AVIUM* SUBSP. *PARATUBERCULOSIS* AT A REGIONAL SCALE BASED ON INTERNAL BIOSECURITY AND ANIMAL MOVEMENTS

G. BEAUNÉE*, E. VERGU AND P. EZANNO

SUMMARY

Trade movements represent a major route for the spread of pathogens such as *Mycobacterium avium* subsp. *paratuberculosis* (*Map*) that causes paratuberculosis, in metapopulations of cattle herds. Our objective was to assess scenarios combining measures of *Map* spread control based either on test at purchase or internal biosecurity (including hygiene improvement, culling, or calf management). A metapopulation model was developed accounting for population and infection dynamics in each dairy herd. Within herd infection dynamics were connected through observed animal trade movements. When considered separately, simulated interventions slowed down the disease spread, but did not induce a decrease in the number of infected herds. Interestingly, in simulations combining several measures, both effects were achieved. In addition to introducing a model of *Map* spread at a regional scale, our study highlights the key challenges of controlling *Map* spread in a region endemically infected.

INTRODUCTION

Movements of livestock form complex networks linking farms, geographically close or distant, and represent one of the major route by which many infectious pathogens propagate at a large scale (Buhnerkempe et al., 2014; Bajardi et al., 2012). In a metapopulation of cattle herds, in addition to animal trade, the diversity of cattle farming systems (e.g. concerning the herd size) and of contacts among farms in a region (in terms of frequency, type of animals) also influences disease spread. In recent years, the number of databases concerning the traceability of livestock had increased in European countries. Information in these databases can be described by networks, where farms represent nodes and trade relationships define links. Such networks were investigated using methodological tools from social network analysis (Dutta et al., 2014; Bajardi et al., 2011) to assess their vulnerability with respect to the spread of pathogens.

Paratuberculosis, or Johne's disease, is a worldwide disease caused by *Mycobacterium avium* subsp. *paratuberculosis* (*Map*) that is considered to be mainly introduced into farms by purchasing infected stock (Behr & Collins, 2010). It is a chronic inflammatory bowel disease of cattle and other ruminants infected by *Map* (Behr & Collins, 2010). As one of the most important infectious diseases in dairy cattle, paratuberculosis has a large economic impact for producers due to decreased milk production, premature culling, reduced slaughter value, low

---

* Gaël Beaunée, UR1404 MaIAGE - INRA - Domaine de Vilvert, 78352 Jouy-en-Josas Cedex, France & UMR1300 BioEpAR - INRA-Oniris - Atlanpole - La Chantrerie BP 40706, 44307 Nantes Cedex 03, France. Email: gael.beaunee@jouy.inra.fr

fertility, and an increased animal replacement rate (Ott et al., 1999; Lombard et al., 2005). Infection by *Map* usually occurs in the first year of life (Windsor & Whittington, 2010). Newborns are the most susceptible animals, and an increase with age in the resistance to infection is observed. Transmission can occurred vertically (*in utero* transmission) (Whittington and Windsor, 2009) or horizontally (ingestion of the bacterium via colostrum, milk, or faeces contaminated by *Map*) (Van Roermund et al., 2007). Paratuberculosis is a slow progressive disease, and the progression of individual animals through different *Map* infection states is a complex continuous process alternating excreting and non-excreting stages and later leading to clinical signs.

To control *Map* spread at a regional scale, various measures focusing on the control of movements of infected animals between herds or on the reduction in the exposure to the pathogen of susceptible animals in infected herds can be implemented. To limit the between herd spread of *Map* through animal trade, diagnostic tests at purchase can be performed. However, these tests have low sensitivities, especially in the early stages of the disease. To decrease within herd exposure, biosecurity measures can be used (Marcé et al., 2011b), based on culling, hygiene improvement and calf management. However, each of these measures is expected to be insufficient to reach control of *Map* spread or to necessitate high levels of implementation that cannot be attained in practice. In this context, there is a need for evaluating combination of such measures at a regional scale.

Because *Map* infection occurs mainly in young stock and is characterised by a long latency period before the onset of clinical signs and because of the low sensitivity of diagnostic tests in the early stages of the disease, field studies investigating the transmission of *Map* are expensive and cannot be used to compare control measures. Therefore, a modelling approach is relevant to fulfil such an objective.

Our objective was to represent, using a modelling approach, *Map* spread in a metapopulation of dairy cattle herds in order to compare control measures effectiveness, when used alone or in combination. In this perspective, a metapopulation model that fully coupled the within-herd population and infection dynamics of each farm of the metapopulation through animal movements based on observed data was developed. Control strategies were then included in the model and their impact assessed through intensive simulations.

MATERIALS AND METHODS

Animal trade data between herds and contact network

Animal trade data from the French cattle identification database from 2005 to 2009 was used. This database records the life history of every animal from birth to death, including movements between holdings (i.e. farms, markets, and assembling centers). Based on this information, a directed (trade relationships are polarised), weighted (the number of animals sold or bought is variable amongst pairs of herds) and time-varying (trade relationships are not necessarily stable over time) contact network was built, with herds as nodes and their trade relationships as links. The information on slaughterhouses and exports was not included, as they act only as sinks and do not play any role in the between-farm spread of *Map*. As the duration of presence of the animals on markets and assembling centres is rather short and thus this presence is expected not to be related to new infections, the network was rebuilt to consider farm-to-farm movements.

Our study focused on dairy cattle located in Brittany, in Northwestern France. This is a major region for dairy production, characterised by a high density of dairy cattle herds. Herds were selected according to their type and size. Only herds with more than 30 animals, assumed to be professional herds dedicated to dairy production, were considered. French dairy cattle herds are composed mainly of female cows with breeding being based on artificial inseminations. Therefore, only the movements of females of dairy or crossed breeds were considered in the network, neglecting fattening activities that most often are conducted in a different building or area of the farm.

The resulting metapopulation was composed of 16,076 herds (rather sellers than buyers), which are the nodes of the network. The network, aggregated over the 5-year period, consisted of 680,929 animal movements (links), including 150,568 movements among herds belonging to the metapopulation. The exchanged animals were mainly young calves (32.7% before 10 weeks of age, corresponding to weaning) and cows (53.8% older than 2.5 years of age).

Within-herd model of *Map* spread

To describe the within-herd *Map* spread, the model introduced by Marcé et al. (2011a, b) was used. All transitions between states and infection processes are fully described in Marcé et al. (2011a). In brief, Marcé's model is a stochastic compartmental model in discrete time (one-week time step) representing *Map* spread within a structured dairy cattle herd. It consists in the coupling of herd population dynamics with *Map* indirect transmission between animals located in age groups. This model includes most of the available knowledge on the infection, and was therefore selected as the constitutive block at the farm scale.

Animals are distributed into 6 mutually exclusive infection states (Fig. 1): susceptible (*S*) to the infection before 1 year of age; resistant (*R*) at older ages; young transiently shedders after infection (*T*), potentially giving rise to calf-to-calf indirect transmission due to the local contamination of the calf environment; latently infected and not infectious anymore (*L*); subclinically infected and infectious, without symptoms (*Is*); clinically affected and highly infectious (*Ic*), removed from the herd after an average duration of 6 months.

Animals in states *T*, *Is* and *Ic* shed *Map* in their faeces and thus contaminate farm environments. *Map* is able to survive in the environment. Therefore, different farm environments (*Ei*) were taken into account (one per age group and one for the whole environment of the farm; Fig. 1). *Map* transmission occurs through 5 routes: (1) vertically from the infected dam to her foetus (*in utero* transmission), (2-3) horizontally through the ingestion of contaminated colostrum or contaminated milk, and (4-5) through indirect contact with a contaminated local environment (contaminated by shedding calves) or with the general environment of the farm (contaminated by all shedders). The shedding level is known to be highly heterogeneous among infected animals according to their infection state, as well as over time for a given infected animal in a given state. This is accounted for in the model.

The preliminary analysis of the model revealed that raising calves in individual pens during a few weeks had almost no effect on *Map* spread within the herd (Marcé et al., 2011b). Therefore, Marcé's model was simplified accordingly. Calves are assumed here to be managed in collective pens since their birth, and therefore to be exposed to the associated environment also since birth.

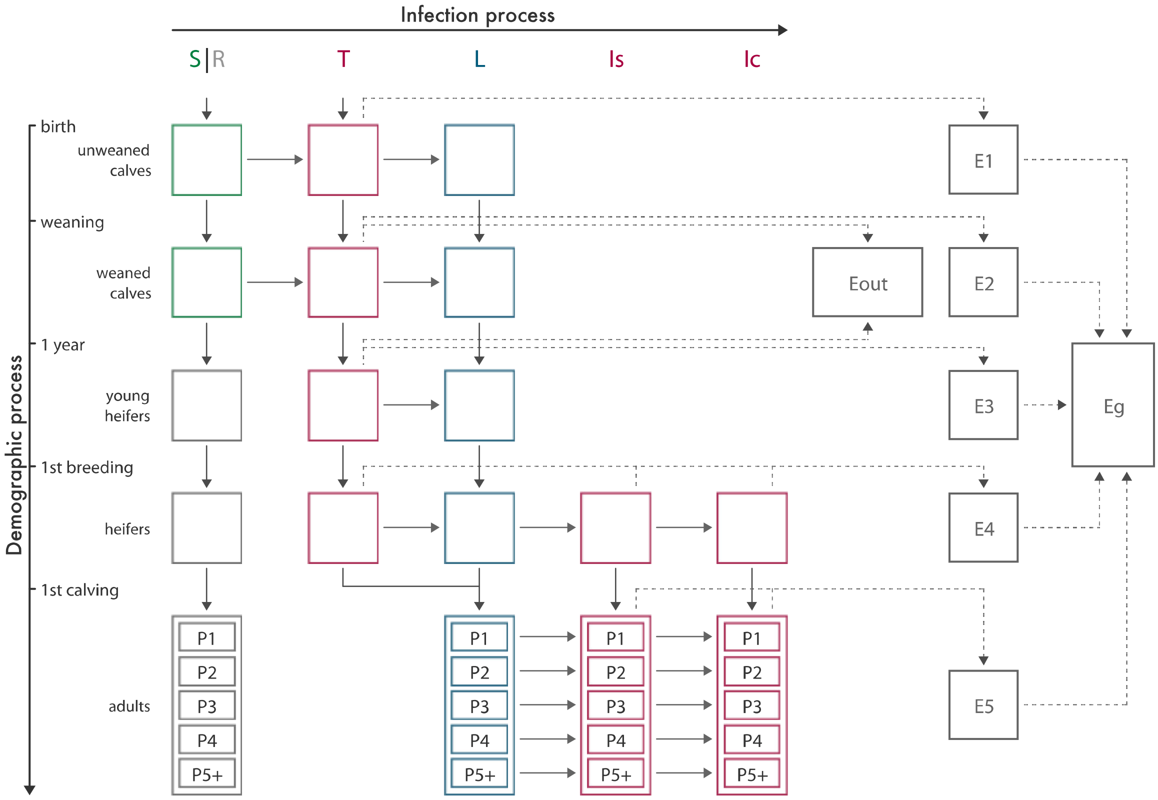


Fig. 5 Conceptual model of the spread of *Map* in a closed dairy herd. *S*, susceptible; *R*, resistant; *T*, transiently infectious; *L*, latently infected; *Is*, *Ic*, subclinically and clinically infectious, respectively. *Ei*, indoor environment in housing *i*, with *i*=1,…,5 (depends on age and season); *Eg*, environment of the whole farm; *Eout*, outdoor environment of grazing calves. *Pj*, cows in parity *j*, with *j*=1,…,5; dotted lines: contribution to the environment contamination. Exit rates of each compartment are not represented (adapted from Marcé et al., 2011a)

Between-herd model of *Map* spread

To go from the farm scale to a regional metapopulation scale, within-herd dynamics were coupled through the observed movements of animals. Movements were observed for a 5-year period and were assumed identical for any period of the same length in simulations of *Map* spread over periods longer than 5 years.

In the regional model, animal movements were plugged from the database, corresponding to a deterministic component of the model, whereas the assignment of the health statuses of moving animals was stochastic. Therefore, date, origin, destination and age of animals moving were implemented deterministically. For each movement, the health status of the moved animal was randomly selected according to the prevalence of infection in the source herd. Animals with clinical signs (*Ic*) were not allowed to move. All of the other health statuses were concerned by animal movements. More specifically, to assign the health status (*X*) to each animal in age *a* moving from herd *i* to herd *j*, a multinomial distribution was used with probabilities defined by the vector of prevalences in each health state (except *Ic*) in age group *a* and herd *i*. For animals purchased from outside Brittany, the health status was determined according to the prevalence of infection in the same age group in the entire simulated metapopulation.

Conditions for simulation

Parameter values of the within-herd model were the same as in Marcé et al. (2011a), except the herd size that was defined for each farm according to observed data.

Initially, 30% of the farms were considered infected, which corresponds to the expected current herd prevalence in France (Guicharnaud, 2009). Initially infected farms were randomly selected. A level of intra-herd prevalence at the start of the Map circulation between herds was randomly defined for each herd (based on preliminary simulations of the intra-herd dynamics varying from 1 to 10 years). For each scenario, results were obtained from 500 runs over 10 years.

Control strategies implemented and assessed through simulations

Tests at purchase: Sensitivity and specificity values used were based on values found in the literature (Nielsen & Toft, 2008). Two sets of values (Table 1) corresponding to two different scenarios were used: ELISA-1 (values according the most frequently used test) and ELISA-2, which correspond to tests with low and medium efficacies, respectively. All movements were tested.

Table 1. Sensitivity (Se) and specificity (Sp) of diagnostic tests assessed by simulation

Scenarios	Se for T	Se for L	Se for Is	Se for Ic	Sp
ELISA-1	0.15	0.07	0.75	0.80	0.95
ELISA-2	0.50	0.25	0.80	0.85	0.99

Internal biosecurity: First, improving hygiene consists in *Map* removal from milk and colostrum by use of substitute or pasteurisation (leading in the model to the blocking of the two transmission routes concerned), and in the decrease of *Map* abundance through cleaning of all farm environments (corresponding in the model to an increase in the removal rate of the bacteria) (values of removal rate used: 0.6, 0.8, 1.0, reference value: 0.4). Second, culling strategies consist in a quicker removal of clinically affected animals, reducing the mean time spent by these animals in the farm after the onset of clinical signs (value used: 13 weeks, reference value: 26 weeks). Test-and-cull strategies also were considered, implemented once per year, applied as soon as at least one affected individual was detected during the previous year. These strategies were also defined by the number of animals tested (50% or 100%), their age (all animals after first calving) and sensitivity and specificity of the tests (values in Table 1). Third, calf management, corresponding to the separation of calves from adults to reduce their exposure to shedding adults (values used for the level of exposure: 0.75, 0.50, 0.25, reference value: 1.0), was considered.

Each of the different measures implemented has been assessed alone and in combination with other strategies, resulting in 34 scenarios.

RESULTS

Tests at purchase alone

Control strategies based only on testing animals at purchase achieved to reduce the speed of *Map* spread but not to decrease the proportion of infected herds in the metapopulation, compared to the initial situation (Fig. 2). The effectiveness was better for strategies based on the more accurate test. However, none allowed to decrease the prevalence (in infected herds) at the metapopulation level or to stop *Map* spread.

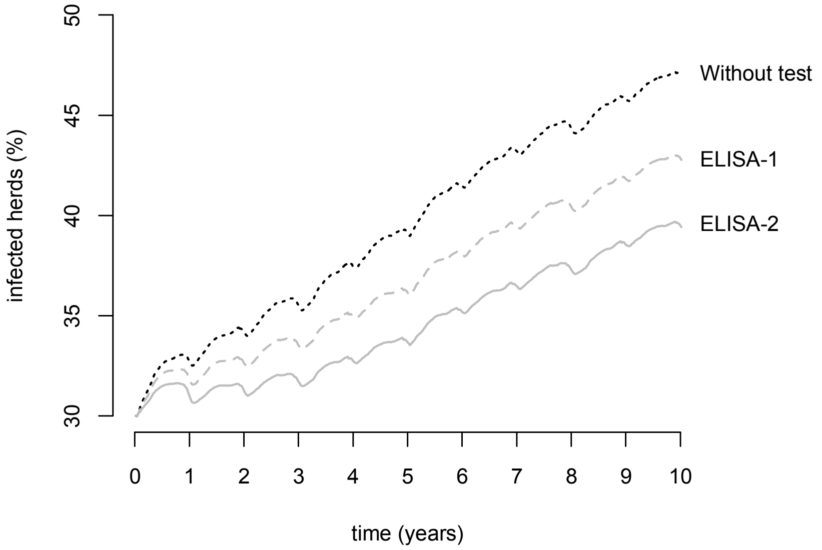


Fig. 6 Average (over 500 runs) proportion of infected herds over time, with and without tests at purchase.

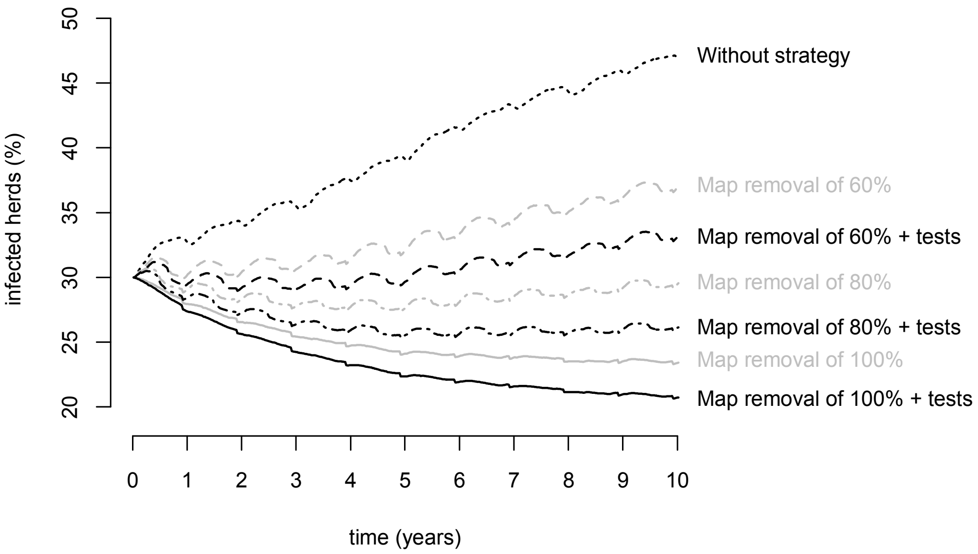


Fig. 7 Average (over 500 runs) proportion of infected herds over time, with and without cleaning of farm environments and tests at purchase.

Internal biosecurity based on hygiene improvement alone and in combination

Increasing bacteria removal in farms every week lowered the proportion of infected herds (Fig. 3). When combined with tests at purchase, it slightly enhanced the predicted effect. Only a cleaning process performed every week and achieving to remove more than 80% of the bacteria present in the farm environment yielded the decrease in herd prevalence.

Internal biosecurity based on culling alone and in combination

Increasing the culling rate of affected animals after the onset of clinical signs prevented the increase over time of herd prevalence. When combined with tests at purchase, a decrease in the proportion of infected herds was achieved (Fig. 4).

The test and cull strategy implemented had only limited effect when considered alone, testing 50% of the animals (in the interval of age selected) having no effect at all (Fig. 4). The use of test ELISA-1 and ELISA-2 gave similar results.

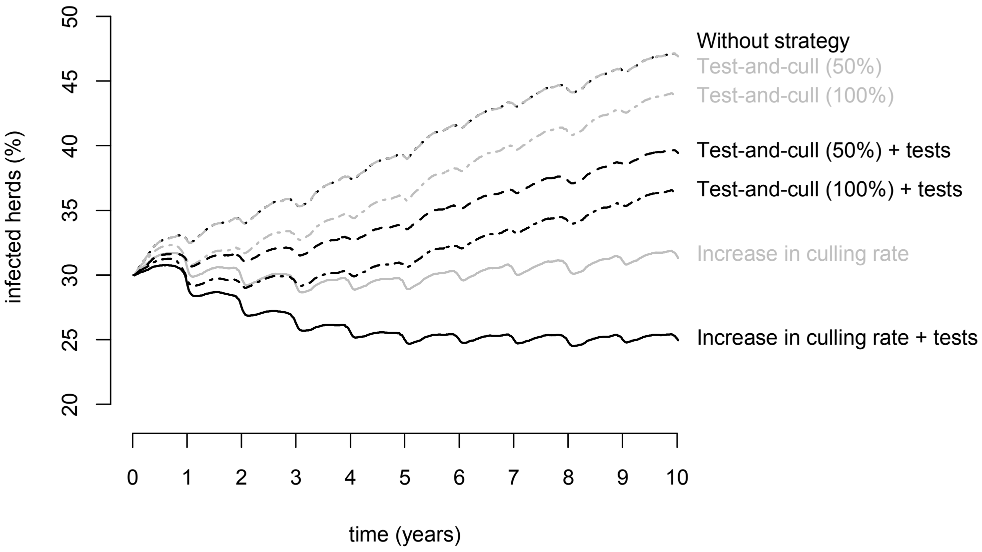


Fig. 8 Average (over 500 runs) proportion of infected herds over time, with and without quick culling strategies and tests at purchase.

Internal biosecurity based on calf management alone and in combination

Decreasing the exposure of calves to shedding adults largely reduced *Map* spread (Fig. 5). However, a decrease of 75% in the exposure (25% of exposure compared to 100% in the reference scenario) was needed to achieve a decrease in herd prevalence compared to the initial situation. When combined with tests at purchase, the highest decrease in herd prevalence was predicted compared to other combinations of interventions.

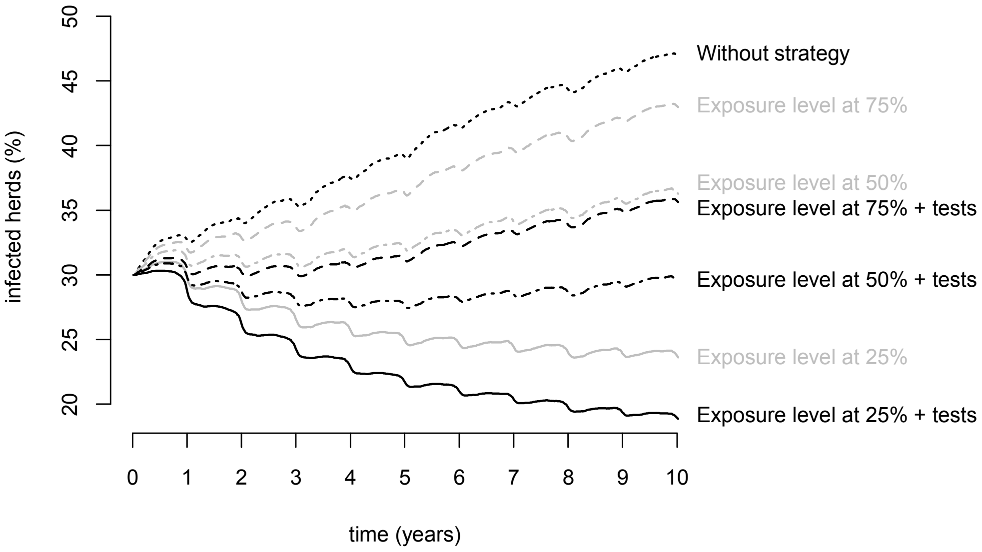


Fig. 9 Average (over 500 runs) proportion of infected herds over time, with and without reducing calf exposure to shedding adults and tests at purchase.

Combination of control measures

When more than two control measures were combined, the proportion of infected herds was reduced further (Fig. 6), even at a moderate level of each measure (hygiene: 0.60, calf management: 0.50, culling: test-and-cull and early removal of affected animals: 13 weeks). While taken alone and with the same characteristics, each of the strategies did not achieve to reduce the herd prevalence. Depending on the combination of measures used, the proportion of infected herds in the metapopulation was reduced by one third to two thirds.

DISCUSSION

As many other diseases, paratuberculosis is mainly introduced in herds by purchasing infected stocks. Therefore, in a perspective of controlling the disease spread at a regional scale, it is necessary both to protect herds free of paratuberculosis from contamination through infected animal purchase and to reduce the impact of the disease in infected herds.

In order to protect uninfected herds, it is necessary to set up a control of animal movements. One manner to do this is to alter the contact network topology by modifying the distribution of trade animal movements over the metapopulation of herds, by promoting exchanges between herds with a same status or by purchasing from herds with better statuses with respect to the infection. Previous studies have shown that such measures could have an impact on pathogen spread (Ezanno et al., 2005; Gates et al., 2013; Gates & Woolhouse, 2013). However, they would require a good knowledge of the epidemiological status of the metapopulation, which is difficult in the case of paratuberculosis, partly due to the silent nature of the disease.

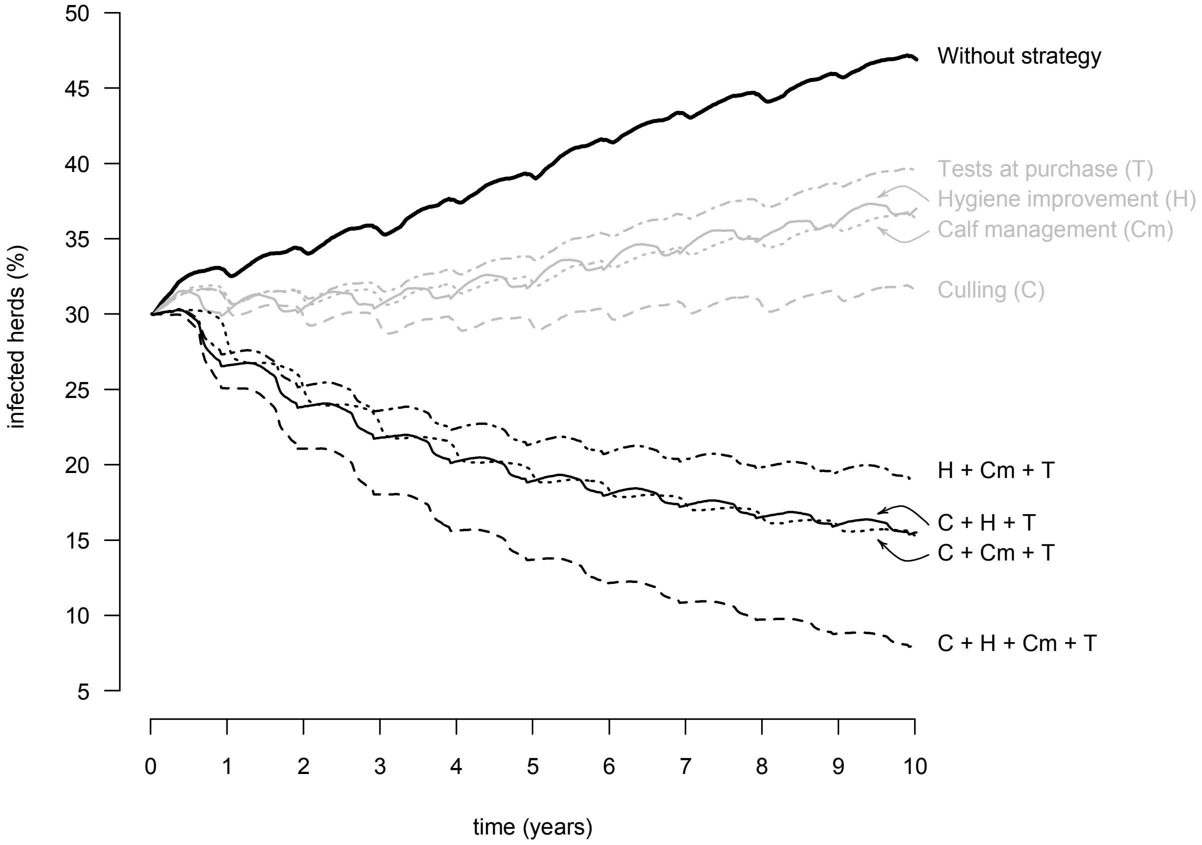


Fig. 10 Average (over 500 runs) proportion of infected herds over time for different combinations of control measures.

Another way to act on movements is to implement tests at purchase. The results obtained by intensive simulations suggested a positive global effect of such measures, but with a limited impact because they did not allow a decrease in herd prevalence. In addition, an immediate result for tests at purchase was assumed, which is not feasible in practice. However, this unrealistic assumption could be overcome by considering that animals enter into a quarantine period from the moment the test is performed until the availability of the test results. Our simulations highlighted the relevance of this type of large-scale strategies and the need to develop more sensitive detection methods.

The reduction in the disease level within herds is possible due to internal biosecurity measures. Previous studies have highlighted the impact of some measures on the within-herd prevalence, especially in the case of paratuberculosis (Marcé et al., 2011b). The impact of such measures beyond the herd level was assessed by quantifying it through the herd prevalence within the metapopulation. Indeed, by reducing the within-herd prevalence, the use of these strategies lowered the probability of transmitting the disease through animal trade.

All internal biosecurity measures are not equivalent. As expected, the use of substitute or pasteurisation for milk and colostrum has almost no effect, which is consistent with the fact that the contributions of these transmission routes are low (Marcé et al., 2011a). Concerning the other measures, when used alone, they allowed reducing *Map* spread in the metapopulation. However, only a high level of hygiene and a strict calf management enabled a decrease in the proportion of infected herds. None of the strategies considered has led to the fadeout of infection over 10 years. Combining each of these biosecurity measures with control of animal movements always enhanced the decrease in herd prevalence. Only hygiene and calf management measures with very drastic levels yielded a reduction in the herd prevalence. However, these efficiency levels are too high and are associated to important costs and constraints and could probably not be maintained long enough in practice to have a significant effect.

Until now, strategies combining control measures concerning animal trade and internal biosecurity had not been evaluated. Simulations performed in this study showed that combining at least two control strategies (at plausible levels) could slow down the progression of the pathogen and decrease the amount of infected herds. These results hold for the case where all farms identically participate to the control scheme. Supplementary simulations would be needed in order to explore the impact of interventions differentially applied to distinct farms.

The modelling approach developed in this study mimicked demographic and epidemiological processes in detail, allowing the evaluation of various control strategies targeting different components of the transmission process.

Paratuberculosis is a slow progressive disease, a silent endemic disease that may go unnoticed for years, due to the presence of the latent stage. Its control should be based on combinations of control measures at different levels: first, by reducing within herd infection level through internal biosecurity measures, and second, by controlling animal trade in order to avoid new infections. Since no effective treatment exists, the effectiveness of the global control will depend on an efficient coordination of interventions and on the characteristics of available diagnostic tools.

ACKNOWLEDGEMENTS

The French Research Agency, program Investments for the future, project ANR-10-BINF-07 (MIHMES), the European fund for the regional development of Pays de la Loire (FEDER), and INRA are acknowledged for providing financial support. The Groupement de Défense Sanitaire de Bretagne and the French Ministry of Agriculture (DGAl) are thanked for providing the movement data used in this work.

REFERENCES

Bajardi, P., Barrat, A., Natale, F., Savini, L. and Colizza, V. (2011). Dynamical patterns of cattle trade movements. PLoS One 6, e19869

Bajardi, P., Barrat, A., Savini, L. and Colizza, V. (2012). Optimizing surveillance for livestock disease spreading through animal movements. J. R. Soc. Interface. 9, 2814–2825

Behr, M.A. and Collins, D.M. (2010). Paratuberculosis: organism, disease, control. CABI

Buhnerkempe, M.G., Tildesley, M.J., Lindström, T. and Grear, D.A. (2014). The Impact of Movements and Animal Density on Continental Scale Cattle Disease Outbreaks in the United States. PLoS One 9, e91724

Dutta, B.L., Ezanno, P. and Vergu, E. (2014). Characteristics of the spatio-temporal network of cattle movements in France over a 5-year period. Prev. Vet. Med. 117, 79-94

Ezanno, P., van Schaik, G., Weber, M.F. and Heesterbeek, J.A.P. (2005). A modeling study on the sustainability of a certification-and-monitoring program for paratuberculosis in cattle. Vet. Res. 36, 811-826

Gates, M.C., Volkova, V.V. and Woolhouse, M.E.J. (2013). Impact of changes in cattle movement regulations on the risks of bovine tuberculosis for Scottish farms. Prev. Vet. Med. 108, 125-136

Gates, M.C. and Woolhouse, M.E.J. (2013). Controlling endemic cattle diseases through the targeted manipulation of contact network topology. In Epidemics 4th, Amsterdam, Netherlands

Guicharnaud, M. (2009). Description de la prevalence de la paratuberculose chez les bovins laitiers dans le monde: revue et analyse. Ecole Nationale Veterinaire de Nantes

Lombard, J.E., Garry, F.B., McCluskey, B.J. and Wagner, B.A. (2005). Risk of removal and effects on milk production associated with paratuberculosis status in dairy cows. J. Am. Vet. Med. Assoc. 227, 1975-1981

Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U. and Fourichon, C. (2011a). Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. Vet. Res. 42, 36

Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U. and Fourichon, C. (2011b). Within-herd contact structure and transmission of Mycobacterium avium subspecies paratuberculosis in a persistently infected dairy cattle herd. Prev. Vet. Med. 100, 116-125

Nielsen, S.S. and Toft, N. (2008). Ante mortem diagnosis of paratuberculosis: a review of accuries of ELISA, interferon-γ assay and faecal culture techniques. Vet. Microbiol. 129, 217-235

Ott, S.L., Wells, S.J. and Wagner, B.A. (1999). Herd-level economic losses associated with Johne’s disease on US dairy operations. Prev. Vet. Med. 40, 179–192

van Roermund, H.J.W., Bakker, D., Willemsen, P.T.J. and de Jong, M.C.M. (2007). Horizontal transmission of Mycobacterium avium subsp. paratuberculosis in cattle in an experimental setting: calves can transmit the infection to other calves. Vet. Microbiol. 122, 270–279

Windsor, P.A. and Whittington, R.J. (2010). Evidence for age susceptibility of cattle to Johne’s disease. Vet. J. 184, 37–44

Whittington, R.J. and Windsor, P.A. (2009). In utero infection of cattle with Mycobacterium avium subsp. paratuberculosis: a critical review and meta-analysis. Vet. J. 179, 60–69

DYNAMIC BETWEEN HERD MODEL FOR Q FEVER SPREAD IN DAIRY CATTLE TO QUANTIFY THE IMPACT OF DIFFERENT TRANSMISSION PATHWAYS AT REGIONAL SCALE

P.S. PANDIT*, P. EZANNO, E. VERGU, B.L. DUTTA, S. ARNOUX , F. BEAUDEAU AND T. HOCH

SUMMARY

A dynamic spatial stochastic model of the spread of *Coxiella burnetii* between dairy cattle herds is presented. The objective of the study is to identify the dominant route of transmission for a major region for dairy cattle farming (Finistère) in France. First, the ability of the model to replicate the observed annual incidence (in number of herds) was assessed. Based on the receiver operating characteristics analysis, the model performed best at infection probability cut-off of 0.28. The model predicted 261 incident herds on average, with sensitivity of 76% and specificity of 77%. At this infection probability cut-off, 79% incident herds were infected because of airborne transmission of the pathogen, while the rest of the herds were infected because of introduction of an infectious cow during the cattle trade. Irrespective of the infection probability cut-off, windborne transmission caused the majority of the introductions compared to the transmission due to cow trade.

INTRODUCTION

The rising number of Q fever cases in humans has become a major concern in recent years. In Europe and especially in the Netherlands, large numbers of outbreaks were seen during 2007-2011 (Roest et al., 2011; Dijkstra et al., 2012). Q fever is caused by *Coxiella burnetii* which is generally seen in numerous animal taxa. Although ubiquitous in nature, livestock remains a major source of concern for zoonotic transfer of the infection. People who are in close contact with livestock are known to be at higher risk of acquiring the infection (Schimmer et al., 2010). The disease is of increasing concern for public health and control of the disease in livestock is essential to prevent the zoonotic transmission. Windborne transmission of the pathogen to relatively longer distances from livestock to humans is very well documented on multiple occasions (Pritchard et al., 1989; Tissot-Dupont et al., 2004; de Bruin et al., 2012; Commandeur et al., 2014; De Lange et al., 2014).

Infection in ruminants may occasionally result in abortions, which also causes large amounts of bacterial shedding along with birth products. In small ruminants sporadic abortions or outbreaks of abortions may be observed. Cattle, sheep and goats are also asymptomatic carriers and can shed bacteria in massive numbers at parturition (Arricau Bouvery et al., 2003). Studies until now have shown that the infection in ruminants is quite prevalent. Prevalence of infected cattle herds varied considerably across the world, from

---

* Pranav Pandit, UMR 1300INRA/Oniris "Biologie, Epidémiologie et Analyse de Risque en Santé Animale" (BioEpAR), LUNAM Université- La Chantrerie CS 40706, F 44307 Nantes. Email: pranav.pandit@oniris-nantes.fr

4.4% to 100% (median 37.7%) while intra-herd prevalence varied from 0 to 47% (median 26.3%). Similarly, in sheep, the herd level prevalence varied from 0 to 89% (median 25%) and in goats the range is 0-100% (median 26%) (Guatteo et al., 2011).

In cows, infected animals shed the bacteria through milk, faeces, birth products and vaginal mucus (Guatteo et al., 2006; Rodolakis, 2009). Cattle get infected by inhalation of the shed bacteria. As described during zoonotic spillovers from livestock to humans, airborne transmission is an important risk factor for cows too; along with cattle trade (Nusinovici et al., 2014). Even though windborne transmission and movements of infected cattle clearly influence the spread of *C. burnetii* at regional level, their relative contribution is not completely understood.

Strategies of controlling the infection within a herd are based upon our understanding of the transmission of the infection within a herd and mainly focus on reducing the environmental contamination by bacteria. Vaccination (phase I antigen), cleaning, disinfection of farm and reduction of contacts with wildlife and ticks are recommended methods of the disease control within herds (Arricau-Bouvery et al., 2005; Guatteo et al., 2008; Taurel et al., 2012; Taurel et al., 2014). In parallel, strategies which can control the spread of the infection over a region are undetermined, mainly because of gaps in our knowledge about the contributions of the different processes involved in the spread of the infection over a region.

To address the objective of understanding the relative contribution of windborne transmission and cattle trade in the regional spread of the *C. burnetii* in a cattle meta-population, a dynamic spatial stochastic model was developed. The model consists of a part which describes infection dynamics within different dairy herds, which are bridged with each other by dispersion model and by movements of cows. Modelling tools are now frequently used in assessing potential control strategies in livestock and animal diseases (Ferguson et al., 2001; McReynolds et al., 2014), but parameterisation of unknown or unmeasurable model parameters has been a perennial issue. Furthermore, methods to assess the reliability of the model and its accuracy, when used for retrospective analysis of outbreak, are not well established. This also leads to certain amount of ambiguity when such models are used for assessing the success of strategies against upcoming outbreaks (Tildesley et al., 2008). Hence, to evaluate the performance of the proposed Q fever metapopulation model, receiver-operating characteristics analysis (ROC) was adapted. The model was assessed for its accuracy in predicting the spread of the infection in cattle herds by comparing model outputs with the observed spread of infection in the Finistère Department in France.

MATERIALS AND METHODS

This section includes general conceptualisation of the metapopulation model, followed by the description of the Finistère Department scenario, where the accuracy of the model was tested against the observed field data. Following that, methods used for the analysis of the model outputs to address the objective of identifying important route of between-herd transmission are described.

Modelling the regional spread of *C. burnetii* in dairy cattle herds

The model for Q fever transmission over a region can be conceptualised by dividing the model into two distinct parts. The first part describes the infection spread within an infected dairy herd. The infection dynamics within a herd is a stochastic model adapted from Courcoul at al. (2011). The second part of the model connects such local models of herds to describe regional propagation leading to the between herd transmission section of the model. Regional spread of the infection is described by two processes, namely the dispersion of the infectious particles by wind and the introduction of infected animals through cattle trade.

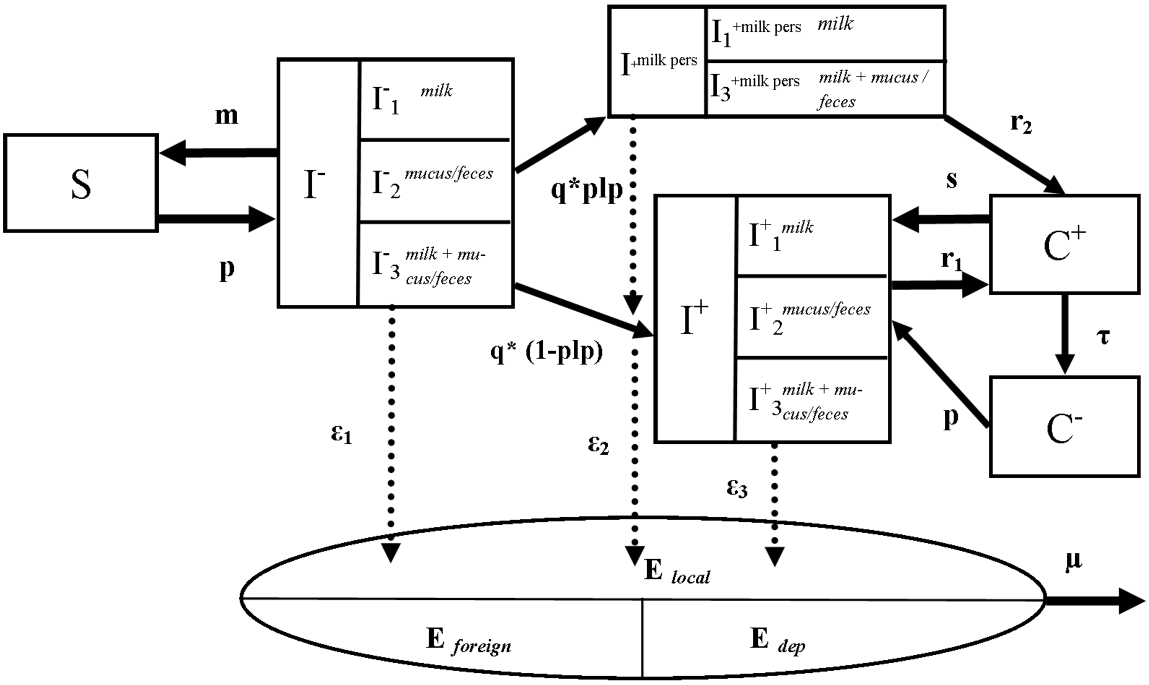


Fig. 11 Flow diagram describing the modelled spread of C. burnetii within a dairy cattle herd. The health states are as following. S: susceptible, non-shedder cow without antibodies, I−: shedder cow without antibodies, I+: shedder cow with antibodies, I+ milk pers: shedder cow with antibodies shedding in milk in a persistent way, C+: non-shedder cow with antibodies and C−: non-shedder cow without antibodies which was infected and had antibodies in the past. I− and I+ cows are in the shedding route category 1 if they shed in milk only, 2 if they shed in vaginal mucus/faeces only and 3 if they shed in milk and vaginal mucus/faeces. I+ milk pers cows are in the shedding category 1 if they shed in milk only and 3 if they shed in milk and vaginal mucus/faeces. E represents the environmental bacterial load. Elocal is the bacteria shed by local animals in the E compartment, Eforeign is the bacteria shed by foreign animals and Edep is the bacteria deposited in E compartment from different infectious herds by airborne dispersion. ε1, ε2 and ε3 are the quantities of bacteria shed during a time step by an individual I−, I+ and I+milk pers respectively, and contaminating the environment. These quantities are the sum of all quantities of bacterial load shed by all the shedders through all the shedding routes and reaching the environment of the herd. Details of the shedding levels and the proportions of cows shedding through different routes are given in Courcoul et al. (2011). Description and values of the parameters used in the model are given in Table 1.

Intra-herd model: The intra herd model is a complex infection dynamics model of *C. burnetii* within a dairy cattle herd in Western France. It is a stochastic, individual based model with one week as simulation time step. The model of infection dynamics is conceptualised using standard compartmental structure (Fig. 1) with added complexity of shedding routes, sero-positivity and intermittency in shedding. Infected cows shed the bacteria through different routes (milk, faeces and mucus) to an environmental compartment which subsequently becomes source of exposure for the susceptible cows. The contribution of bacteria to the environment compartment can occur via three different sources: 1) shedding of bacteria by local animals (cows belonging to the same herd) 2) shedding of bacteria by *foreign animals* (cows which originated from different herds and were shedders at the time when they were bought) and 3) deposition of bacteria because of airborne spread from other infectious herds. Moreover, population dynamics within the herd is also incorporated into the model with integration of culling, lactation and parity. The model assumes that nulliparous cows are always susceptible at calving as seen in a longitudinal study (Guatteo et al., 2008). Hence, they get incorporated into the model as 'susceptible' once they enter their first lactation. The model includes infection transmission only for cows. The model also assumes that there is a constant loss of bacteria from the herd environment, due to natural death of the bacteria and their elimination by management activities and wind.

Table 1. Parameters of the intra herd model

Parameter	Summary	Value
m	Transition probability $I^{-} \Rightarrow S$	0.7
q	Transition probability $I- \Rightarrow I+$	0.02
pIp	Proportion of cows going from I^{-} to I^{+} and becoming $I^{+milk\ pers}$	0.5
r_1	Transition probability $I^{+} \Rightarrow C^{+}$	0.2
r_2	Transition probability $I^{+milk\ pers} \Rightarrow C^{+}$	0.02
s	Transition probability $C+ \Rightarrow I+$	0.15
τ	Transition probability $C^{+} \Rightarrow C^{-}$	0.0096
μ	Death rate related to natural mortality (μ_{death}) and bacteria elimination by the wind ($\mu_{plume\ source}$).	0.2
p	Probability of infection of susceptible cows in the herd	$1\text{-}e^{(-E)}$

Dispersion model: The airborne transmission of the pathogen was modelled using Gaussian dispersion model, incorporating deposition. The smaller droplets generated by sneezing, coughing, splashing and other activities remain suspended in the air and dry fast enough to produce smaller particles called as droplet nuclei which can remain suspended in the air for long duration and can be transported along with the wind to distant places, unlike larger particles. Hence, the inherent capacity of windborne transmission of any infectious agent depends on production of appropriate range of droplet particle sizes with viable pathogens, which can dry fast enough and form droplet nuclei (WHO, 2007). Here, we assume that a part of bacteria shed by cows through different routes form droplet nuclei, which remain infectious and become source for generation of plume which is then transported by the wind to another herd. Multiple studies have suggested a higher risk of windborne transmission of Q fever within the radius of 5 km from the source in moderate environmental conditions (Schimmer et al., 2010; Wallensten et al., 2010). Hence we restrict our dispersion model to a radius of 5 km from the source herd.

The transport and deposition of the infectious particles was modelled by Gaussian Dispersion Equation which accounts for deposition due to settling and gravitation. The model was first developed by Ermak (1977), and is subsequently illustrated by Stockie (2011). A part of the bacteria leaving the environment compartment ($E\mathrm{x}\mu_{plume\ source,}$) of the source herd generates the plume. The concentration of bacteria reaching a herd (destination herd) from the source herd is calculated following Eq. (1).

$$C_{(xyz)} = \frac{Q}{2\pi U\sigma_y\sigma_z} e^{\left(\frac{-y^2}{2\sigma_y{}^2}\right)} \times e^{\left(\frac{-W(z-h)}{2K_z} - \frac{W^2\sigma_z{}^2}{K_z{}^2}\right)} \times$$

$$\left[e^{\left(\frac{-(z-h)^2}{2\sigma_z{}^2}\right)} + e^{\left(\frac{-(z+h)^2}{2\sigma_z{}^2}\right)} - \frac{\sqrt{2\pi}W_o\sigma_z}{K_z} \times e^{\left(\frac{W_o(z+h)}{K_z} + \frac{W_o{}^2\sigma_z{}^2}{K_z^2}\right)} \times erfc\left(\frac{W_o\sigma_z}{\sqrt{2}K_z} + \frac{(z+h)}{\sqrt{2}\sigma_z}\right)\right] \quad (1)$$

where $Q = E \times \mu_{plume\ source}$, W = deposition velocity due to gravitation, $W_o = W - 0.5W_{set}$, W_{set} (settling due Stocke's law) $= \frac{2\rho g r^2}{9\eta}$, and $k_z = 0.5a_z b_z U x^{(b_z-1)}$, the standard deviations of dispersion coefficients for y and z axis are $\sigma_y = a_y x^{b_y}$, $\sigma_z = a_z x^{b_z}$ for the environment stability class C (3-5 m/s wind velocity), *U* is the wind velocity, *erfc* is the complementary error function.

Hence, deposition of bacteria at herd *i* based on the cumulative plume concentration from all possible infectious herds *j* is given as:

$$Dep_i = (area_i \times W \times \textstyle\sum^j C_{i,j}) \quad (2)$$

with $C_{i,j} = C_{xyz,}$ where *x, y* are differences in respective adjusted coordinates of herd *i* (destination herd) and *j* (source herd). Coordinates were adjusted according to the direction of the wind as described in Stockie (2011) and *z* is the height of generation of plume at source herd while *h* is the height of reception at destination herd; both assumed to be 4 meters. Area for each herd was approximated using average space recommendation for a cow and the number of cows in a given herd. The details of the parameter values used for the dispersion model are given in Table 2.

Table 2. Parameters of the dispersion model

Parameter	Summary	Estimation	Unit	Reference
g	Gravitational acceleration	9.8	ms^{-2}	--
z	Height of plume generation	4	m	
h	Height of plume reception	4	m	
η	Dynamic viscosity of air	1.80E-05	$kgm^{-1}s^{-1}$	--
ρ	Density of particles	1150	kgm^{-3}	approximated from Godin et al (2007)
r	Radius of particle	1.00E-06	m	approximated from www.camfilfarr.com
W	Deposition velocity	0.01	ms^{-1}	(Ssematimba et al., 2012)
a_y, b_y, a_z, b_z	Guifford-Pasquill stability class 'C' stability parameters	0.34, 0.82, 0.27, 0.82	s^{-2}	(Stockie, 2011)

Modelling animal trade: The trade of cows was modelled based on the observed data. The data included details of the source and destination herd and the age of the cow at the time of transfer (details of the data are presented in the following section). The probability of transfer of an infectious cow to a herd depends directly upon the prevalence of the infection within the specific age group (based on the parity of animal from the epidemiological model) in the source herd. According to the data, a cow from the given age group of the source herd was randomly chosen to move to the destination herd. The probability of acquiring infection during possible interactions in markets with infectious cows was considered negligible and hence ignored. The model only considered movements within the herds of the region and did not account for movements to and from herds outside the study region.

Description of the data used for scenario of Finistère Department, France

Q fever data in dairy herds: In May 2012, almost all the dairy herds (2883 out of 2982 herds had geolocation and herd size data available) in the Department of Finistère were tested for antibodies against *C. burnetii* using ELISA tests on bulk tank milk samples. Infection free herds according to this test were re-tested again in May 2013 to describe the spread of the infection within a year and identify the newly infected herds. Out of 866 herds tested negative in May 2012, 826 herds were tested again in May 2013: 306 herds were found positive at this date, leading to an incidence risk of 37.04 %.

Data for wind velocity: Wind velocity data required for dispersion modelling were procured from publically available European Centre for Medium Range Weather Forecasts database (ECMRW, 2013). Northward wind component and eastward wind component data for Finistère Department for the year 2012 were procured. The daily data were later converted to weekly averages for utilisation in the model.

Cattle trade data: France maintains a register of cattle movements within the country (Dutta et al., 2014). For the purpose of the study, data for the movements of cows from one dairy herd to another in the Finistère Department only, for the time period between May 2012 and June 2013 were extracted from the register (Source: Groupements de Défense Sanitaire de Bretagne, France). In total 835 out of 2,883 dairy herds participated in the 2,234 movements during the year of study. 474 herds sold their animals while 491 herds bought these animals with mean of 4.7 animals sold (out strength) to an average of 1.43 herds (out-degree) and mean of 5.3 cows bought (in strengths) from an average of 1.63 herds (in-degree).

Description of Finistère scenario and ROC analysis of the model outputs

Simulation settings: Every iteration of the Finistère scenario consisted of two separate steps. In the first step, initial conditions were simulated for prevalent herds in agreement with field observations in May 2012. To achieve them, independent intra-herd models for these herds, initiated by a single introduction of an infectious animal, were run until observed sero-prevalence was reached. Once the expected initial sero-prevalence in all the known prevalent herds was obtained, the metapopulation model was run for the duration of one year. The between herd-transmission was governed by wind dispersion and movements of cows between herds.

Model outputs and identification of cause of infection in 'Incident herds': Amongst 100 iterations of the model, each initially susceptible herd either remained infection free or got infected. An Infection Probability (IP) for an initially susceptible herd thus was estimated by the number of runs the herd got infected in a given number of iterations. The model also gave an output for average contribution of bacteria in infection free herds by windborne dispersion and by foreign animals at the time of generation of the first case in local animals of the herd. Every time there was a movement of a shedding cow, the destination herd got relatively large contribution from the newly introduced infectious cow compared to the contribution from the wind. Hence, the dominant route at the time of generation of the first case was identified as the cause of infection for the incident herd, leading to a binary classification of herds based on the cause of infection.

Variation of model outputs over different infection probability cut-offs: Infection Probability for each herd was used to classify an initially susceptible herd into incident herd and subsequently to estimate the overall incidence for the spread of the infection within a year. Hence, different infection probabilities were assessed as cut-offs to classify herds as infected (Incident herds). The behaviours of the model outputs such as total incidence and contributions of transmission pathways were also observed at different cut-offs of infection probabilities.

Measures of agreement: The accuracy of the model at different cut-offs was analysed by comparing the model outputs with the data. This was performed using standard ROC analysis (Greiner et al., 2000), in which observed incident herds in May 2013 were used as reference for the probability of initially susceptible herds to become infected as predicted by the model (herd level comparison). To assess to which extent the dispersion model was predicting the incidence better around an expected incident herd, if not at exact herd level, the precision in the ROC analysis was relaxed and the output for a neighbourhood around the expected incident herd was compared to data. The comparison was done for neighbourhood distances of multiple radii (1, 2, 3 or 4 km). Overall model performance for herd level comparison and neighbourhoods were assessed using AUC (Area Under Curve), while the optimum cut-off values for infection probability were selected based on the sensitivity (Se), specificity (Sp), accuracy $\left({}^{true\ positve\ +\ true\ negative}\big/_{total\ population}\right)$ (noted by Acc) and Youden index $(\mathrm{Sensitivity} + \mathrm{Specificity} - 1)$ (noted by J) at different cut-offs. Criteria such as sensitivity ≈ specificity (where ≈ means approximately equal to), maximum accuracy and maximum Youden index were considered to optimise the infection probability cut-off.

RESULTS

In 100 iterations, 847 out of 866 initially infection free herds in May 2012 got infected at least once. 96 % introductions of infection in these infection free herds were attributed to windborne transmission while the rest were attributed to cattle trade between the herds. For different cut-offs of the infection probability, the size of the infection spread predicted by the model decreased drastically. Incidence predicted by the model for different infection probability cut-offs is shown in Fig. 2. Simultaneously, the incidence attributed to airborne dispersion decreased similarly and the incidence attributed to trade of animals decreased gradually. Highest relative contribution of animal trade in the total incidence was 31.7% and was observed at 0.65 infection probability cut off.

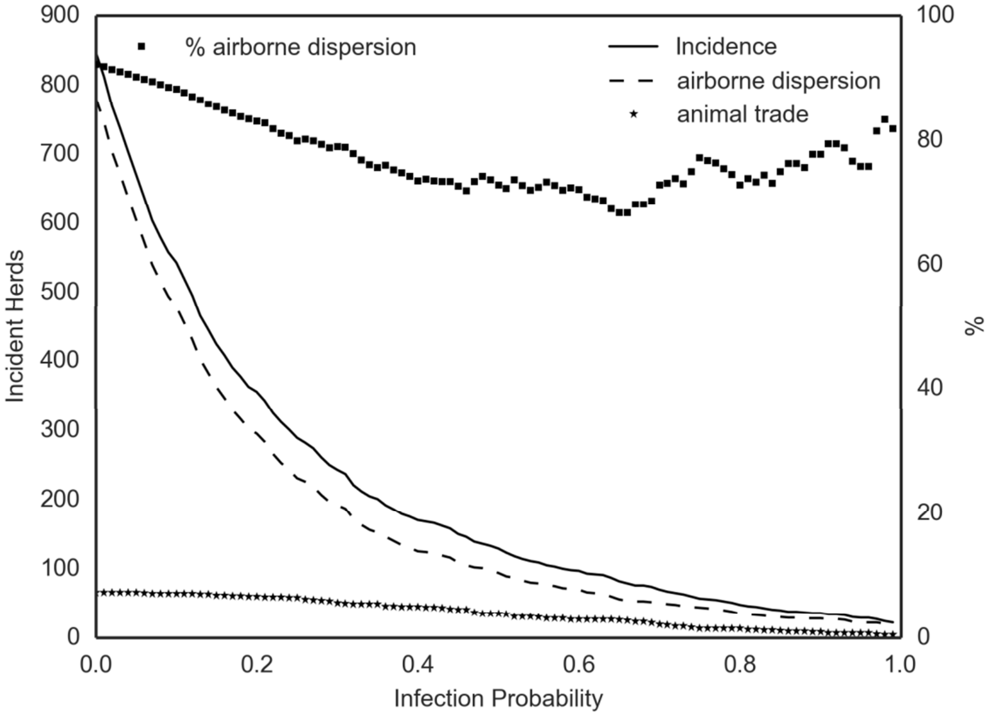


Fig. 12 Overall incidence and incidence attributed to infection causes at different cut-offs of infection probability. Y axis on the right hand side shows % herds infected because of airborne dispersion.

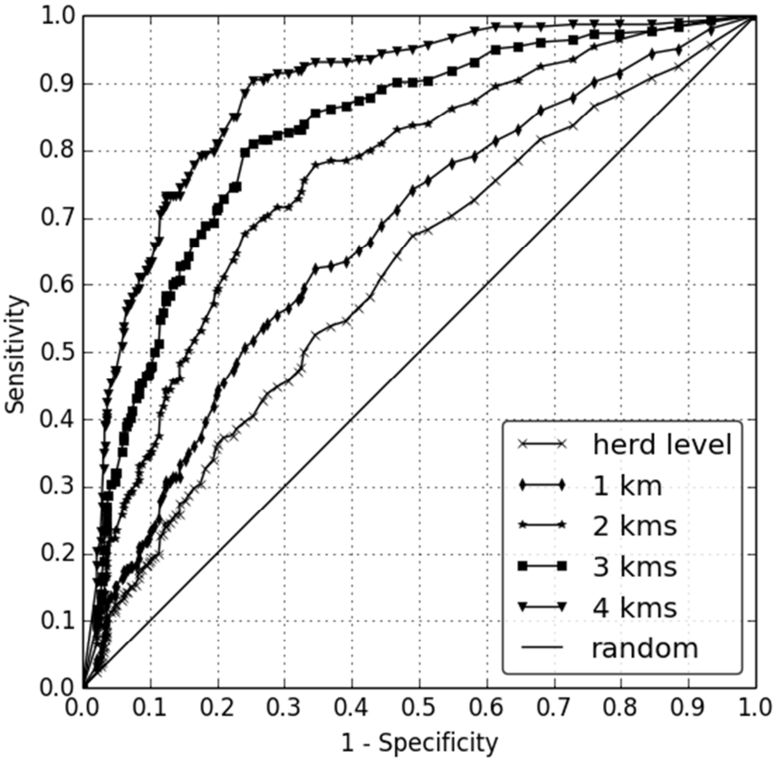


Fig. 3 ROC curve and performance of the model at the herd level and for different neighbourhood radii.

Herd level ROC analysis showed that the model was moderately informative in correctly classifying herds. The analysis showed AUC of 0.61 at herd level, while the analysis done for neighbourhoods of 1, 2, 3, and 4 km showed higher AUC of 0.67, 0.76, 0.83 and 0.88 respectively (Fig. 3). Neighbourhoods of 1, 2, 3, and 4 km on average had 0.5, 1.9, 4 and 6.8 susceptible herds. Hence, a subjective compromise was made to consider a neighbourhood of 3 km for further analysis, based on the fact that the model performed better with lower number of average susceptible neighbours.

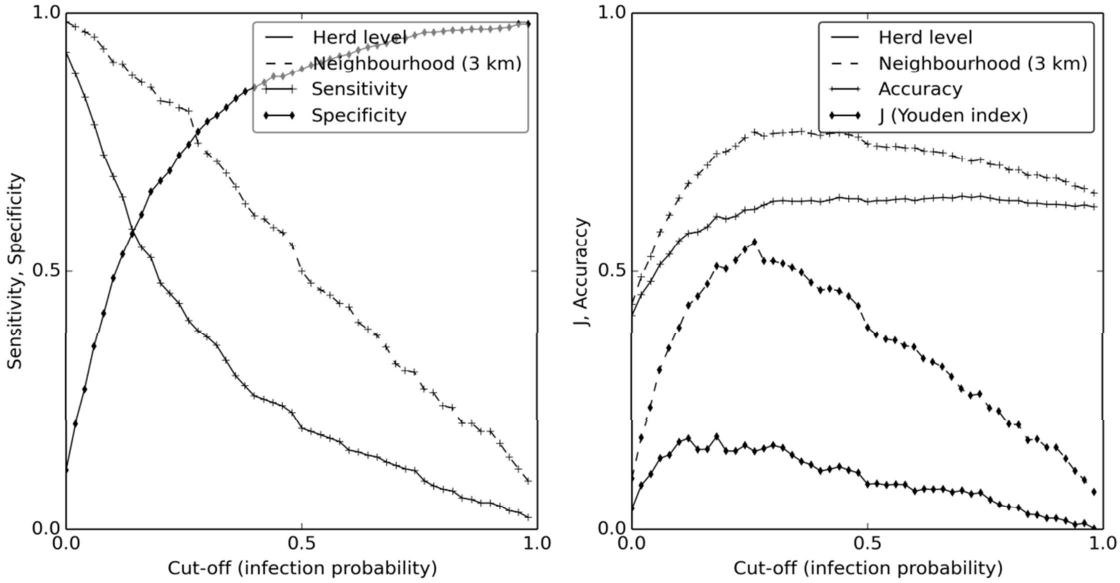


Fig. 4 Sensitivity, specificity, accuracy and Youden Index of the model at the herd level (solid lines) and for a neighbourhood of 3 km (dashed lines). The specificity of the model at herd level as well as for a neighbourhood of 3 km is the same and is shown by one single curve

Table 3. Performance of the model at the herd level and neighbourhood analysis.

	Herd level			Neighbourhood (3 km)		
Estimator	Se≈Sp	Acc_{max}=0.64	J_{max}=0.18	Se≈Sp	Acc_{max}=0.77	J_{max}=0.55
IP	**0.14**	**0.70**	**0.11**	**0.28**	**0.27**	**0.27**
Se	0.58	0.12	0.68	0.76	0.79	0.79
Sp	0.57	0.95	0.50	0.77	0.74	0.74
Acc	0.57	0.64	0.57	0.76	0.77	0.77
J	0.15	0.07	0.18	0.52	0.55	0.55
Incidence	445	70	519	261	274	274
% airborne transmission	85.8	72.8	87.7	79.3	79.9	79.9

The criterion of sensitivity ≈ specificity was observed at 0.14 and 0.28 infection probability for herd level and neighbourhood of 3 km, respectively. Maximum accuracy for herd level and for neighbourhood of 3 km was seen at 0.7 and 0.27 infection probabilities, while maximum Youden index was seen at 0.11 and 0.27 infection probabilities, respectively (Fig. 4). Sensitivity (Se), specificity (Sp), accuracy (Acc), Youden index (J), number of incident herds (Incidence) and proportion of herds infected because of airborne transmission of the pathogen (% airborne transmission) at these cut-offs of Infection Probability are given in Table 3. As shown in Table 3, for neighbourhood of 3 km, cut-offs of 0.27 and 0.28 gave similar estimates of criteria in consideration. Keeping this in mind, we narrowed down to a single possible cut-off value of infection probability of 0.28 for neighbourhood of 3 km. For herd level, model performed better around 0.11, 0.14 and 0.70 infection probability cut-offs. At 0.28 infection probability cut-off for neighbourhood of 3 km, the model predicted 261 incident herds on average, with sensitivity of 76 % and specificity of 77 %. The incidence predicted at these cut-offs is mapped in Fig. 5.

DISCUSSION

Quantitative estimation of contribution of airborne spread and cow trade in the regional spread of Q fever in dairy cattle herds was done and showed significant contribution of windborne transmission. Trade of infectious cows contributes in lesser extent to the regional spread of the disease. Nusinovici et al. (2014) showed that in Finistère department windborne transmission and cattle trade both are risk factors for seropositive herds (Nusinovici et al., 2014). They also showed that higher proportion of cases were attributable to windborne transmission than to animal movements when animal density is higher. Model predictions are in accordance with the study mentioned and ascertain each other’s conclusions. While windborne infection has the ability to introduce infection in larger number of herds, the size and longevity of such intra herd outbreaks needs to be compared with the ones initiated by the introduction of a shedding cow.

The model here considers cow trade within the dairy herds in an administrative department. Inclusion of cow transactions from the rest of the herds outside the department will surely affect the contribution of cattle trade. There is also slight underestimation of windborne transmission from beef herds nearby. Hence, model can become more precise with availability of data about beef herds and other livestock flocks in and around the region. The model only measures the contribution of transmission pathways in initiating the infection in susceptible herd, which is the primary case. Further analysis to understand the overall contribution in terms of secondary cases irrespective of the cause of introduction of the disease will throw more light on the detailed impact of these two routes.

Results presented here also give insights about the possible control strategies that might be applied on the regional scale, specifically in preventing the spread of infection in infection free herds. Windborne transmission is generally difficult to control and vaccination of herds to reduce the bacterial shedding may help in reducing the exposure to bacteria in infection free herds (Taurel et al., 2012). Testing of animals before trading may also help in controlling the infection. But efficiency of each of these interventions and mixtures of these preventive strategies needs to be assessed.

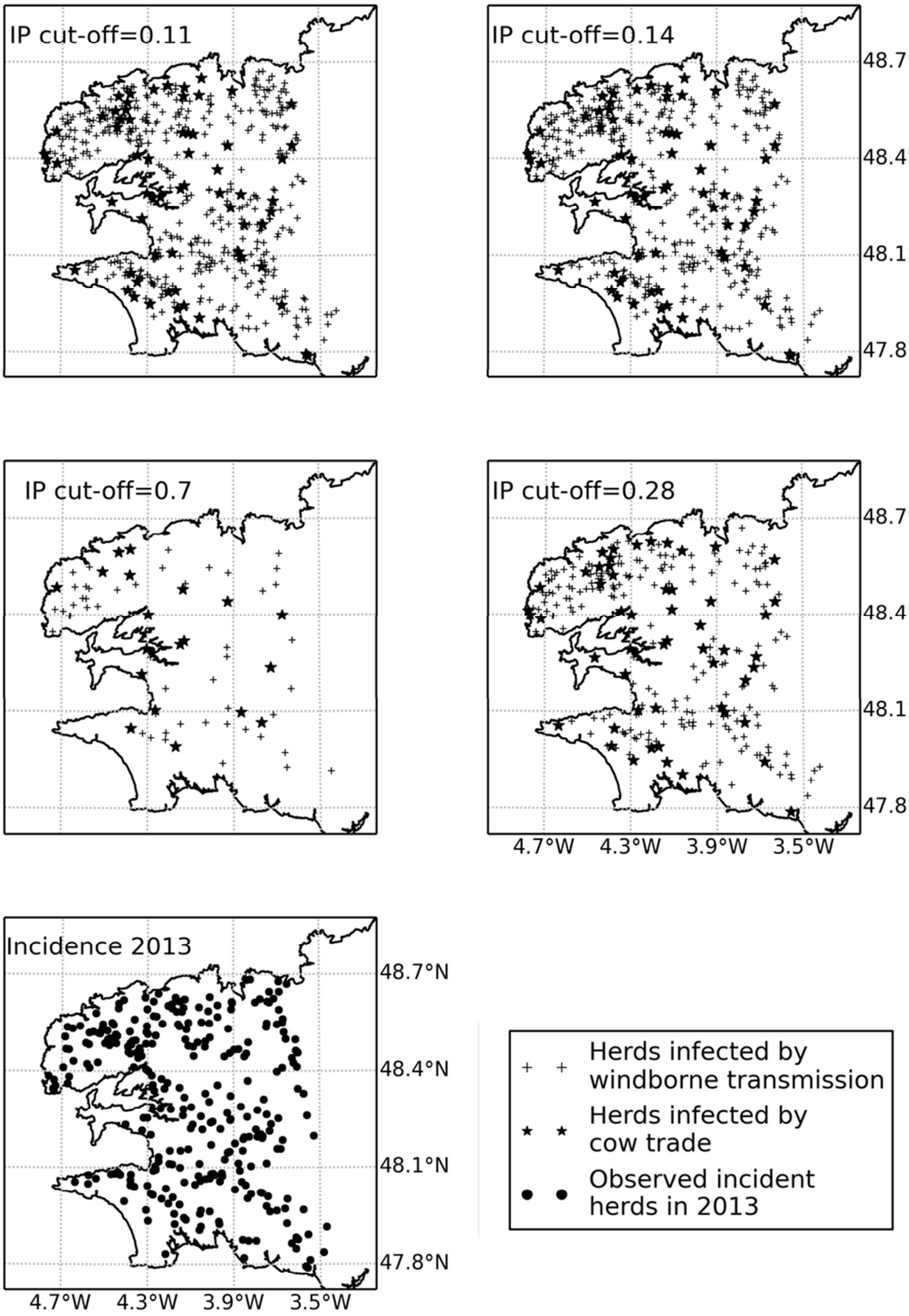


Fig. 5 Maps showing incident herds in Finistère department France, as predicted by the model at different cut-offs of infection probabilities. Infection probability (IP) cut-offs 0.11, 0.14 and 0.70 are possible optimum cut-offs for herd level and 0.28 optimum cut-off is for the neighbourhood of 3 km. Last map shows incident herds observed in 2013 (according to ELISA for bulk tank milk).

The ROC analysis was adapted to analyse the performance of an animal disease model, which is rarely done, mainly because of unavailability of field data. In the presence of field data, this type of analysis can also be used to calibrate unknown parameters of the model to best fit the data, along with traditional methods. Such analysis of any model also gives end users of the model an easy estimator about the model performance while using it in the field as a tool. The ROC analysis of the model output showed adequate level of accuracy of the model at a neighbourhood level. Even though the model was only moderately informative at herd level comparison, the overall competence of the model to predict spread at regional level of the disease was satisfactory. The dispersion model applied here is inherently spatial, and in general the dispersion models perform better with precise information of environmental parameters such as wind speed and direction (Gloster et al., 2010). Hence, to incorporate the spatial uncertainty caused by imprecision arising due to Gaussian model, the evaluation of the model outputs was relaxed by comparing the results over neighbourhood rather than at herd level.

The preferred neighbourhood distance for the neighbourhood ROC analysis here was 3 km. This was a subjective decision based on the number of susceptible neighbours present in the given vicinity and the performance of the model. Hence, if the model has to be applied for another geographical region the neighbourhood distance may depend on the herd density as well as the initial proportion of prevalent herds.

These results support the use of this model for in silico assessment of control strategies for the regional spread of Q fever in cattle herds, but refinement of the model based on intense field data may surely improve the model further.

ACKNOWLEDGEMENTS

The French Research Agency, program Investments for the future, project ANR-10-BINF-07 (MIHMES), the European fund for the regional development of Pay de la Loire (FEDER), and INRA and Oniris are acknowledged for their financial support. The Groupement de Defense Sanitaire de Bretagne and the French Ministry of Agriculture (DGAl) are thanked for providing the movement data used in this work.

REFERENCES

Arricau Bouvery, N., Souriau, A., Lechopier, P. and Rodolakis, A. (2003). Experimental *Coxiella burnetii* infection in pregnant goats: excretion routes. Vet. Res. 34, 423-433

Arricau-Bouvery, N., Souriau, A., Bodier, C., Dufour, P., Rousset, E. and Rodolakis, A. (2005). Effect of vaccination with phase I and phase II *Coxiella burnetii* vaccines in pregnant goats. Vaccine 23, 4392-4402

Commandeur, M., Jeurissen, L., van der Hoek, W., Roest, H.J. and Hermans, T.C. (2014). Spatial relationships in the Q fever outbreaks 2007-2010 in the Netherlands. Int. J. Environ. Health Res. 24, 137-157

Courcoul, A., Monod, H., Nielen, M., Klinkenberg, D., Hogerwerf, L., Beaudeau, F. and Vergu, E. (2011). Modelling the effect of heterogeneity of shedding on the within herd *Coxiella burnetii* spread and identification of key parameters by sensitivity analysis. J. Theor. Biol. 284, 130-141 de Bruin, A., van der Plaats, R.Q., de Heer, L., Paauwe, R., Schimmer, B., Vellema, P., van Rotterdam, B.J. and van Duynhoven, Y.T. (2012). Detection of *Coxiella burnetii* DNA on small-ruminant farms during a Q fever outbreak in the Netherlands. Appl. Environ. Microbiol. 78, 1652-1657

De Lange, M.M., Schimmer, B., Vellema, P., Hautvast, J.L., Schneeberger, P.M. and van Duijnhoven, Y.T. (2014). *Coxiella burnetii* seroprevalence and risk factors in sheep farmers and farm residents in The Netherlands. Epidemiol. Infect. 142, 1231-1244

Dijkstra, F., van der Hoek, W., Wijers, N., Schimmer, B., Rietveld, A., Wijkmans, C.J., Vellema, P. and Schneeberger, P.M. (2012). The 2007–2010 Q fever epidemic in The Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol. Med. Microbiol. 64, 3-12

Dutta, B.L., Ezanno, P. and Vergu, E. (2014). Characteristics of the spatio-temporal network of cattle movements in France over a 5-year period. Prev. Vet. Med. 117, 79-94

Ermak, D.L. (1977). An analytical model for air pollutant transport and deposition from a point source. Atmos. Environ. 11, 231-237

Ferguson, N.M., Donnelly, C.A. and Anderson, R.M. (2001). The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. Science 292, 1155-1160

Gloster, J., Jones, A., Redington, A., Burgin, L., Sørensen, J.H., Turner, R., Dillon, M., Hullinger, P., Simpson, M., Astrup, P., Garner, G., Stewart, P., D'Amours, R., Sellers, R. and Paton, D. (2010). Airborne spread of foot-and-mouth disease - Model intercomparison. Vet. J. 183, 278-286

Godin, M., Bryan, A.K., Burg, T.P., Babcock, K. and Manalis, S.R. (2007). Measuring the mass, density, and size of particles and cells using a suspended microchannel resonator. Appl. Phys. Lett. 91, 123121

Greiner, M., Pfeiffer, D. and Smith, R.D. (2000). Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev. Vet. Med. 45, 23-41

Guatteo, R., Beaudeau, F., Berri, M., Rodolakis, A., Joly, A. and Seegers, H. (2006). Shedding routes of *Coxiella burnetii* in dairy cows: implications for detection and control. Vet. Res. 37, 827-833

Guatteo, R., Seegers, H., Joly, A. and Beaudeau, F. (2008). Prevention of *Coxiella burnetii* shedding in infected dairy herds using a phase I *C. burnetii* inactivated vaccine. Vaccine 26, 4320-4328

Guatteo, R., Seegers, H., Taurel, A.F., Joly, A. and Beaudeau, F. (2011). Prevalence of *Coxiella burnetii* infection in domestic ruminants: a critical review. Vet. Microbiol. 149, 1-16

McReynolds, S.W., Sanderson, M.W., Reeves, A. and Hill, A.E. (2014). Modeling the impact of vaccination control strategies on a foot and mouth disease outbreak in the Central United States. Prev. Vet. Med. 117, 487-504

Nusinovici, S., Hoch, T., Widgren, S., Joly, A., Lindberg, A. and Beaudeau, F. (2014). Relative contributions of neighbourhood and animal movements to *Coxiella burnetii* infection in dairy cattle herds. Geospat. Health 8, 471-477

Pritchard, G.C., Borland, E.D., Wood, L. and Pritchard, D.G. (1989). Severe disease in a dairy herd associated with acute infection with bovine virus diarrhoea virus, *Leptospira harjo* and *Coxiella burnetii*. Vet. Rec. 124, 625-629

Rodolakis, A. (2009). Q Fever in dairy animals. Ann. N. Y. Acad. Sci. 1166, 90-93

Roest, H.I., Hogerwerf, L., van der Brom, R., Oomen, T., van Steenbergen, J.E., Nielen, M. and Vellema, P. (2011). Q fever in the Netherlands: current status, results from veterinary research and expectations of the coming years. Tijdschr. Diergeneeskd. 136, 340-343

Schimmer, B., Ter Schegget, R., Wegdam, M., Züchner, L., de Bruin, A., Schneeberger, P.M., Veenstra, T., Vellema, P. and van der Hoek, W. (2010). The use of a geographic information system to identify a dairy goat farm as the most likely source of an urban Q-fever outbreak. BMC Infect. Dis. 10, 69

Ssematimba, A., Hagenaars, T.J. and de Jong, M.C. (2012). Modelling the wind-borne spread of highly pathogenic avian influenza virus between farms. PLoS One 7, e31114

Stockie, J.M. (2011). The mathematics of atmospheric dispersion modeling. Siam Rev. 53, 349-372

Taurel, A.F., Guatteo, R., Joly, A. and Beaudeau, F. (2012). Effectiveness of vaccination and antibiotics to control *Coxiella burnetii* shedding around calving in dairy cows. Vet. Microbiol. 159, 432-437

Taurel, A.F., Guatteo, R., Lehebel, A., Joly, A. and Beaudeau, F. (2014). Vaccination using phase I vaccine is effective to control *Coxiella burnetii* shedding in infected dairy cattle herds. Comp. Immunol. Microbiol. Infect. Dis. 37, 1-9

Tildesley, M.J., Deardon, R., Savill, N.J., Bessell, P.R., Brooks, S.P., Woolhouse, M.E., Grenfell, B.T. and Keeling, M.J. (2008). Accuracy of models for the 2001 foot-and-mouth epidemic. Proc. Biol. Sci. 275, 1459-1468

Tissot-Dupont, H., Amadei, M.A., Nezri, M. and Raoult, D. (2004). Wind in November, Q fever in December. Emerging Infect. Dis. 10, 1264-1269

Wallensten, A., Moore, P., Webster, H., Johnson, C., van der Burgt, G., Pritchard, G., Ellis-Iversen, J. and Oliver, I. (2010). Q fever outbreak in Cheltenham, United Kingdom, in 2007 and the use of dispersion modelling to investigate the possibility of airborne spread. Euro Surveill. 15: 19521

World Health Organization. (2007). Infection prevention and control of epidemic-and pandemic-prone acute respiratory diseases in health care: WHO interim guidelines

MOBILE BARRIERS AS EMERGENCY MEASURE TO CONTROL OUTBREAKS OF AFRICAN SWINE FEVER IN WILD BOAR

M. LANGE* AND H.-H. THULKE

SUMMARY

African Swine Fever (ASF) is spreading invasively in Eastern European swine populations. Due to the lack of a vaccine, options for control measures are sought for emergency management of ASF in wild boar populations. The high lethality of ASF infections in European wild boar suggests compartmentalisation of infected from naive wild boar populations through temporary barriers. The aim of the strategy is to isolate an already affected outbreak area until the virus fades-off therein. Contrary, local depopulation is meant to actively reduce the wildlife host density. The compartmentalisation and local depopulation approach were compared in a theoretic simulation experiment using a process-based epidemiological computer model representing wild boar demography and ASF epidemiology. Both strategies performed comparably well in the ideal scenario i.e. impermeable barriers and unchanged movement behaviour of surviving animals during local depopulation activities. In simulations where the barriers were imperfect and the population reduction incurred perturbations, the compartmentalisation was more reliable than local population reduction. The effectiveness, however, depended decisively on behavioural ecology of animals in the acute disease stage.

INTRODUCTION

African swine fever is a viral disease of suids. The African swine fever virus (ASFV) originates from the African continent (Costard et al., 2009) and infects warthogs, bushpigs, wild boar and domestic pigs (Penrith et al., 2013). The disease can cause up to 100 percent mortality in pigs (Dixon et al., 2008; Chapman et al., 2011) while warthogs do not develop clinical symptoms (Thomson et al., 1980). ASF is considered an endemic disease in several African countries, where the virus is maintained either in an ancient sylvatic cycle between warthogs and ticks of the *Ornithodoros moubata* complex or in a domestic cycle with or without tick involvement (Penrith et al., 2009; Beltrán-Alcrudo et al., 2009; Costard et al., 2013).

During the recent emergence of the disease in the Caucasus region, Russia, Belarus, Ukraine and subsequent entry into the EU, ASF detections in wild boar were regularly reported (Khomenko et al., 2013; OIE, 2014). The risk of wild boar mediated spread of ASF into new territories (De la Torre et al., 2013) is documented for example by entry events into EU member states (Gallardo et al., 2014; EFSA, 2014). However, and other than in livestock, the available options to control potential spread of ASFV in wild boar populations are rather limited. No vaccination method is available. Drastic host density reduction was usually ineffective in supporting direct control of a wildlife disease (Wobeser, 1994) and is agreed to

---

* Corresponding author: Martin Lange, Helmholtz-Centre for Environmental Research Leipzig – UFZ, Permoserstraße 15, 04318 Leipzig, Germany. Email: martin.lange@ufz.de

be unsuitable as large-scale measure against wildlife ASF (EFSA, 2014). Additionally, population reduction by intensive hunting is facing particular problems, like potential disturbance effects (Sodeikat & Pohlmeyer, 2002; Thurfjell et al., 2013), or lack of acceptance by the public (Massei et al., 2011). Nevertheless, the application of localised population reduction in wild boar is still debated due to the limited range of alternatives (EFSA, 2010; Anonymous, 2014; Hõbemägi, 2014; Clifton, 2014).

Compartmentalisation may be enacted through temporary mobile barriers, e.g. wildlife fences. Mobile barriers could enclose affected subpopulations, and moreover can be adapted to changing situations or new detections. It is tempting to explore the potential of the approach in terms of local emergency activities. Indeed, barriers of wildlife fences are frequently used to protect crops from wild boar damage, to exclude invasive species like feral pigs (Massei et al., 2011), and to reduce wildlife/vehicle collisions on highways (see, e.g. Clevenger et al., 2001; Glista et al., 2009).

The principle of both strategies is the interruption of the transmission chain. For the depopulation strategy, this is intended by actively reducing the host population density and thereby decreasing the number of secondary cases caused by each infected host. The barriers strategy aims at separating the infected area from surrounding, naïve sub-populations and awaiting self-limitation of the infection. Both strategies are most effective if the entire infected area would have been covered. However, after detection of an ASFV case or a sero-positive wild boar, the actually infected area is still unknown. Therefore, both strategies must follow an adaptive approach aiming at (buffered) coverage of the presumably infected population. The principle of protecting the non-affected sub-population, however, is different for the two approaches. While the compartmentalisation strategy delineates the border between infected and protected sub-populations, the depopulation strategy adds a buffer of reduced density around the detected infected area to reduce the risk of hosts dispersing into the protected sub-population.

The objective of this study was the comparison of depopulation-based emergency management of ASF outbreaks with alternative options based on temporary establishment of mobile barriers. At the time of this study experimental field studies regarding the effectiveness of local depopulation or compartmentalisation as emergency measures against spread of ASF in wild boar populations did not exist. A process-based, spatially-explicit and individual-based model of ASFV in wild boar populations was used to compare local depopulation and barrier-based enclosure assuming different efficacy and side-effects.

MATERIALS AND METHODS

Model description

Overview: The ASF wild boar model is a compilation of a spatially explicit, stochastic, individual based demographic model for wild boars (*Sus scrofa*) in a structured landscape of habitat area. Superimposed is a transmission and disease course model for the ASFV. The model is documented following the ODD protocol (Overview, Design, Details; Grimm et al., 2006; Grimm et al., 2010). The complete documentation protocol (ODD) of the model can be found at http://ecoepi.eu/ASFWB.

Surveillance and management: A schematic diagram of management and surveillance is shown in Fig. 1. The measures are implemented as adaptive processes, based on virological and serological testing of randomly sampled wild boar individuals. The (unknown) actually infected area (grey in Fig. 1) does not interfere with the simulations regarding design of zones and application of measures. Before detection of the first case of a simulation, spatially uniform disease surveillance is performed by sampling and testing in regular intervals t_m, where the sampling density is determined by the hunting parameter h_{base}. The parameter refers to the share of the population that is shot and tested for virus- and sero-positivity during one hunting campaign. Habitat cells containing animals with positive diagnostic are labelled infected (tests are assumed perfectly sensitive and specific).

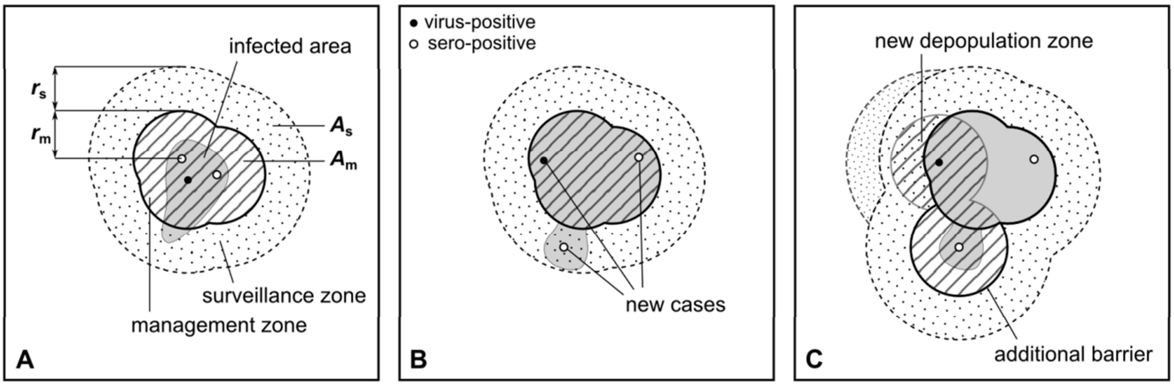


Fig. 1 Schematic diagram of management and surveillance. A) Initial case detections through virus-positive (filled dots) and sero-positive (hollow dots) animals, and measures implemented thereafter: management zone A_m, enclosed by barriers (solid lines) or with depopulation (hatched area). In both cases with associated intensified surveillance in a surrounding buffer (dotted area A_s). B) Situation at detection of cases after the initial campaign. C) Measures implemented thereafter: Any detection (virus- and sero-positive) outside the management zone A_m triggers the establishment of new barriers (solid lines) or a new depopulation area (lower part of hatched area). Additionally, virus-positive case detections inside the management zone trigger a new depopulation area (upper part of hatched area). Grey area: true infected area (unknown), circles: detected cases (filled: virus-positive, hollow: sero-positive); Solid lines: location of the movement barrier in radial distance r_f of the case detections; Hatched area: depopulation area; Dotted area with dashed edge: surveillance area of increased hunting in radial distance r_h of the movement barrier. Fine dotted area: additional surveillance zone under depopulation, triggered by virus-positive case detection in management zone.

On detection of positive animals, control, fencing and monitoring measures are implemented (see Fig. 1A) and performed during the subsequent interval t_m. Around all detected virus- or sero-positive animals (black and hollow circles in Fig. 1A, resp.), a management area A_m is determined by buffering the respective cells with the width specified by radius r_m (hatched area). Under the barriers strategy, a fence is constructed around A_m (solid lines), while under the depopulation strategy, one population reduction campaign is performed in A_m (hatched area). Around A_m, an additional buffer with radius r_s is employed. The resulting area A_s is subject to increased hunting for monitoring purposes (dotted area with dashed outline in Fig. 1A). In the area A_s, hunting and testing is performed with increased hunting pressure parameter h_{inc}. For all other areas, the baseline hunting is maintained with h_{base}. Furthermore, from the first case detection onwards, each infectious carcass is detected in A_m and A_s with probability h_{carc} per surveillance campaign. Detected carcasses are removed from the model.

Once the initial campaign is performed, both strategies slightly deviate upon further case detections (Fig. 1B). In both strategies, any case (virus- or sero-positive or infected carcass) outside the management zone A_{m} triggers an extension of the zones (Fig. 1C). Under the barriers strategy, a fence is constructed to enclose the newly declared management zone ('additional barrier' in Fig. 1C). The surveillance zone is redefined by buffering the extended management zone by r_{s} (coarse dotted area in Fig. 1C).

Under the depopulation strategy, an additional update of the zones is triggered by subsequent detections of virus-positive animals or infected carcasses inside the management zone. Buffering the new detections by r_{m} defines the depopulation zone for the next campaign (hatched area 'new depopulation zone' in Fig. 1C), and that area is added to the management zone. The surveillance zone is redefined by buffering the extended management zone by r_{s} (coarse and fine dotted area in Fig. 1C).

Simulation experiments: Five management strategies were simulated:

1. N: reference scenario without any management
2. B00: perfect barriers, without permeability ($p_{err} = 0.0$)
3. B10: barriers with 10% permeability ($p_{err} = 0.1$)
4. H2-: depopulation to 2 heads/km² (culling of ≈ 60% of the population), no disturbances ($d_{target} = 2$, $p_{neigh} = 0.0$, $\hat{p}_{core}^{(\mathrm{f})} = 0.9$, $\hat{p}_{core}^{(\mathrm{m})} = 0.8$)
5. H2+: depopulation to 2 heads/km², with disturbances ($d_{target} = 2$, $p_{neigh} = 0.333$, $\hat{p}_{core}^{(\mathrm{f})} = \hat{p}_{core}^{(\mathrm{m})} = 0.333$)

Each strategies, except N, was simulated for different radii of the management zone $r_m \in \{4km, 8km, 12km, \dots, 40km\}$. The radius of the surveillance zone was fixed at $r_s = 20km$ for all strategies. Each combination of management strategy and radius of the management zone was simulated with 120 repetitions, resulting in a total of 4,920 simulations. All simulations were run until virus extinction (i.e. no infected animals and carcasses), but for a maximum of 20 years.

In addition, strategies N, B10 and H2+ were simulated under more pessimistic assumptions of the behaviour of moribund hosts. Here, a lower probability of carcass deposition in the core area was assumed with $p_{core}^{(\mathrm{f})} = 0.75$, $p_{core}^{(\mathrm{m})} = 0.33$. The radii of the management zone and the 120 repetitions were as described before.

Analysis: The outcome of the dependent variables of individual simulation was aggregated by management scenario and radius of the management zone. The distributions of the dependent variables are presented as boxplots.

RESULTS

Optimistic assumptions

The finally infected area without management (N) and under the optimistic management options B00 (barriers without permeability) and H2- (depopulation without disturbance) is shown in Fig. 2a as function of the radius of the management zone. Without management, the average infected area is 7,183 km² (median 1,424 km, left-most box in Fig. 2a). Perfect barriers (B00, grey boxes) reduce the average infected area to 542 – 1,648 km², depending on the radius of the management zone. The smallest infected area is achieved at a radius of 8 km, while the area increases with larger radii. Depopulation without disturbance (H2-, hollow boxes) reduces the average infected area to 609 - 972 km², with inconclusive effect size regarding changing radii.

The outbreak duration for the three management scenarios N, B00 and H2- is shown in Fig. 2b. Without management, the average duration is 4.2 years (median 3.2 years, left-most box in Fig. 2b). Perfect barriers (B00, grey boxes) reduce the average virus presence to 1.4 - 2.6 years, with a minimum at 4 km radius. Depopulation without disturbance (H2-, hollow boxes) reduces the average virus presence to 1.5 - 2.0 years, with the maximum at 4 km radius.

Realistic assumptions

The infected area and the duration of outbreaks assuming barriers with 10% permeability (B10) and depopulation with disturbance (H2+) are shown in Fig. 3 as functions of the radius of the management zone. Permeable barriers (B10, grey boxes in Fig. 3a) reduced the average infected area to 835 km² - 4,071 km², with the minimum at a radius of 8 km. Depopulation with disturbance (H2+, hollow boxes in Fig. 3a) reduced the average infected area from 7,183 km² to 1,753 km² with 20 km radius, while a radius of 4 km resulted in an increase of the average to 20,737 km². The average duration of outbreaks (Fig. 3b) was reduced by the permeable barriers (B10, grey boxes) to 2.0 years (radius 4 km) – 3.6 years (radius 40 km). Depopulation with disturbance (H2+, hollow boxes) resulted in a reduction to 2.3 years for a radius of 20 km, and in an increase to 4.9 years for 4 km.

Comparison of most effective strategies

The direct comparison of most useful management zone for permeable barriers (B10) and depopulation with disturbance (H2+) were found for 8 km and 20 km, resulted in an average infected area of 835 km² and 1,753 km² after average virus presence of 2.0 years and 2.3 years. Barriers approach required 6,464 animals to be shot for surveillance and an average of 273 km barriers length while depopulation required 25,649 animals to be killed for surveillance and depopulation.

Pessimistic behavioural assumptions

Under the pessimistic behaviour scenario, the absence of management (N) resulted in an average infected area of 36,600 km², i.e. effectively the entire model landscape of 40,000 km² was infected. Barriers with 10% permeability (B10) reduced the infected area to 31700 km² at best if 8 km were applied as radius of the management zone. Depopulation with disturbance (H2+) resulted in at least 10,100 km² if applying population reduction in 36 km radius. The average duration of virus presence without management (N) was 4.6 years. Barriers as well as depopulation were not able to reduce the durations of the outbreak, except for depopulation with 4 km radius, resulting in 4.2 years. The average duration of outbreaks was increased by depopulation up to 8.3 years (16 km), and up to 7.6 years by barriers (12 km).

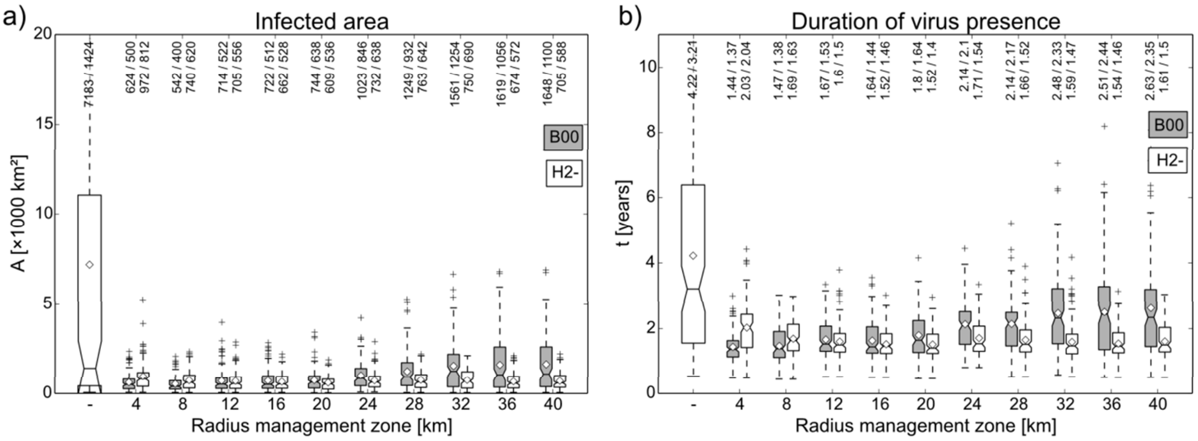


Fig. 2 a) Infected area and b) duration of virus presence for no management (N, left-most box), and dependent on the radius of the management zone for barriers with 0% permeability (B00, grey boxes) and depopulation to 2 heads/km² without disturbance (H2-, hollow boxes). Diamond symbols denote the arithmetic mean. Numbers on top of each box diagram refer to the mean / median of the simulations.

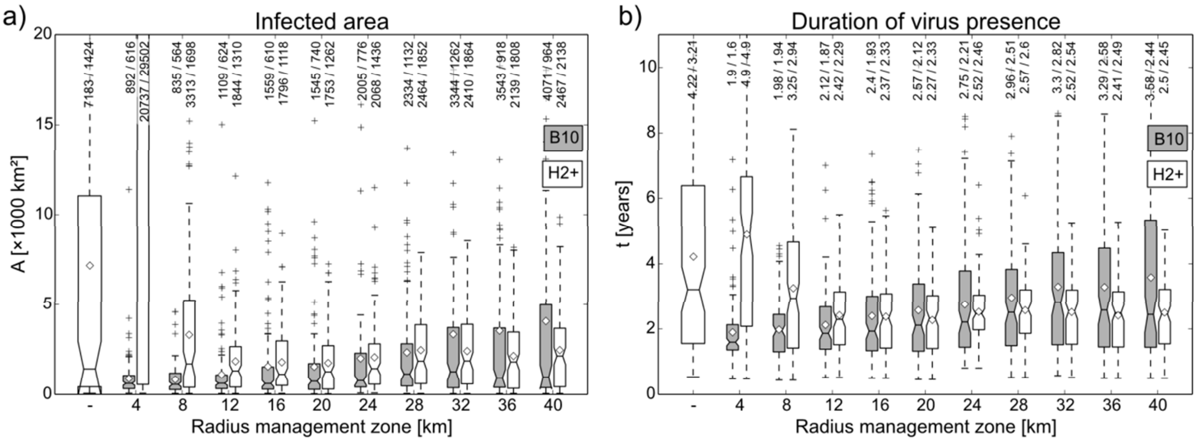


Fig. 3 a) Infected area and b) duration of virus presence for no management (N, left-most box), and dependent on the radius of the management zone for barriers with 10% permeability (B10, grey boxes) and depopulation to 2 heads/km² with disturbance (H2+, hollow boxes). Numbers on top of each box diagram refer to the mean / median of the simulations.

DISCUSSION

The present study provides understanding on how different management measures interacted with the spread of ASF virus infection in large wild boar populations. An individual-based eco-epidemiological model of ASFV in wild boar was used to compare two basic strategies: 1) local population reduction and 2) enclosure of the outbreak using mobile barriers. The comparative evaluation was based on two measures to characterise the effect of the management strategies: 1) the total size of the outbreak and 2) the duration of the outbreak.

Optimistic assumptions

Under idealistic assumptions, i.e. depopulation without population perturbation and impermeable barriers, both strategies achieved similar, distinct reductions of the size and the duration of the simulated outbreaks (e.g. more than 90% (average) respective 50% (median) of the final size of the infected area applying barriers). With the barriers strategy the outcome measures weakened by increasing radial extension of the enclosure zone, while they improved slightly with respective extensions of the depopulation zone. The preferred radii of the increments of the management zone differed between the two simulated strategies, being 8 km for the barriers strategy and 20 km for depopulation. At these values, the final outcome was comparable between the strategies i.e. the infected area was on average about 540 km² and 610 km², for barriers and depopulation respectively, and the duration of the outbreaks was about 1.5 years.

For the barriers strategy, the unwanted increase of the size and duration of outbreaks with increasing radius of added enclosure elements is reasonable because infections have to spread over the entire enclosure before extinction of the ASFV. Thus larger extensions to the enclosure result in larger infected areas and longer circulation of the infection. The smallest simulated radius of subsequent extensions, 4 km, resulted in a slight increase of the outbreak size compared to the most effective design, which is caused by the minimum chance to timely enclose the actual infected area. With the depopulation strategy, larger radii perform better as they provide a wider belt of lowered population density, which reduced the spatial spread of the infection towards new areas. From 12 km onwards, the effect of an enlarged management zone was negligible.

Realistic assumptions

Under more realistic assumptions, i.e. depopulation causing population perturbations (Sodeikat & Pohlmeyer, 2002; 2003; Thurfjell et al., 2013) and 10% chance of failures for the mobile barriers, the effect of both strategies was reduced. The preferred radius remained unchanged for both strategies. The final infected area on average under the barriers strategy was half the size following depopulation, i.e. barriers; on average 835 km² at 8 km compared to depopulation; 1753 km² at 20 km. The duration of the simulated outbreaks still was not much different between the strategic scenarios, comparing about 2.0 to 2.3 years.

Decreasing the radius of the compartmentalisation zone below 8km resulted in an extension of the average barrier length by approximately 100 km. Here, the strategy fails to reliably enclose the entire infected, but unknown area, resulting in the construction of new barriers, as soon as cases are detected outside the enclosure. An increase of the radius above 8 km results in increased barrier length, as the enclosure becomes unnecessarily large. Thus, in the simulations the radius of the most effective barriers strategy was 8 km.

For the depopulation approach, the results achieved with 12 km were similar to those using 20km radius. Applying 12km, however, lead to the lowest number of animals killed for surveillance and population reduction, i.e. approximately 21,000 heads. The radius of 20 km required killing of approximately 25,500 animals although the final area is smaller and duration of outbreaks shortened. Below 12 km radius, the depopulation is not able to sufficiently reduce spread of the infection, resulting in repeated extensions of the management zone with an associated increase of the number of hunted animals. An increase of the radius above 20 km results in unnecessarily large management zone, thus the number of hunted animals rose, but the outbreak size and duration did not alter.

For all radii the permeable barriers reduced the average infected area and the duration of outbreaks found without management. The effect size on the infected area was 5-15% less using permeable barriers with radii up to 20 km (Fig. 2a vs Fig. 3a) compared to perfect barriers. The depopulation with perturbation and small radii resulted in an increase of both outcome measures compared to the simulation outcome without management. This phenomenon of depopulation is described for other epidemiological systems and was due to increased spatial reach of infected individuals escaping the depopulation activity. While the failure rate of mobile barriers could be evaluated from existing experiments (Lavelle et al., 2011), the actual movement behaviour of escaping animals will reflect their disease state, the local habitat ecology or the time of the year. Because of the limited experimental and observational evidence, the predicted detrimental effect of population perturbation on the control performance is uncertain to both directions.

Pessimistic scenario of host behaviour

Both strategies with realistic assumptions (i.e. B10 and H2+) were additionally simulated under pessimistic scenarios on the behaviour of moribund animals. Under the more optimistic assumptions, most of the infected individuals retreat into their core home range area before death (90% of females, 80% of males), where they are not accessible for members of neighbouring herds. Thus, only a small share of the present carcasses can contribute to the spatial spread of the infection. In the second scenario, moribund animals were assumed to die in their core area with a probability according to the time spent there by healthy animals, i.e. animals do not retreat when moribund. Here, the results of a telemetry study by Keuling et al. (2008) were interpreted as a probability of 75% for females. For males, a probability of 33% was assumed according to the time males are reported to share the female core area and the ratio of core vs. shared area from the same source.

The results of the pessimistic scenario suggest that neither depopulation nor a strategy based on barriers would be beneficial in the case of a host behaviour according these assumptions. The barriers strategy is not able to reduce the outbreak size, and depopulation is only able to do so by a limited amount and with a large radius of the management zone. The failure of the barriers approach is reasoned by large pressure through an aggressive epidemic wave and the fact that a single infected individual crossing the barrier results in a new epidemic wave with high probability. The failure of the depopulation strategy is due to an insufficient reduction of the population density to reduce R_0 below one in this scenario of aggressive spread.

CONCLUSIONS

The compartmentalisation strategy may be worth considering as measure for the localised emergency management of ASF in wildlife although possible conservation issues were not included in the strategy evaluation. The effectiveness in the outbreak simulations, however, depended decisively on behavioural ecology of animals in the acute disease stage, pinpointing a relevant knowledge gap for improved predictions. Assuming most plausible scenarios regarding disease development, barriers protectiveness and depopulation induced perturbations; the outcome of compartmentalisation was more reliable than local population reduction. Tactically, the most effective barriers and population strategy on average required 273 km barriers plus 6,464 animals shot and 25,649 animals shot, respectively. Therefore 15 meters of temporary barriers have to be established per animal saved from shooting (i.e. 25,500 – 6,500 animals per 270 km barrier length). This is an economic but not an animal welfare argument as many wild boar enclosed by the barriers may eventually die from ASF. Finally, situations may occur where ASF incursion through the wildlife route into an area is foreseen but particular landscape structures would support the effectiveness of the barriers approach. The related protective role of barriers seems worth to be assessed, further enhancing preparedness.

REFERENCES

Anonymous (2014). Wild boar culling in Finland. The Pig Site. Retrieved 2014/12/15, from http://www.thepigsite.com/swinenews/38397/boar-culling-in-sweden

Beltrán-Alcrudo, D., Guberti, V., de Simone, L., DeCastro, J., Rozstalnyy, A., Dietze, K., Wainwright, S. and Slingenbergh, J. (2009). African swine fever spread in the Russian Federation and the risk for the region. EMPRES Watch Dec. 2009

Chapman, D.A.G., Darby, A.C., Da Silva, M., Upton, C., Radford, A.D. and Dixon, L.K. (2011). Genomic analysis of highly virulent Georgia 2007/1 isolate of African swine fever virus. Emerg. Infect. Dis. 17, 599-605

Clevenger, A.P., Chruszcz, B. and Gunson, K.E. (2001). Highway mitigation fencing reduces wildlife-vehicle collisions. Wildl. Soc. Bull. 29, 646-653

Clifton, M. (2014). Lithuania advised against plan to kill 90% of wild boars to fight African swine fever. Animals 24-7. Retrieved 2014/12/15, from http://www.animals24-7.org/2014/03/21/lithuania-tries-to-kill-90-of-wild-boars-to-fight-african-swine-fever/

Costard, S., Mur, L., Lubroth, J., Sanchez-Vizcaino, J.M. and Pfeiffer, D.U. (2013). Epidemiology of African swine fever virus. Virus Res. 173, 191-197

Costard, S., Wieland, B., deGlanville, W., Jori, F., Rowlands, R., Vosloo, W., Roger, F., Pfeiffer, D.U. and Dixon, L.K. (2009). African swine fever: how can global spread be prevented? Philos. Trans. R. Roy. Soc. Lond., B, Biol. Sci. 364, 2683-2696

De la Torre, A., Bosch, J., Iglesias, I., Muñoz, M.J., Mur, L., Martínez-López, B., Martínez, M. and Sánchez-Vizcaíno, J.M. (2013). Assessing the risk of African swine fever introduction into the European Union by wild boar. Transbound. Emerg. Dis. in press

Dixon, L.K., Abrams, C.C., Chapman, D.G. and Zhang, F. (2008). African swine fever virus. In: Animal viruses - moleculer biology. Mettenleiter, T.C. and Sobrino, F. (eds.). Caister Academic Press, Norfork, UK

EFSA (2010). Scientific opinion on African swine fever. The EFSA Journal 8, 1556

EFSA (2014). Evaluation of possible mitigation measures to prevent introduction and spread of African swine fever virus through wild boar. The EFSA Journal 12, 3616

Gallardo, C., Fernández-Pinero, J., Pelayo, V., Gazaev, I., Markowska-Daniel, I., Pridotkas, G., Nieto, R., Fernández-Pacheco, P., Bokhan, S., Nevolko, O., Drozhzhe, Z., Pérez, C., Soler, A., Kolvasov, D. and Arias, M. (2014). Epidemiological analysis of two first cases of African swine fever in wild boars in Poland. Emerg. Infect. Dis. 20, 1544-1547

Glista, D.J., DeVault, T.L. and DeWoody, J.A. (2009). A review of mitigation measures for reducing wildlife mortality on roadways. Landsc. Urban Plan. 91, 1-7

Grimm, V., Berger, U., Bastiansen, F., Eliassen, S., Ginot, V., Giske, J., Goss-Custard, J., Grand, T., Heinz, S., Huse, G., Huth, A., Jepsen, J.U., Jørgensen, C., Mooij, W.M., Müller, B., Pe'er, G., Piou, C., Railsback, S.F., Robbins, A.M., Robbins, M.M., Rossmanith, E., Rüger, N., Strand, E., Souissi, S., Stillman, R.A., Vabø, R., Visser, U. and DeAngelis, D.L. (2006). A standard protocol for describing individual-based and agent-based models. Ecol. Modell. 192, 115-126

Grimm, V., Berger, U., DeAngelis, D.L., Polhill, J.G., Giske, J. and Railsback, S.F. (2010). The ODD protocol: A review and first update. Ecol. Modell. 221, 2760-2768

Hõbemägi, T. (2014). Battle against ASF requires concerted efforts from all Baltic states. BBN. Retrieved 2014/12/15, from http://www.bbn.ee/article/2014/9/15/battle-against-asf-requires-concerted-efforts-from-all-baltic-states

Keuling, O., Stier, N. and Roth, M. (2008). Annual and seasonal space use of different age classes of female wild boar *Sus scrofa* L. Eur. J. Wildl. Res. 54, 403-412

Khomenko, S., Beltrán-Alcrudo, D., Rozstalnyy, A., Gogin, A., Kolbasov, D., Pinto, J., Lubroth, J. and Martin, V. (2013). African swine fever in the Russian Federation: risk factors for Europe and beyond. EMPRES Watch 28

Lavelle, M.J., Vercauteren, K.C., Hefley, T.J., Phillips, G.E., Hygnstrom, S.E., Long, D.B., Fischer, J.W., Swafford, S.R. and Campbell, T.A. (2011). Evaluation of fences for containing feral swine under simulated depopulation conditions. J. Wildl. Manage. 75, 1200-1208

Massei, G., Roy, S. and Bunting, R. (2011). Too many hogs? A review of methods to mitigate impact by wild boar and feral hogs. Human-Wildlife Interactions 5, 79-99

OIE (2014). World Animal Health Information Database (WAHID). Retrieved 2014/05/09, from http://www.oie.int/wahis_2/public/wahid.php

Penrith, M.L., Guberti, V., Depner, K. and Lubroth, J. (2009). Preparation of African swine fever contingency plans. FAO Anim. Pr. 8, 1-69

Penrith, M.L., Vosloo, W., Jori, F. and Bastos, A.D.S. (2013). African swine fever virus eradication in Africa. Virus Res. 173, 228-246

Sodeikat, G. and Pohlmeyer, K. (2002). Temporary home range modifications of wild boar family groups (*Sus scrofa L.*) caused by drive hunts in Lower Saxony (Germany). Z. Jagdw. 48, 161-166

Sodeikat, G. and Pohlmeyer, K. (2003). Escape movements of family groups of wild boar *Sus scrofa* influenced by drive hunts in Lower Saxony, Germany. Wildl. Biol. 9, 43-49

Thomson, G.R., Gainaru, M.D. and van Dellen, A.F. (1980). Experimental infection of warthog (*Phacochoerus aethiopicus*) with African swine fever virus. Onderstepoort J. Vet. 47, 19-22

Thurfjell, H., Spong, G. and Ericsson, G. (2013). Effects of hunting on wild boar *Sus scrofa* behaviour. Wildlife Biology 19, 87-93

Wobeser, G.A. (1994). Investigation and management of disease in wild animals. Springer, Berlin

ROBUSTNESS OF STATISTICAL METHODS

RANDOM EFFECT SELECTION IN GENERALISED LINEAR MODELS: A PRACTICAL APPLICATION TO SLAUGHTERHOUSE SURVEILLANCE DATA IN DENMARK

M.J. DENWOOD[*], H. HOUE, B. FORKMAN AND S.S. NIELSEN

SUMMARY

We analysed abattoir recordings of meat inspection codes with possible relevance to on-farm animal welfare in cattle. Random effects logistic regression models were used to describe individual-level data obtained from 461,406 cattle slaughtered in Denmark. Our results demonstrate that the largest variance partition was at farm level for most codes, but there was substantial variation in reporting for some meat inspection codes between abattoirs. There was also substantial agreement for the relative under or over-reporting of different slaughter codes within individual abattoirs. This indicates that the sensitivity of routine surveillance in Denmark is affected by differences in the working practices between abattoirs, resulting in biased prevalence estimates. Therefore, it is essential to correct for the variation in reporting between abattoirs before meaningful inference can be made from prevalence estimates based on data derived from meat inspection.

INTRODUCTION

All carcasses from food producing animals in the European Union (EU) are subject to meat inspection according to EU legislation (Anon, 2004), for the primary purpose of ensuring the safety of the food. However, the idea of using this substantial resource of meat inspection data for purposes other than food safety has gained substantial traction over recent years (Dupuy et al., 2013; Harley et al., 2012; Klauke et al., 2013; Knage-Rasmussen et al., 2014; Vial and Reist, 2014). In Denmark, there has been a considerable emphasis on the possibility of using such data for monitoring on-farm animal health and welfare using related meat inspection codes as a proxy for compromised health or welfare on farm (Knage-Rasmussen et al., 2014; Nielsen et al., 2014). The high availability and low cost of meat inspection data are potentially very attractive, but concerns remain about the validity of using such data outside the original remit of food safety. For example, Nielsen et al. (unpublished) demonstrated the relatively poor correlation between the prevalence of some pig health conditions in meat inspection codes and findings from more detailed pathological examination of the same groups of animals. There is also the possibility of variation in reporting level between abattoirs due to differences in abattoir practices and the design/setup of meat inspection lines, which may complicate the comparison of disease prevalence reported from different abattoirs. Before comparing the prevalence of any meat inspection codes between farms, it is therefore essential to account for any difference in the apparent prevalence between farms that may be caused by differences in recording between abattoirs.

---

[*] Matthew James Denwood, Department of Large Animal Sciences, University of Copenhagen, Grønnegårdsvej 8, 1870 Frederiksberg C, Denmark. Email: md@sund.ku.dk

The most common way of accounting for this type of clustering within epidemiological data is to use one or more random effect terms to describe the structural patterns in the data. These have been used for linear models as well as generalised linear models, including logistic regression models (Guo and Zhao, 2000; Li et al., 2011). These random effects are often used to account for known structural relationships that would otherwise break the independence assumptions of the response variable, and have also been shown to be useful to account for over-dispersion at the level of observation (Harrison, 2014). In these cases, the 'significance' of these terms is not of interest, and it is neither necessary nor desirable to consider removing the random effects in an attempt to improve the model fit. However, there are some situations such as that presented here, where the presence or absence of the random effects themselves is of interest, in which case some formal test of the significance of these random effects terms is desirable. In addition, it is very common to undertake some type of model selection process to eliminate candidate fixed effect variables from mixed effect models. In both of these cases, the validity of several commonly used methods of model selection is challenged by the presence of the random effects terms.

The most common method of comparing nested models is using some penalised measure of model fit such as the likelihood ratio test (LRT), variants of Akaike's information criterion (AIC), or the Bayesian information criterion (BIC). Each of these methods compares the maximum likelihood estimate of two or more nested models, with a correction for the relative complexity of the models. This penalty factor is derived from the relative number of degrees of freedom between the models, and is necessary to account for the natural ability of more complex models to produce a superior fit to any given dataset simply by chance. The number of degrees of freedom is relatively simple to calculate for purely fixed effects models, but for random effects and mixed models there is no straightforward method of determining the effective degrees of freedom contributed by the random effect. Standard methods such as the deviance information criterion (DIC) may be used within a Bayesian context (Spiegelhalter et al., 2002), but not in the standard frequentist maximum likelihood framework. Alternatively, a more computationally intensive approach can be taken to model comparison, using data simulated under the null model and fitted to both the null and alternative models. This allows the direct calculation of a distribution of expected likelihood ratio statistics, to which the observed likelihood ratio can be compared. The two advantages of this method are that no assumptions are made about the distribution of the likelihood ratio statistic, and there is no requirement to calculate the unknown quantity describing the number of degrees of freedom. This method has not to our knowledge been widely used within epidemiology, but a similar method has been recommended in the context of mixture models (McLachlan, 1987).

In this paper, we demonstrate the use of simulated data to provide a robust method of model selection for models including random effects. This method is applied to a random-effects logistic regression model describing the observed prevalence of various meat inspection codes, selected on the basis of animal welfare relevance and non-negligible prevalence, in Danish cattle. The primary interest from these data is inference regarding the relative contributions of variance between farms (interpreted as true difference in prevalence of these diseases), compared to variance between abattoirs (interpreted as differences in the sensitivity and specificity of disease recording between abattoirs).

MATERIALS AND METHODS

Meat inspection codes

Cattle meat inspection data were obtained for the entirety of 2012, from all eight cattle abattoirs that slaughtered >10,000 head of cattle in Denmark during 2012. All recorded meat inspection codes in accordance with Danish legislation (Anon, 2011) were available, with an individual animal level recording of presence or absence of each of these codes. The data were then divided into separate datasets describing animals under 18 months of age (n=212,826; denoted 'calves') vs. older cattle (n=248,580; denoted 'adults'), before being aggregated by abattoir (n=8), and farm of origin (n=7,020 for calves; n=10,721 for adults). Slaughter date information was disregarded, but the same time period (all of 2012) was collected for each abattoir. The number of animals slaughtered during the year and recorded frequency of each meat inspection code was obtained for each combination of abattoir of slaughter and farm of origin (this observation level grouping is referred to here as the 'group'). Some meat inspection codes (and combinations) were excluded from modelling analysis on the basis of the following criteria:

- Slaughter plant codes (mostly used for decision making at the abattoir), for example contaminated hide
- Codes possibly related to transport of animals to the slaughterhouse (on the basis that these may not have occurred on farm)
- Acute conditions, which could have occurred during transport (based on assessment by a professor of veterinary pathology in the Department of Veterinary Disease Biology, University of Copenhagen)
- Central nervous system conditions (on the basis that they are relatively non-specific and difficult to assess at the abattoir)
- Codes not related to animal welfare
- Codes relating to non-specific conditions

Related codes were grouped into code combinations where biologically sensible, based on consensus assessment including three of the authors (HH; SSN; BF) and two other experts at the University of Copenhagen. For example, healed fractures recorded separately for various different sites in the carcass were grouped into a single category. A final exclusion criterion was then imposed to remove any meat inspection codes (or combinations of related codes) with a sufficiently low observed prevalence in the calf or adult dataset so that logistic regression models could not reasonably be implemented. This prevalence threshold was set at an observed prevalence of greater than zero in a minimum of 50 separate groups of animals, with the criterion implemented independently for each code and age group. The final dataset describing the number of recorded codes and total number of animals in each group (abattoir of slaughter combined with farm of origin) was created separately for each of the selected codes from the overall calf and adult datasets.

Model fitting

For each of the separate datasets included in the analysis, a random effects logistic regression model was used to describe the recorded prevalence of each meat inspection code (or combination of codes) for each group of animals. A random effect representing the group was fitted to every model in order to account for the residual extra-Binomial variance associated with clustering of observations within each individual combination of abattoir and farm (the rationale for this is discussed in detail by Harrison, 2014). No fixed effects (other than an intercept term) were considered for inclusion in the model. All models were fitted using the glmer function of the lme4 package (Bates et al., 2014) in R (R Development Core Team, 2014). Variance estimates for random effects were taken from the model summary statistics, and estimates for the individual factor level effects within random effects terms were extracted from the random effects terms using the ranef() function. Confidence intervals for all parameters were obtained using parametric bootstrapping from the final fitted model with 250 iterations, which was deemed sufficient to approximate the true confidence interval. Model fit was assessed by comparing the likelihood obtained from the full model to a 95% confidence interval for the likelihood of data simulated under the same model, using the same parametric bootstrap procedure.

Model selection method

The improvement in model fit yielded by each of the two random effects terms (farm and abattoir) was assessed sequentially by comparing the fit of a model without the random effect to be tested (the null model) to the fit of a model including the random effect to be tested (the alternative model). The model fit comparison was done by comparing the difference in log likelihood from the null and alternative models to a distribution of the same statistic generated from simulated data. The probability that the data are consistent with the null model is given by the proportion of simulated likelihood ratio statistics that are greater (or equal) in magnitude to the observed likelihood ratio statistic. Given a desired alpha error rate (in this case a p-value of 0.05), a cut-off can then be imposed for rejecting the null hypothesis in the same way as the usual likelihood ratio test, but without the assumption that the test statistic follows a chi-square distribution, or the requirement to specify a number of degrees of freedom. This exact numerical approximation to the p-value requires only a sufficient number of simulated likelihood ratio test statistics to ensure that the decision to accept or reject the null hypothesis is justified. This procedure was verified to produce the desired alpha error rate of 5% using a simulation study (data not shown).

The simulated test statistic was obtained as follows. First, the parameter estimates obtained from the null model were used to obtain a simulated dataset, with the individual random effect estimates for group resampled from the variance estimate for this random effect. Both null and alternative models were then re-fitted to the simulated data, before recording the difference in log likelihood observed between the two fitted models. This simulated likelihood ratio was then compared to the likelihood ratio observed from the true dataset to determine if the observed likelihood ratio was greater than that obtained using data simulated under the null model. This process was repeated until the target threshold of $p=0.05$ lay outside (either above or below) the 99% confidence interval for the true p-value. If the 99% confidence interval still contained 0.05 after 1000 bootstrap iterations (representing a high degree of certainty about a p-value very close to the cut-off value), the estimate at that point was used to determine the outcome of the likelihood ratio test.

Model selection procedure

A forward step-wise selection algorithm was used to test the candidate random effects. Starting from the simplest model we considered, with intercept and group random effect terms fitted, the additional random effects representing the farm of origin ('Farm') and abattoir of slaughter ('Abattoir') were sequentially considered for inclusion in the model using the method specified above. The 'Abattoir' random effect was first considered for inclusion in the model, followed by the 'Farm' random effect. In the cases where the 'Abattoir' effect was initially rejected for inclusion but the 'Farm' effect was included, the 'Abattoir' effect was subsequently re-tested for inclusion.

RESULTS

Data summary

The number of unique farms of origin for each abattoir, and the number of farms sending animals to different abattoirs, is shown in Figure 1. The majority of farms sent animals to only one abattoir, but around 12% of farms sent animals to up to four abattoirs. A small number of farms (38 in total) sent animals to five or six abattoirs, and a single farm sent one or more adult cow to all eight abattoirs during 2012 (data point omitted from Fig. 1). There were a total of 13,681 and 8,109 observed combinations of farm and abattoir (group) for adults and calves, respectively.

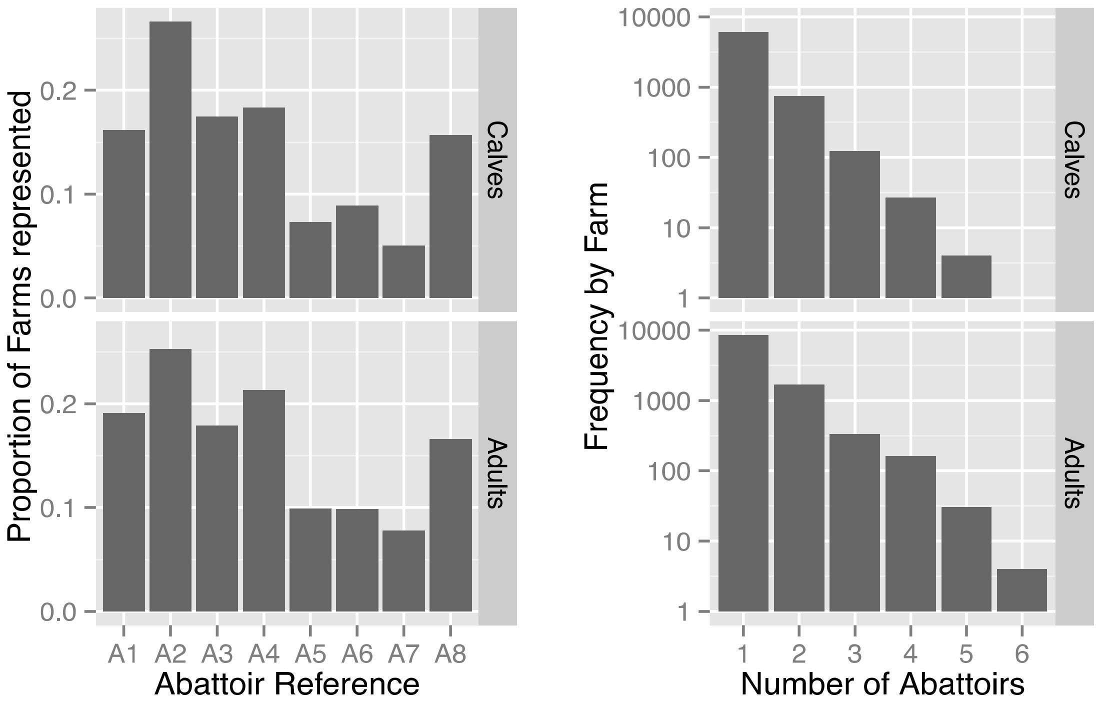


Fig. 1 The proportion of farms sending one or more animal to each abattoir (left) and number of farms (on the log scale) sending animals to multiple abattoirs (right) for calves (top) and adult cattle (bottom) in Denmark during 2012

Of the 92 slaughterhouse codes recorded, the following were removed: 6 slaughter plant codes; 8 transport-related codes; 16 acute conditions; 2 CNS conditions; 12 conditions not related to animal welfare; and 4 non-specific codes. Of the remaining 44 slaughter codes, 19 were used individually and 25 were grouped into 9 separate combinations of related codes, giving a total of 28 code combinations each for calves and adults. Of these 28 codes, 5 were removed from the adult data, and 14 were removed from the calf data, due to low prevalence.

Modelling results

After exclusion of unsuitable meat inspection codes, a total of 37 datasets (23 adult; 14 calves) with a total of 24 disease codes were taken forward for modelling. Of these, there was no evidence for a random effect of Abattoir or Farm in 12 datasets. Descriptions of the remaining 18 unique codes together with random effect estimates and crude estimated prevalence are given in Table 1. Figure 2 shows the corresponding individual abattoir effect estimates (extracted from the random effect component of the fitted model) where the preferred model contained both farm and abattoir random effects.

Table 1. Model inference for the meat inspection codes used for cattle slaughtered in Denmark during 2012. Crude prevalence estimates are shown alongside random effects variance estimates for Farm and Abattoir where these were fitted in the final model. Estimates in italics indicate models with poor fit, and underlined estimates indicate non-overlapping 95% confidence intervals between abattoir and farm variance estimates.

Code	Description	Calves			Adults		
		Prev %	Abb. σ^2	Farm σ^2	Prev %	Abb. σ^2	Farm σ^2
PYR	Pyrexia	0.10	0.33	0.44	0.27	--	*0.3*
ENDO	Endocarditis	0.03	--	--	0.19	--	*0.29*
LW	Lung worm	0.03	--	--	0.19	3.18	--
CGE	Chronic gastroenteritis	0.05	--	--	0.24	0.9	0.57
RD	Renal disease	0.19	1.54	--	0.56	1.11	--
UD	Chronic uterine disease	0.00	--	--	0.05	--	*2.07*
HD	Hoof disease	0.03	--	--	0.23	8.1	--
OST	Osteomyelitis	0.04	--	*2.02*	0.16	--	--
CA	Chronic arthritis and arthrosis	0.43	0.19	--	0.42	--	--
MA	Muscle atrophy	0.02	--	--	0.35	25.52	--
SE	Sores and eczema	0.01	--	--	0.04	--	*0.04*
PNEU	Chronic pneumonia and pleuritis	8.81	0.38	0.77	3.96	0.6	0.19
CARD	Chronic pericarditis and traumatic reticulo-pericarditis	4.00	0.2	0.49	5.33	0.25	0.19
LD	Liver disease	12.14	**0.08**	**1.63**	12.00	**0.15**	**1.33**
ABS	Abscesses	0.84	0.13	0.27	2.50	0.11	0.28
HF	Healed fracture	0.30	--	--	1.51	**0.08**	**0.46**
SA	Skin abrasions	1.14	0.2	0.48	6.70	0.27	0.31
SR	Scabies and ringworm	0.09	*0.04*	--	0.01	--	--

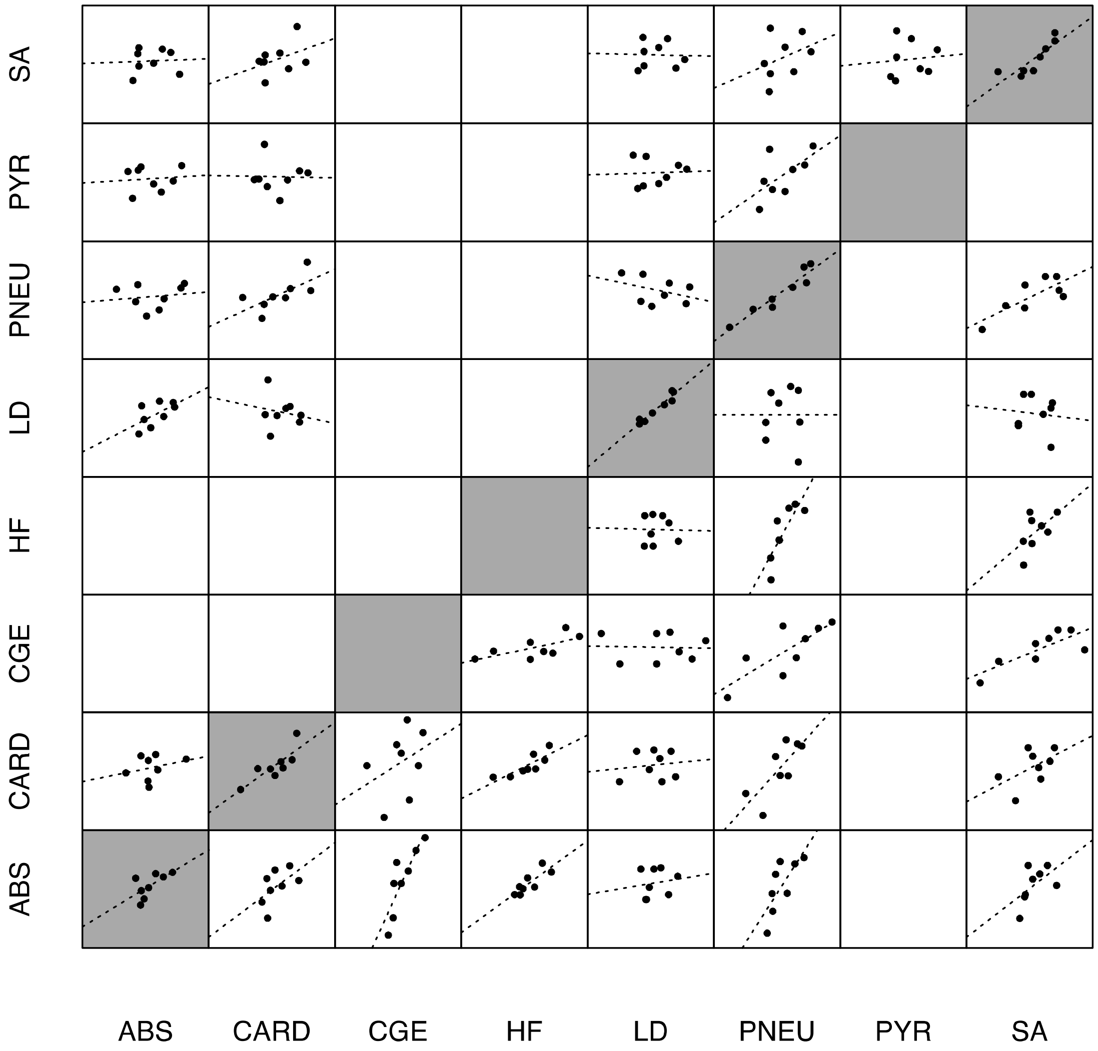


Fig. 2 Comparison between the eight individual abattoir estimates for preferred models with both farm and abattoir random effects, with regression lines shown dotted. The diagonal (grey shading) compares estimates from adults (x axis) and calves (y axis) for the same code. Off diagonal compares estimates between codes for calves (above diagonal) or adults (below diagonal). Axes are fixed to a scale of between -1.8 and 1.8 (on the logit probability scale).

There was evidence of random effects for both abattoir and farm for pyrexia (PYR) in calves; chronic gastroenteritis (CGE) and healed fracture (HF) in adults; and chronic pneumonia and pleuritis (PNEU), chronic pericarditis and traumatic reticulo-pericarditis (CARD), liver disease (LD), abscesses (ABS), and skin abrasions (SA) in both age groups. Where the full model was preferred, the mean estimate for the variance attributable to abattoir was smaller than that due to farm in 10 out of 13 cases, although the largest estimates for variance due to abattoir were obtained from lung worm (LW) and muscle atrophy (MA) in adults, and renal disease (RD) in both age groups, where no farm random effect was fitted. There was a significantly higher (non-overlapping 95% confidence intervals) variance estimate for abattoir compared to farm for healed fractures (HF) in adults, and liver disease (LD) in both adults and calves. There was no evidence for lack of fit for any model with both farm and abattoir random effects, but a bootstrapped distribution of likelihoods obtained using simulated data did not contain the observed likelihood for five of the models including just a farm random effect, and one of the models including just an abattoir random effect (shown in italics). Some care should therefore be exercised when interpreting the results from these six models.

In addition to the overall random effect of abattoir, it may be useful to compare the estimates for individual abattoir effects contained within the fitted random effect structure. There was a clear positive linear relationship between the estimated abattoir effects for adults and calves for the same code (Figure 2; diagonal plots). For the six codes with highest observed prevalence, there was generally positive agreement within age groups between abattoir estimates for PNEU and other slaughter codes, as well as between ABS, CARD, HF, SA and other slaughter codes for adults. However, there was very little agreement between the abattoir effects for LD and the other conditions.

DISCUSSION

Of the 92 slaughter codes available, 44 were deemed by animal welfare experts to be potentially indicative of on-farm welfare. Even after grouping related conditions, only 4 of the 28 potentially relevant codes had a prevalence of over 1% in both adults and calves (an additional two codes had a prevalence of over 1% in adults only). Therefore, even with a dataset of over 100,000 animals grouped into approximately 10,000 groups of animals, considerable difficulties remained in modelling these rare outcomes. However, there was significant evidence for a random effect of abattoir (with or without a random effect of farm) in either adults or calves for 14 of the code combinations, which tended to be those with the highest prevalence. Where both farm and abattoir random effects were indicated, the estimate for the variance due to farm tended to be larger than that of abattoir. The relative importance of these standard deviation estimates to the prevalence on the logit scale can be compared using the square root of the estimates given in Table 1, although it should be noted that the abattoir random effect is likely to be under-estimated to a greater degree than that for farm due to the smaller number of grouping levels. However, the farm effect variance was estimated to be the larger of the two for three of the codes for adults (PNEU, CARD & CGE), and there are also a number of conditions for which there is evidence for an effect of abattoir but not for farm; LW, HD, MA in adults, CA in calves, and RD in both age groups. This observation is consistent with a greater degree of variation between abattoir practices in relation to these codes, for example examination of feet and kidneys, which is a highly plausible conclusion. It is also worth noting that the prevalence of some of these conditions varies considerably between age groups, which supports the decision to model data from calves and adults separately.

There was strong evidence that the individual abattoir effects were consistent between some codes, for example PNEU vs. ABS, CARD, CGE, HF and SA, indicating that the abattoir-specific factors which tended towards higher or lower levels of reporting are consistent between some abattoir codes. This is likely to be due to variation in inspection procedures, such as the amount of time available to examine carcasses and training procedures for staff within the same abattoir, as well as differences in recording practices between abattoirs, such as paper-based vs. electronic recording. One notable exception is LD, the abattoir code with the highest prevalence, which does not show any correlation with the abattoir effects for other codes, but does show near perfect correlation for the estimates in calves vs. adults. This may represent the different slaughterhouse procedure for examining the liver as a discrete organ compared to many of the other conditions, which tend to be assessed directly from the carcass. However, it is also worth noting that the abattoir level variance for LD was small both in absolute terms and when compared to the relatively large estimates for the farm-level variance for the same condition.

The most likely interpretation of the observed consistency between abattoir effects for different codes is that abattoirs with high sensitivity of recording for some conditions tend also to have a high sensitivity of recording for other conditions. A more thorough inspection procedure at some abattoirs would be expected to result in greater sensitivity to detect a variety of different codes at these abattoirs, for example by having inspection procedures that better facilitate inspection of the carcass, leading to a higher detection rate for a number of different codes relative to an abattoir with different procedures. It may also be possible that recording one code on a carcass may lead to a more detailed inspection and therefore higher probability of detecting other codes in the same carcass. However, the correlations presented in Fig. 2 are for the overall abattoir effect of detecting these codes, and do not represent any possible correlation in detecting different codes on the same carcass, so we do not expect this possible effect to be a major contributor to the overall pattern observed. Another possible interpretation for the correlation between abattoir effects for different codes is that the recording practices do not differ between abattoirs, but a systematic bias exists in the decisions for farmers to send animals to different abattoirs based on the age, health status, breed or condition of their animals. This would lead to a discrepancy in the true prevalence of the relevant abattoir codes at different abattoirs, even after correcting for the farm of origin, because the abattoirs are receiving animals from different populations. However, given the small number of major abattoirs in Denmark and high proportion of farms sending animals to only one abattoir, we find the first interpretation to be most likely. Conversely, negative correlations between abattoir effects for different codes may imply a certain level of cross-classification between codes, although no such effect was observed in these data due to the grouping of related codes.

The use of random effects models to describe parameters of interest presented two main methodological challenges. Firstly, the standard likelihood ratio test could not be applied to the model selection, because the assumptions regarding the chi-square distribution of likelihood ratio are invalidated by the nature of random effects. We solved this problem using a computationally intensive method to directly simulate a distribution of likelihood ratios under our null hypothesis, to which the observed likelihood ratio could be applied (McLachlan, 1987). This method was verified to give the desired 5% type-I error rate based on simulated data, and is generally applicable to robust model selection in the context of mixed models. The second methodological aspect of our work concerns the 95% confidence intervals of the parameters of interest; in this case the variance estimates for farm and abattoir random effects, as well as the individual estimates for the effect of each abattoir contained within the overall random effects term. There similarly exists no viable distributional approximation on which to base 95% confidence intervals for these parameters, but parametric bootstrapping approaches can be used to generate these intervals directly. A further difference between fixed effect models and random effect models is the effect of 'shrinkage' in random effects models. This tends to pull the estimates for individual levels within random effects terms towards the centre of the distribution, and is known to lead to underestimates of the variance of random effects terms in some situations (Burnham & White, 2002). The assumption of an approximately normal distribution of effect estimates between farms and abattoirs is also important, although in practice inference made from random effects models is relatively robust to this assumption as long as the true distribution is continuous and uni-modal. In our case, we believe that the use of random effects terms is justified because of the large number of theoretically additive factors contributing to the overall distribution of effects between farms and abattoirs, and any shrinkage of individual effect estimates towards zero is conceptually conservative and therefore also justifiable in this situation.

In conclusion, our results support the hypothesis that in most cases the majority of the observed variance is due to differences between farms, but we also show that abattoir-specific effects contribute a significant portion of the observed variation in reported prevalence of some slaughter codes. This indicates that the sensitivity of routine surveillance in Denmark is affected by differences in the working practices between abattoirs, and it is therefore crucial to account for these differences before making use of information derived from slaughter codes to make comparisons regarding animal welfare between farms.

ACKNOWLEDGEMENTS

This project was funded by The Danish Agrifish Agency under The Ministry of Food, Agriculture and Fisheries of Denmark. The authors would like to thank Sine Norlander Andreasen, Anne Marie Michelsen and Henrik Elvang Jensen for their valuable assistance interpreting and grouping the meat inspection codes.

REFERENCES

Anon (2004). Regulation (EC) No 854/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption

Anon (2011). Cirkulære om udøvelse af kødkontrol. CIR1H nr 9611 af 19/12/2011. (Government Circular on conduct of meat inspection in Denmark, in Danish). Danish Veterinary and Food Administration, Glostrup, Denmark

Bates, D., Maechler, M., Bolker, B. and Walker, S. (2014). lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1-7. http://cran.r-project.org/package=lme4

Burnham, K.P. and White, G.C. (2002). Evaluation of some random effects methodology applicable to bird ringing data. J. Appl. Stat. 29, 245–264. doi:10.1080/02664760120108755

Dupuy, C., Morignat, E., Maugey, X., Vinard, J., Hendrikx, P., Ducrot, C., Calavas, D. and Gay, E. (2013). Defining syndromes using cattle meat inspection data for syndromic surveillance purposes: a statistical approach with the 2005-2010 data from ten French slaughterhouses. BMC Vet. Res. 9, 88. doi:10.1186/1746-6148-9-88

Guo, G. and Zhao, H. (2000). Multilevel Modeling for Binary Data. Annu. Rev. Sociol. 26, 441–462. doi:10.1146/annurev.soc.26.1.441

Harley, S., More, S., Boyle, L., Connell, N.O. and Hanlon, A. (2012). Good animal welfare makes economic sense : potential of pig abattoir meat inspection as a welfare surveillance tool. Ir. Vet. J. 65, 1. doi:10.1186/2046-0481-65-11

Harrison, X. (2014). Using observation-level random effects to model overdispersion in count data in ecology and evolution. PeerJ 2, e616. doi:10.7717/peerj.616

Klauke, T.N., Piñeiro, M., Schulze-Geisthövel, S., Plattes, S., Selhorst, T. and Petersen, B. (2013). Coherence of animal health, welfare and carcass quality in pork production chains. Meat Sci. 95, 704–11. doi:10.1016/j.meatsci.2013.03.022

Knage-Rasmussen, K.M., Rousing, T., Sørensen, J.T. and Houe, H. (2014). Assessing animal welfare in sow herds using data on meat inspection, medication and mortality. Animal 1–7. doi:10.1017/S1751731114002705

Li, B., Lingsma, H.F., Steyerberg, E.W. and Lesaffre, E. (2011). Logistic random effects regression models: a comparison of statistical packages for binary and ordinal outcomes. BMC Med. Res. Methodol. 11, 77. doi:10.1186/1471-2288-11-77

McLachlan, G.J. (1987). On Bootstrapping the Likelihood Ratio Test Stastistic for the Number of Components in a Normal Mixture. Appl. Stat. 36, 318. doi:10.2307/2347790

Nielsen, S.S., Michelsen, A.M., Jensen, H.E., Barington, K., Opstrup, K.V. and Agger, J.F. (2014). The apparent prevalence of skin lesions suspected to be human-inflicted in Danish finishing pigs at slaughter. Prev. Vet. Med. 117, 200–6. doi:10.1016/j.prevetmed.2014.08.003

R Development Core Team (2014). R: A Language and Environment for Statistical Computing. http://www.r-project.org.

Spiegelhalter, D.J., Best, N.G., Carlin, B.P. and van der Linde, A. (2002). Bayesian Measures of Model Complexity and Fit. J. R. Stat. Soc. Ser. B Statistical Methodol. 64, 583–639

Vial, F. and Reist, M. (2014). Evaluation of Swiss slaughterhouse data for integration in a syndromic surveillance system. BMC Vet. Res. 10, 33. doi:10.1186/1746-6148-10-33

THE IMPACT OF SAMPLE SIZE ON UNDERSTANDING DISEASE DYNAMICS IN LIVESTOCK MOVEMENT NETWORKS

C.N. PFEIFFER[*], S.M. FIRESTONE, A.J.D. CAMPBELL, J.W.A. LARSEN AND M.A. STEVENSON

SUMMARY

The movement of animals between livestock holdings contributes to infectious disease spread in farm animal populations, and is increasingly investigated with network analysis methods. Tangible outcomes include the identification of high-risk premises for targeting surveillance or control programs. However, knowledge of the effect of sampling or incomplete network enumeration on these investigations is limited. Based on predicted network size, density and degree value distribution, a simulation algorithm is presented that provides an estimate of required sampling proportions, to ensure results of network analyses based on sampled or incomplete data provide population estimates of known precision. Results demonstrate that, for network degree metrics, sample size requirements vary with sampling method. This approach can be used to tailor study designs for investigations of specific livestock movement networks and their impact on disease dissemination within populations.

INTRODUCTION

Understanding the pattern of animal movements between livestock holdings presents an opportunity to target surveillance and control activities to premises with increased risk of infectious disease spread, a valuable approach when jurisdictions are required to maximise their impact with limited resources. Social network analysis (SNA) provides a means for quantifying networks of animal movements, and has been used increasingly in the context of preventative veterinary medicine, with applications from tuberculosis transmission in possums in New Zealand (Porphyre et al., 2008) to equine influenza spread in Australia (Firestone et al., 2012). Early applications of SNA in livestock movement networks followed the 2001 UK foot and mouth disease (FMD) outbreak (Webb, 2005; Woolhouse et al., 2005; Ortiz-Pelaez et al., 2006). As traceability and network analysis have become a priority in many countries, the legislated requirement to declare movements of livestock from one geographical location to another has become commonplace, and the analysis of such data has been pursued across the world (Bigras-Poulin et al., 2006; Baptista & Nunes, 2007; Natale et al., 2009; Volkova et al., 2010; Rautureau et al., 2011; Aznar et al., 2011; Rautureau et al., 2012; Smith et al., 2013). However, throughout this recent literature there is little mention of the impact of sampling or completeness of data obtained from such sources, and sample size calculations are notably absent from analytic approaches.

---

[*] Caitlin Pfeiffer, Mackinnon Project, Faculty of Agricultural and Veterinary Sciences, University of Melbourne, 250 Princes Highway, Werribee, VIC 3030, Australia. Email: caitlin.pfeiffer@unimelb.edu.au

Before discussing the impact of sampling on the precision of network metrics, it is prudent to consider the key network measures applied to describe livestock movement networks. The network comprises premises where the species of interest are kept (*nodes*, such as farms or saleyards), and movements of animals between a pair of premises (*edges*). Most livestock movement networks are directed, in that edges represent a one-way movement from a unique source farm to a unique destination. A comprehensive review of SNA concepts and their application to preventative veterinary medicine is available elsewhere (Martinez-Lopez et al., 2009). Many structural indices are available to describe network characteristics, such as network position (centrality) and connectivity measures (Butts, 2008). A simple but powerful node-based centrality measure is the degree value, the total number of incoming and outgoing edges for a given node (i.e. the total number of other premises each individual farm trades with). In a directed network, the total degree value for each node can be split into in-degree (incoming movements), and out-degree (outgoing movements).

A network's topology can be described at a basic level by the distribution of degree values. While early theoretical work on network analysis focussed on random networks with normal degree distributions, many real-world networks have a highly skewed power-law distribution of degree values, denoted a "scale-free" network topology (Barabási & Albert, 1999). These scale-free networks are typified by most nodes having small degree values, but a small subset of nodes having very high degree values. Such heterogeneity in degree values has been repeatedly identified in livestock movement networks (Bigras-Poulin et al., 2006; Natale et al., 2009; Aznar et al., 2011), where most holdings trade with few others, but a small number of holdings have many trading partners.

The effect of this degree heterogeneity on disease transmission is intuitive; a farm with many trading partners could greatly amplify the spread of an infectious disease through a population. Furthermore, a distinction between the effects of in- and out-degree can be made, as high in-degree premises are more likely to acquire infection from trading partners, while premises with high out-degree can infect a higher number of other farms. If in-degree and out-degree values are positively correlated, "superspreader" nodes (those at higher risk of both acquiring and disseminating an infectious disease) emerge (Galvani & May, 2005). An example of this phenomenon occurred during the 2001 epidemic of FMD in the UK, where livestock saleyards widely disseminated disease prior to the onset of effective control measures (Ortiz-Pelaez et al., 2006). The impact of degree heterogeneity on disease spread is quantified by adjusting the basic reproductive number (denoted R_0, the average number of new infections caused by each infected individual in an entirely susceptible population, whereby if $R_0 > 1$, an outbreak will be perpetuated through the susceptible population, while if $R_0 < 1$ the outbreak will die out). The coefficient of variation of degree values (Eq. (1) is the measure of interest to adjust R_0. R_0 will increase according to the relationship in Eq. (2) (Woolhouse et al., 1998), if CV_{in} and CV_{out} are positively correlated. A negative correlation between degree values will lower R_0, while if there is no correlation the effect is indeterminate.

$$CV = \Sigma / M \tag{1}$$

$$R_0 \propto 1 + CV_{IN}\, CV_{OUT}\, R \tag{2}$$

To calculate the coefficient of variation (*CV), σ* and *m* are the standard deviation and mean of degree values in the network, respectively. In determining the relative change in R_0, CV_{in} and CV_{out} are the coefficient of variation for in-degree and out-degree respectively for the full network, and r is the correlation between in- and out-degree values for all nodes in the network.

$$R_0 \propto 1 + (CV_{\mathrm{TOTAL}})^2 \tag{3}$$

For the special case where $r = 1$ and therefore in- and out-degree are equal for all nodes, Eq. (2) can be simplified to use CV_{total}, the coefficient of variation for all degree values in the network, to give Eq. (3) (May et al., 2001). The magnitude of CV is heavily influenced by high-degree nodes within the network.

In many infectious diseases in human populations, roughly 20% of infectious individuals are responsible for 80% of disease transmission (Galvani & May, 2005), and this phenomenon has also been identified in livestock movement networks (Woolhouse et al., 2005). If premises with the highest degree values can be identified, they can be targeted for surveillance or control strategies to reduce their effect on R_0 (Christley et al., 2005), with evidence suggesting focussing half of control resources on the most infectious 20% of cases is up to three-fold more effective than random control (Lloyd-Smith et al., 2005). But how are these nodes identified? While declared livestock movement data may be available, records are often incomplete. Thus the question arises, what proportion of the network must be completely enumerated to give accurate estimates of the degree distribution?

Investigation of the impact of sampling on network data has been sporadic as SNA methods have developed. The search for a simple, practical method for determining sample size for network investigation has been unrewarding, largely due to the complexity of network data. The number of edges in a network is dependent on several factors including the number of nodes, and most network measures combine node- and edge-level data. As such, deriving mathematical approaches to determine sample size and confidence intervals have proved challenging (Frank, 1988). Furthermore, many sampling investigations have focussed on effects in networks with random topology (Granovetter, 1976, Frank, 1978, Galaskiewicz, 1991, Borgatti et al., 2006), meaning that many findings cannot be directly applied to real-world networks with scale-free characteristics. More recent work has assessed a broader range of topologies, and indicates the important parameters to consider when sampling a network, namely true network topology (Albert et al., 2000), sampling method (Leskovec & Faloutsos, 2006), network density, and sampling proportion (Galaskiewicz, 1991). Sampling methods for network data include random node sampling, but also targeted approaches that utilise the connections in networks, particularly useful when a sampling frame is not available. A common method is snowball sampling (Goodman, 1961), where one node is chosen to sample at random (the *ego* node), and then all directly connected nodes (first-degree neighbours, or *alters*) of that ego are also sampled in the first “wave” of the snowball. Second and subsequent “waves” can also be included if desired, with each wave sampling all alters of the nodes in the previous wave. Snowball sampling has been shown to provide robust estimates of in-degree with relatively small sample sizes and wave numbers (Johnson et al., 1989).

Degree has repeatedly been shown to be more tolerant of the effects of sampling than other centrality measures (Borgatti et al., 2006, Costenbader & Valente, 2003). In livestock movement data, the total, in- and out-degree values for a node (how many sources and destinations they trade animals with) can be determined from information collected from that node alone, independently of whether the source or destination nodes are included in the sample. This is in contrast to sociological networks, where in-degree and especially out-degree are dependent on the presence of both individuals in the sampled network, although in-degree remains robust and the effects of sampling appear repeatable (Galaskiewicz, 1991). The ease with which degree can be sampled, its reported robustness to error and missing data, and its relevance for animal disease control, make it a useful measure to illustrate sampling strategies.

This paper aims to propose a simulation algorithm for estimating the required sample size for assessment of the degree values of a network given assumptions about the true network's degree distribution, number of nodes, number of edges (or density), sampling method, and the power and precision required for an investigation. Further, a descriptive sensitivity analysis is presented for the robustness of the sample size predictions made by the algorithm between simulated networks with variations in degree distribution, number of nodes, and sampling method.

MATERIALS AND METHODS

Simulation algorithm

The proposed approach (Fig. 1) takes a theoretical, simulated network, constructed to replicate the real-world network of interest, simulates sampling of that theoretical network multiple times, and assesses the agreement between degree metrics from the samples with the true measure in the full network at a desired level of precision.

Network simulation: Networks with two distinct topologies were generated, random and scale-free. Directed random networks were simulated with the Erdos-Renyi model (Erdos a&nd Renyi, 1959), with edge probability equal to 1 – number of nodes. Scale-free networks were simulated with the Barabasi-Albert model (Barabási & Albert, 1999). To simulate a more realistic variation for in- and out-degree, the scale-free networks were generated with undirected edges, each edge then being converted to two reciprocal directed edges and 50% of the edges removed at random. A total of 20 networks of each topology were generated with 100, 1000 and 10,000 nodes in turn, altogether giving 20 × 2 × 3 = 120 networks. The networks were divided into 12 sets for comparison, each set containing 10 networks of equal size and topology. Network density (Eq. 4) and global clustering coefficient (also known as transitivity, an indicator of the level of local clustering present in the network (Butts, 2008)) were calculated to describe the simulated networks.

$$D = E / (N \times (N\text{-}1)) \qquad (4)$$

Network density, D, is the proportion of edges (e) present from the number theoretically possible based on the number of nodes present (n).

Calculation of network measures: For each of the 120 networks, the distributions of total degree, in- and out-degree were assessed by calculating the median, mean, standard deviation (*SD*) and coefficient of variation (*CV*) for each distribution, giving a total of 3 × 4 = 12 measures for each network.

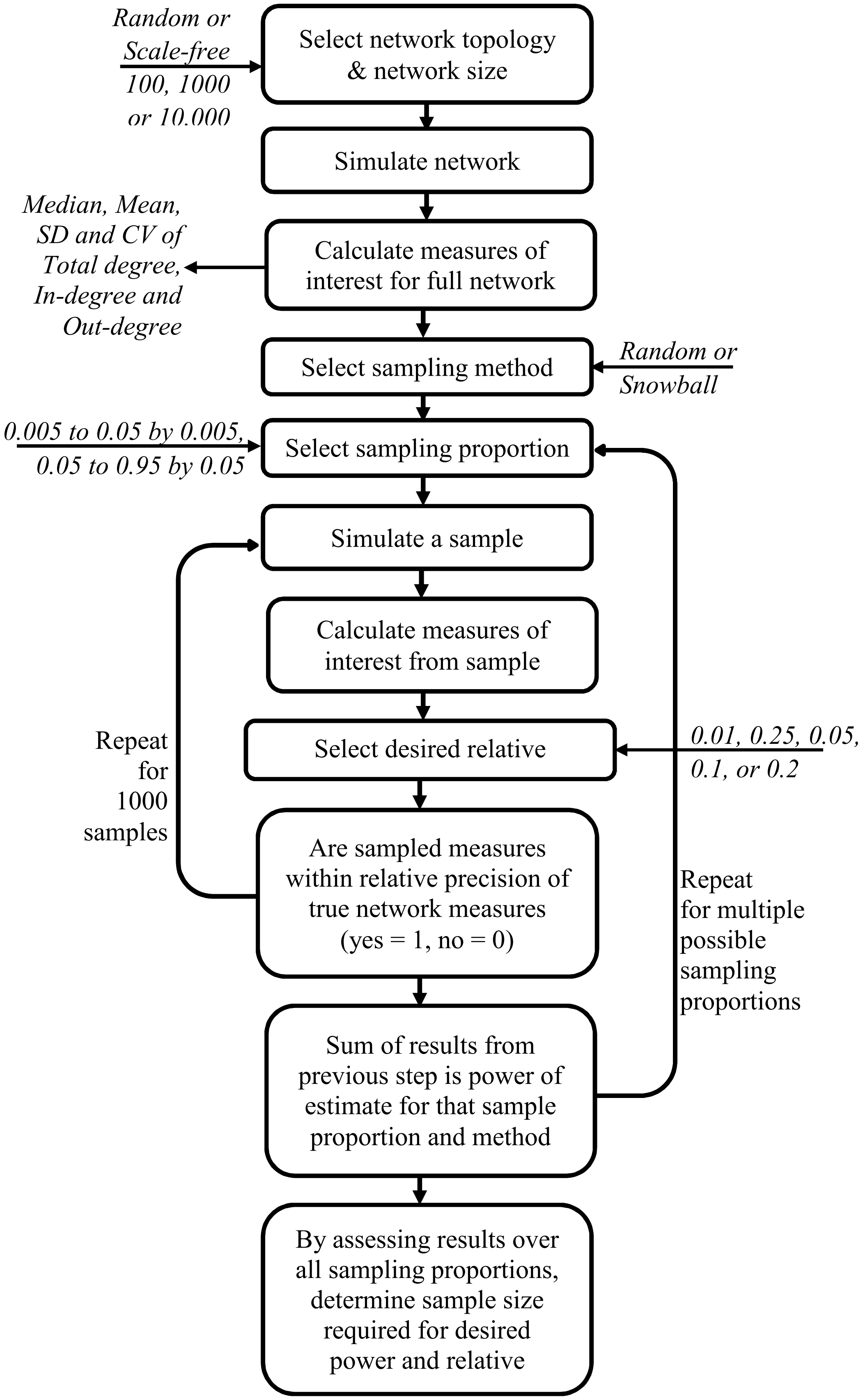


Fig. 1 Sampling algorithm. *Italics* indicate values or categories used for each variable in this paper.

Sampling simulation: Six of the 12 network sets, each representing one combination of network size and topology, were sampled with random node selection, while the remaining six sets underwent snowball sampling. For random sampling, the required proportion of nodes was selected at random, and the true total, in- and out-degree values of each node in the sample were taken.

The snowball sampling method simulated a single wave of snowball sampling, whereby a random node was selected, all alters of that node were identified, and all of these nodes then included in the sample. A second random node was selected, and that second node and alters were also included in the sample, excluding any nodes that had already been sampled. This sampling method was repeated until the total number of nodes sampled was equal to the required sampling proportion. The true total, in- and out-degree values for the sampled nodes were then calculated.

Sampling proportions from 0.05 to 0.95 in steps of 0.05 were tested in every network, as well as sampling proportions from 0.005 to 0.05 in steps of 0.005 in networks with 1000 or 10,000 nodes. Sampling at each proportion was repeated 1000 times in each network.

Precision and determination of power: Precision values of ±1%, 2.5%, 5%, 10% and 20% were tested. The results of the 12 measures were calculated for each sample. These sample values were then compared to the true network value, and whether the sample value was within the specified relative precision of the true network value was evaluated. This was repeated for each of the 1000 samples at a given sampling proportion and sampling method, and the proportion of samples within each relative precision of the true value determined, equivalent to the power of the estimate at that sampling proportion. A power of 80% was used as the cut-off to determine the minimum sample proportion required, for a given measure at a particular level of relative precision.

Sensitivity analysis of measures

The consistency of requisite sampling proportion findings at a given power and precision was assessed by comparing the minimum, mean and maximum sample size required in each of the 12 sets of networks. These investigations aimed to address the following effects:

- The repeatability of the algorithm, specifically whether simulating different networks with the same size and topology would give similar sampling proportion outcomes.
- The impact of network topology on required sampling proportion.
- The effect of sampling method on the necessary proportional sample size.
- The consequences of varying network size for sampling proportion, at the level of an order of magnitude.

Network generation, sampling simulation and all analyses were performed with R statistical software v3.1.1, except snowball sampling in networks of 1000 and 10,000 nodes v3.0.1. due to parallel computing (R core team, 2014), using the igraph (Csardi & Nepusz, 2006) and incursion (Stevenson & Sanson, 2013) packages.

RESULTS

Characteristics of simulated networks

A descriptive summary of the 120 simulated networks is presented (Table 1). The larger networks with low density are typical of livestock movement networks previously reported, such as the cattle movement network in Denmark with approximately 30,000 nodes and density <0.0001 (Bigras-Poulin et al., 2006) or sheep movement in Scotland with approximately 15,000 nodes and density 0.0003 (Volkova et al., 2010). The true total degree measures for each set of networks is summarised below, giving minimum and maximum values for each measure from 20 simulated networks of that type (Table 2).

Table 1. Number of nodes, mean number of edges, mean network density and mean global clustering coefficient for 6 hypothetical livestock movement networks (Numbers in parentheses are the minimum and maximum values for each measure based on 20 simulations, where these values differed from the mean)

Topology	Number of nodes	Number of edges	Density	Global clustering coefficient
Random	100	103 (89-114)	0.010 (0.009-0.012)	0.017 (0.000-0.032)
Scale-free	100	99	0.010	0
Random	1000	991 (940-1061)	0.001	0.002 (0.000-0.007)
Scale-free	1000	999	0.001	0
Random	10,000	9980 (9701-10119)	0.0001	0.0002 (0.000-0.001)
Scale-free	10,000	9999	0.0001	0

Table 2. Total degree measures of 6 simulated networks. Minimum and maximum values are given for each network based on 20 simulations

		Total degree							
	Number	Median		Mean		*SD*		*CV*[a]	
Topology	of nodes	min	max	min	max	min	max	min	max
Random	100	2.00	2.00	1.78	2.28	1.30	1.66	0.60	0.79
Scale-free	100	1.00	1.50	1.98	1.98	1.91	3.55	0.96	1.79
Random	1000	2.00	2.00	1.88	2.12	1.34	1.45	0.67	0.74
Scale-free	1000	1.00	1.00	2.00	2.00	2.63	4.50	1.32	2.25
Random	10,000	2.00	2.00	1.94	2.02	1.39	1.44	0.69	0.72
Scale-free	10,000	1.00	1.00	2.00	2.00	3.28	4.28	1.64	2.14

[a] Coefficient of variation (Eq. 1)

Sampling algorithm results: 10,000 node networks

Results were generated for all sample sizes and relative precisions in all 120 networks. As an illustration of the algorithm, results from four 10,000 node networks are presented, representing the combination of the two network topologies and two sampling methods, for three relative precision levels (±1%, ±5% and ±10% precision), giving the sample size required to estimate the *CV* of total degree. Results for the in- and out-degree sample sizes were similar to the total degree results described below.

The effect of sampling proportion on power using random sampling in a random network is shown in Fig. 2. At ±5% precision, a sampling proportion of 4% of the network (representing 400 nodes) is required to estimate *CV* of total degree with 80% power. If ±10% precision is adequate, the sampling proportion drops to 1% of the network under the same conditions. For the same network, assuming 80% power and ±5% precision, the median, mean and *SD* of total degree can be estimated by sampling 0.5%, 3.5% and 4% of nodes, respectively. Thus, if all four measures were required, a total sample size of 400 nodes would be sufficient in this network.

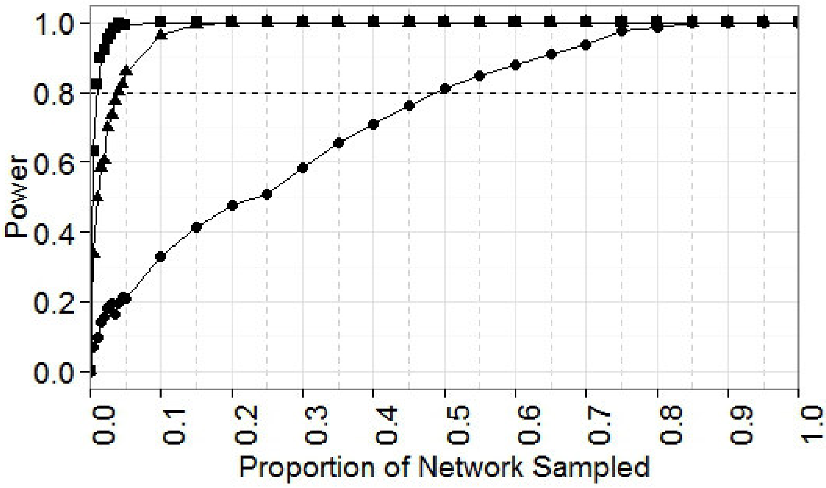


Fig. 2 Sample proportion required to determine the coefficient of variation of total degree when random sampling is used in a 10,000 node random network. Circle, triangle and square series indicate results for ±1%, ±5% and ±10% precision respectively, while the dashed horizontal line indicates 80% power.

Snowball sampling in a random network is illustrated in Fig. 3. Snowball sampling with a single wave to estimate *CV* of total degree requires 95% of nodes to be sampled for 80% power and ±5% precision. With the same power and precision assumptions, the median, mean and *SD* of total degree of this network can be estimated by sampling 15%, 95% and 30% of nodes, respectively. The lack of precision in estimates of the mean at smaller sample sizes drives the need for such a large sample to estimate *CV*. If all measures were required, 9500 nodes would need to be included in the sample. This indicates that, was snowball sampling to be used, almost the whole network must be enumerated, and an alternative sampling method or network census should be considered. If no feasible alternative were available, up to 500 nodes missing at random would be tolerable.

The outcome of random sampling in a scale-free network can be seen in Fig. 4. To estimate *CV* with 80% power and ±5% precision, 90% of nodes must be randomly sampled. For the median, mean and *SD* of total degree at the same power and precision, sampling proportions of 0.1%, 20% and 90% are required, respectively. In this case, lack of precision in estimates of the *SD* at smaller sample sizes means a large sample (9000 nodes) is needed to estimate *CV*. If up to 10% of nodes are missing at random, the estimate of *CV* will still have ±5% precision with 80% power.

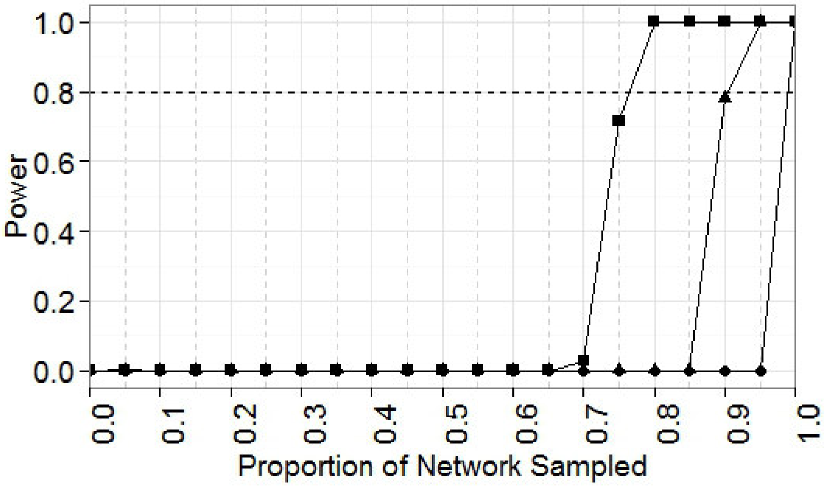


Fig. 3 Sample proportion required to determine the coefficient of variation of total degree when snowball sampling is used in a 10,000 node random network. Circle, triangle and square series indicate results for ±1%, ±5% and ±10% precision respectively, while the dashed horizontal line indicates 80% power.

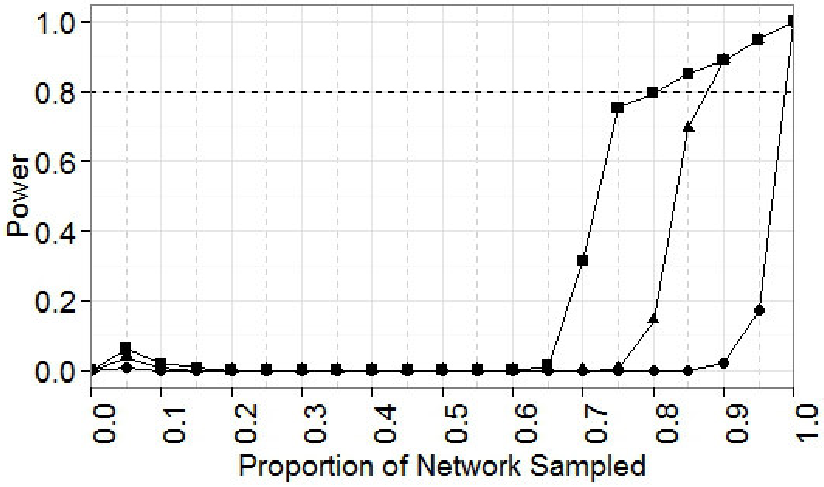


Fig. 4 Sample proportion required to determine the coefficient of variation of total degree when random sampling is used in a 10,000 node scale-free network. Circle, triangle and square series indicate results for ±1%, ±5% and ±10% precision respectively, while the dashed horizontal line indicates 80% power.

Finally, Fig. 5 shows the effect of snowball sampling in a scale-free network. To estimate *CV* with 80% power and ±5% precision, snowball sampling with a single wave from each randomly selected node will require a sampling proportion of 50%. The median, mean and *SD* of total degree can be estimated with the same power and precision with sampling proportions of 70%, 95% and 90% respectively. Interestingly, in contrast to random sampling, with snowball sampling the *CV* can be estimated with the desired precision at a lower sample size (5000 nodes) than *SD* or the mean. This was observed in all 10 replications of this simulation with different 10,000 node scale-free networks, with consistent findings of 95%, 90% and 50% for the mean, *SD* and *CV* respectively.

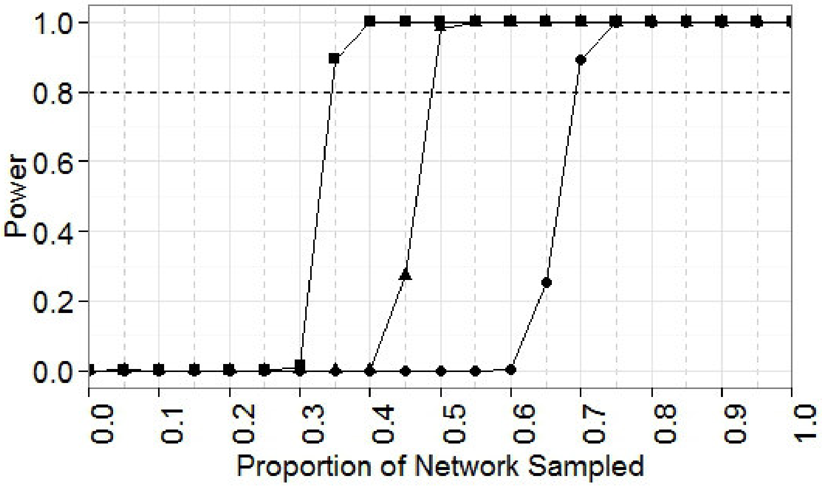


Fig. 5 Sample proportion required to determine the coefficient of variation of total degree when snowball sampling is used in a 10,000 node scale-free network Circle, triangle and square series indicate results for ±1%, ±5% and ±10% precision respectively, while the dashed horizontal line indicates 80% power.

Descriptive sensitivity analysis

The repeatability of the algorithm, as well as the impacts of network topology, sampling method and network size on required sample size can be assessed by comparing the mean and range of metric results for each of the 12 sets of networks. Results for required sampling proportion to give 80% power and ±5% precision for the four total degree measures are given in Appendix 1.

For a set of 10 networks of equivalent network size and topology, the same sampling method produces sampling proportion estimates with a range <0.15 for most measures investigated. Median measures in small networks (100 nodes) are the exception, where wide ranges of relative sample sizes were returned under all four combinations of sampling method and network topology. For example, in a scale-free network with snowball sampling, sample proportions from 0.55 to 0.95 were produced, indicating a single simulation may not be reliably determine required sample size. The range of sample proportions for all measures in larger networks (1000 and 10,000 nodes) demonstrated far less variation, with most producing sample proportions within 0.15 of each other across the 10 replications.

Snowball sampling in random networks gave increased variation in sample proportion results for networks of 100 or 1000 nodes. The same issue was not detected when snowball sampling was used in scale-free networks. Agreement between the 10 replications was particularly high for total degree measures in the 10,000 node networks of both topologies, with the range of sample proportions within 0.1 for all measures except *SD* in random networks with snowball sampling (range = 0.15).

DISCUSSION

Differing sampling methods in networks with common features returned different sample size estimates, particularly for the scale-free networks. In scale-free networks using snowball sampling, while large sample sizes are required to estimate mean and *SD* of total degree, a far smaller sample size is required to estimate *CV*. This demonstrates that sampling methods should be selected taking into account the particular network measure of interest. If investigating the effect of a scale-free network on R_0, and in- and out-degree are known to be strongly positively correlated, then only 50% of the network is required to accurately estimate the CV and therefore adjust R_0 accordingly. This is an important finding, and shows that a simulation-based approach can be useful in providing a means to select a network sampling method best-suited to estimate a specific network measure of interest.

With an increased requirement for precision in degree metrics, comes an increase in required sample size. However, there are other important influences on sample size estimates for SNA: network density, topology, and sampling method as previously highlighted. Reliable estimates of sampling proportion are dependent on valid assumptions of a network's structure. Livestock movement networks are commonly scale-free with some clustering, and so topology is not difficult to predict. Density can be estimated from the mean total degree of the network, and we have found that in large networks of low density (approximately 10,000 nodes), this can be estimated with a random sample from approximately 20% of nodes. The challenge here is that the sample proportion of 20% is based on an assumption of low density, while attempting to estimate a variable that influences density. Thus, the quantifiable impact of density on the sampling proportion must be further investigated to assess the validity of this approach.

It is important to consider the impact of the relative precision of metric estimations when using this algorithm, and to set this value in the context of the particular research question at hand. The measure of interest might be estimated on the basis of results in other similar networks, and the desired absolute precision quantified. If a relative precision of ±10% is determined to be sufficient, this can markedly reduce the sample size required compared to ±5% precision. This advantage can have practical implications and may be the deciding factor in feasibility of a particular investigation.

Further, consider that this simulation algorithm will address the effect of chance in sampling networks, but does not necessarily eliminate systematic error in sampling. Where random sampling is called for (including in selecting the initial nodes for snowball sampling), true randomisation is critical to maintain the power of the degree measure estimates determined from the investigation. Identifying and attempting to control all biases is as critical in network data as in other epidemiological datasets.

The results presented indicate that the proposed algorithm for determining sampling proportion in typical livestock movement networks is repeatable in networks of moderate size, in the order of 1000 nodes or greater. An upper confidence level could be applied to sample size estimates to account for minor variation that can occur between simulations. For networks similar to those presented here, a confidence level of sampling proportion of ± 0.1

would be appropriate, such that if the required sample proportion from a single simulation gave a result of 0.4 (40% of nodes), one might sample 50% of nodes to ensure the requisite power and precision were achieved.

This paper has aimed to assess the effect of sampling method on the proposed simulation algorithm, rather than validating particular sampling methods for livestock movement network analysis. Consequently, the complexities of snowball sampling have not been completely investigated, such as the number of waves of sampling from each randomly selected node. This algorithm could, however, be used to compare snowball sampling with different numbers of waves, as well as other related sampling methods including random walk (where one node is chosen at random for each wave), or forest fire (where each neighbouring node's inclusion in a wave is determined by a set probability).

The simulation of a "typical" network based on underlying assumptions about network topology, density and size is dependent on the availability of a model for simulating such a network. Several such models are available in existing software, but an understanding of how the model creates the network and whether it is truly representative of the real network of interest is critical to the validity of sample size results. Furthermore, many network models fail to incorporate a realistic level of clustering, the models presented in this paper notwithstanding, and this may also influence the validity of sample size results produced by this approach. Investigating other models that accurately replicate livestock movement networks that might be used in this algorithm would be a valuable direction for future work. Furthermore, this algorithm should be validated by testing it with real network data, and with other network metrics of interest.

While in the past network sampling has been largely neglected in veterinary applications of SNA, this algorithm demonstrates that it is possible to estimate the sample size required for network investigation. Based on a small number of assumptions, this simulation approach can be used by investigators to design valid studies that give precise estimates of meaningful network metrics.

ACKNOWLEDGEMENTS

This research was supported by a Victorian Life Sciences Computation Initiative (VLSCI) grant, number VR0277, on its Peak Computing Facility at the University of Melbourne, an initiative of the Victorian Government, Australia. This work is part of the Local Area Network for Disease Investigations (LANDI) project at the Mackinnon Project, Faculty of Veterinary and Agricultural Sciences, University of Melbourne, funded by the Victorian Cattle and Sheep and Goat Compensation Funds administered by the Victorian Government Department of Environment and Primary Industries (DEPI). C. Pfeiffer receives support from an Australian Postgraduate Award from the Australian Government.

REFERENCES

Albert, R., Jeong, H. and Barabási, A.-L. (2000). Error and attack tolerance of complex networks. Nature 406, 378-382

Aznar, M.N., Stevenson, M.A., Zarich, L. and Leon, E.A. (2011). Analysis of cattle movements in Argentina, 2005. Prev. Vet. Med. 98, 119-127

Baptista, F.M. and Nunes, T. (2007). Spatial analysis of cattle movement patterns in Portugal. Vet. Ital. 43, 611-619

Barabási, A.-L. and Albert, R. (1999). Emergence of scaling in random networks. Science 286, 509-512

Bigras-Poulin, M., Thompson, R.A., Chriel, M., Mortensen, S. and Greiner, M. (2006). Network analysis of Danish cattle industry trade patterns as an evaluation of risk potential for disease spread. Prev. Vet. Med. 76, 11-39

Borgatti, S.P., Carley, K.M. and Krackhardt, D. (2006). On the robustness of centrality measures under conditions of imperfect data. Soc. Networks 28, 124-136

Butts, C. T. (2008). Social network analysis: a methodological introduction. Asian J. Soc. Psychol. 11, 13-41

Christley, R.M., Pinchbeck, G., Bowers, R., Clancy, D., French, N., Bennett, R. and Turner, J. (2005). Infection in social networks: using network analysis to identify high-risk individuals. Am. J. Epidemiol. 162, 1024-1031

Costenbader, E. and Valente, T.W. (2003). The stability of centrality measures when networks are sampled. Soc. Networks 25, 283-307

Csardi, G. and Nepusz, T. (2006). The igraph software package for complex network research, InterJournal, Complex Systems 1695. http://igraph.org/

Erdos, P. and Renyi, A. (1959). On random graphs. Publ. Math. 6, 290-297

Firestone, S.M., Christley, R.M., Ward, M.P. and Dhand, N.K. (2012). Adding the spatial dimension to the social network analysis of an epidemic: investigation of the 2007 outbreak of equine influenza in Australia. Prev. Vet. Med. 106, 123-135

Frank, O. (1978). Sampling and estimation in large social networks. Soc. Networks 1, 91-101

Frank, O. (1988). Random sampling and social networks. a survey of various approaches. Math. Sci. Humaines 104, 19-33

Galaskiewicz, J. (1991). Estimating point centrality using different network sampling techniques. Soc. Networks 13, 347-386

Galvani, A.P. and May, R.M. (2005). Epidemiology: dimensions of superspreading. Nature 438, 293-295

Goodman, L.A. (1961). Snowball sampling. Ann. Math. Stat. 32, 148-170

Granovetter, M. (1976). Network sampling: some first steps. Am. J. Sociol. 81, 1287-1303

Johnson, J.C., Boster, J.S. and Holbert, D. (1989). Estimating relational attributes from snowball samples through simulation. Soc. Networks 11, 135-158

Leskovec, J. and Faloutsos, C. (2006). Sampling from large graphs. In: Proceedings of the 12th ACM SIGKDD international conference on knowledge discovery and data mining. pp. 631-636

Lloyd-Smith, J.O., Schreiber, S.J., Kopp, P.E. and Getz, W. (2005). Superspreading and the effect of individual variation on disease emergence. Nature 438, 355-359

Martinez-Lopez, B., Perez, A.M. and Sanchez-Vizcaino, J.M. (2009). Social network analysis. Review of general concepts and use in preventive veterinary medicine. Transbound Emerg Dis 56, 109-120

May, R.M., Gupta, S. and Mclean, A.R. (2001). Infectious disease dynamics: what characterizes a successful invader? Phil. Trans. R. Soc. B 356, 901-910

Natale, F., Giovannini, A., Savini, L., Palma, D., Possenti, L., Fiore, G. and Calistri, P. (2009). Network analysis of Italian cattle trade patterns and evaluation of risks for potential disease spread. Prev. Vet. Med. 92, 341-350

Ortiz-Pelaez, A., Pfeiffer, D.U., Soares-Magalhaes, R.J. and Guitian, F.J. (2006). Use of social network analysis to characterize the pattern of animal movements in the initial phases of the 2001 foot and mouth disease (FMD) epidemic in the UK. Prev. Vet. Med. 76, 40-55

Porphyre, T., Stevenson, M., Jackson, R. and Mckenzie, J. (2008). Influence of contact heterogeneity on TB reproduction ratio R_0 in a free-living brushtail possum *Trichosurus vulpecula* population. Vet. Res. 39, 1

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/

Rautureau, S., Dufour, B. and Durand, B. (2011). Targeted surveillance of cattle trade using social network analysis tools. Epidemiol. Sante Anim. 58-60.

Rautureau, S., Dufour, B. and Durand, B. (2012). Structural vulnerability of the French swine industry trade network to the spread of infectious diseases. Animal 6, 1152-1162

Smith, R.P., Cook, A.J.C. and Christley, R.M. (2013). Descriptive and social network analysis of pig transport data recorded by quality assured pig farms in the UK. Prev. Vet. Med. 108, 167-177

Stevenson, M.A. and Sanson, R. (2013). incursion: Functions for the analysis of infectious disease outbreaks in animal populations. R package version 0.1-16. http://epicentre.massey.ac.nz/

Volkova, V.V., Howey, R., Savill, N.J. and Woolhouse, M.E. (2010). Sheep movement networks and the transmission of infectious diseases. PLoS ONE 5, e11185

Webb, C.R. (2005). Farm Animal Networks: Unraveling The Contact Structure Of The British Sheep Population. Prev. Vet. Med. 68, 3-17

Woolhouse, M., Etard, J.-F., Dietz, K., Ndhlovu, P. and Chandiwana, S. (1998). Heterogeneities in schistosome transmission dynamics and control. Parasitology 117, 475-482

Woolhouse, M.E.J., Shaw, D.J., Matthews, L., Liu, W.C., Mellor, D.J. and Thomas, M.R. (2005). Epidemiological implications of the contact network structure for cattle farms and the 20-80 rule. Biol. Lett. 1, 350-352

APPENDIX

Table A1. Required sampling proportion for total degree measures. Each row shows the minimum, mean and maximum sample size output for 10 networks of equivalent sample size and topology. Values in bold indicate where the range of sampling proportion outputs is greater than 0.15 within each set of 10 networks.

Number of nodes	Topology	Sampling method	Median of total degree			Mean of total degree		
			Min	Mean	Max	Min	Mean	Max
100	Random	Random	**0.15**	**0.25**	**0.85**	0.7	0.8	0.85
1000	Random	Random	0.035	0.045	0.1	0.25	0.25	0.3
10,000	Random	Random	0.005	0.005	0.005	0.035	0.035	0.035
100	Random	Snowball	**0.25**	**0.5**	**0.85**	0.95	0.95	0.95
1000	Random	Snowball	**0.15**	**0.275**	**0.5**	0.95	0.95	0.95
10,000	Random	Snowball	0.1	0.15	0.2	0.95	0.95	0.95
100	Scale-free	Random	**0.15**	**0.35**	**0.45**	0.9	0.9	0.95
1000	Scale-free	Random	0.005	0.045	0.15	**0.2**	**0.65**	**0.75**
10,000	Scale-free	Random	0.005	0.01	0.01	0.2	0.2	0.25
100	Scale-free	Snowball	0.55	0.8	0.95	0.95	0.95	0.95
1000	Scale-free	Snowball	0.7	0.75	0.8	0.95	0.95	0.95
10,000	Scale-free	Snowball	0.7	0.7	0.75	0.95	0.95	0.95

Number of nodes	Topology	Sampling method	*SD* of total degree			*CV* of total degree		
			Min	Mean	Max	Min	Mean	Max
100	Random	Random	0.75	0.8	0.9	0.8	0.85	0.9
1000	Random	Random	0.3	0.325	0.35	0.3	0.3	0.35
10,000	Random	Random	0.04	0.045	0.045	0.04	0.04	0.045
100	Random	Snowball	0.65	0.725	0.8	0.95	0.95	0.95
1000	Random	Snowball	**0.25**	**0.35**	**0.55**	0.95	0.95	0.95
10,000	Random	Snowball	0.15	0.25	0.3	0.95	0.95	0.95
100	Scale-free	Random	0.9	0.925	0.95	0.8	0.9	0.95
1000	Scale-free	Random	0.9	0.9	0.95	0.8	0.9	0.95
10,000	Scale-free	Random	0.85	0.9	0.9	0.8	0.9	0.9
100	Scale-free	Snowball	0.9	0.9	0.9	**0.6**	**0.675**	**0.85**
1000	Scale-free	Snowball	0.9	0.9	0.9	0.35	0.475	0.5
10,000	Scale-free	Snowball	0.9	0.9	0.9	0.4	0.5	0.5

INCLUDING VARIABLE HISTORICAL INFORMATION IN THE ANALYSIS OF CLINICAL TRIALS: AN APPLICATION OF BAYESIAN POWER PRIOR MODELLING

H. NI*, I. KLUGKIST, C. RIETBERGEN, W. BACK AND M. NIELEN

SUMMARY

Bayesian inference offers a natural framework to aggregate variable existing evidence into a quantitative summary of prior knowledge. In this paper, we applied the Bayesian power prior approach to incorporate historical evidence into the final analysis of new randomised controlled trial data. Data from a Dutch equine trial were used as an illustrative example, where treatment effect from oral supplementation of Glucosamine and Chondroitin Sulphate on stiffness in veteran horses was evaluated. Four relevant historical studies were included in the power prior. The relative importance of each historical study was weighted by two experts, one for the clinical relevance and one for the methodological quality. The expert opinion was used to define the weight parameter for the power prior approach. Posterior inference of the treatment effect was successfully obtained by combining the calculated power prior with the likelihood of the equine trial data, resulting in a more precise effect estimate.

INTRODUCTION

Within Evidence-based Veterinary Medicine (EBVM), a well-designed randomised controlled trial (RCT) is considered the strongest primary evidence (Cockcroft & Holmes, 2003). Aggregation of such high quality evidence in a meta-analysis following a systematic review provides a synthesis of current evidence that may be used to design and power a new RCT.

Recently, in human medicine, there has been increased interest in methods to incorporate existing evidence into the final data analysis of an RCT using a Bayesian approach (Greenhouse & Wasserman, 1995; Spiegelhalter et al., 2004; Neuenschwander et al., 2010; Berry et al., 2011; Rietbergen et al., 2011; Hobbs et al., 2012). Bayesian inference allows evidence from diverse sources to be pooled into the prior distribution, by assuming that their underlying probability models (their likelihoods) share parameters of interest (Spiegelhalter et al., 2004). By adding a prior containing aggregated evidence from historical studies into the analysis of new RCT data, the uncertainty of parameter estimates may decrease. The current state of knowledge is thus based on historical and new evidence combined in posterior estimates.

One promising method is the power prior approach proposed by Ibrahim and Chen (2000). The power prior method combines an initial prior (often uninformative) with the weighted likelihood of one or multiple historical datasets. Central in this technique is the weight parameter, which explicitly allows the researcher to quantify and dynamically utilise

---

[*] Haifang Ni, Padualaan 14, 3584CH, Utrecht, The Netherlands. Email: h.ni-dufour@uu.nl

historical information by means of assigning a weight to each historical study to denote its quality and/or relevance.

In the present paper, we applied the power prior method in a veterinary context. For illustration, an equine RCT on assessing the clinical impact of certain oral supplementation in veteran horses was analysed including historical evidence. Historical studies from across animal species on approximately the same research question were selected and weighted concerning methodological quality or clinical relevance to the equine trial. We are not aware of previous applications in veterinary medicine where historical data are incorporated into a Bayesian analysis of an RCT.

The main objective of our paper is to illustrate the power prior approach in detail and motivate the use of this method in the analysis of a veterinary RCT. Furthermore, although theoretically established, and previously applied in human medicine, we have encountered new obstacles and challenges throughout our application. An extended discussion is therefore given regarding these issues.

MATERIALS AND METHODS

The power prior

When results are available from historical similar studies, it is reasonable to use them as the basis for the prior distribution of the Bayesian analysis of a new study. However, often previous studies are not exactly similar to the clinical research question at hand. The power prior approach (Ibrahim & Chen, 2000) proposes to discount the impact of historical studies by taking the likelihood of the data to a power a. This method assumes that the historical studies and the current study share the same parameters of interest θ, but the informativeness of a historical dataset D_h is weighted by the power a relative to the current data D.

The power prior for a single historical study is expressed as:

$$\pi(\theta \mid D_h, a) \propto L(\theta \mid D_h)^a \times \pi_0(\theta) \tag{1}$$

where $\pi_0(\theta)$ is the initial prior which is often chosen to be uninformative, and $L(\theta \mid D_h)^a$ is the powered likelihood of the historical data. The resulting posterior $\pi(\theta \mid D_h, a)$ can then be used as the prior distribution, that is, the power prior, for the Bayesian analysis of the current data *D*.

The posterior distribution of *θ* is:

$$\pi(\theta \mid D, D_h, a) \propto L(\theta \mid D) \times \pi(\theta \mid D_h, a) \tag{2}$$

Posterior estimates of θ in (2) are obtained through sampling by Markov Chain Monte Carlo (MCMC) methods. More details about MCMC methods can be found in, for instance, Spiegelhalter et al. (2004), Gelman et al. (2008), Toft et al. (2007).

The power *a* is also known as the weight parameter, as it weights the historical likelihood with regard to the data from the current study. Ibrahim and Chen (2000) suggested to restrict the weight parameter to be between 0 and 1, with $a = 0$ equivalent to no incorporation of historical evidence at all, and $a=1$ equivalent to full inclusion of historical evidence. The weight parameter a can be interpreted as a relative precision parameter for the historical data which controls the tails of the resulting power prior for the parameters of interest. As a becomes smaller, the tails of the prior become heavier (Ibrahim & Chen, 2000). In (1), the weight parameter is specified as a fixed value, leading to what is called a conditional power prior. To express uncertainty about the weight parameter, a prior for a can be specified, leading to a so-called hierarchical or joint power prior approach (e.g. Chen & Ibrahim, 2006). In the present paper, we applied the power prior approach with multiple historical studies. Since the joint power prior approach is not yet fully developed for multiple studies (Chen & Ibrahim, 2006; Neuenschwander et al., 2009; Hobbs et al., 2012), we will apply the conditional power prior approach, that is, with study-specific fixed weights.

For multiple historical studies, let $\mathbf{D_h} = (D_{h1},\ldots,D_{hK})$ where D_{hk} is the data from the *k*th historical study for $k=1,\ldots,K$. Further, let $\mathbf{a}=(a_1,\ldots,a_K)$, where a_k is the study-specific weight for the data of the *k*th study D_{hk}. The power prior approach can then be generalised to multiple historical studies as shown in (3) (Ibrahim & Chen, 2000):

$$\pi(\theta \mid \mathbf{D_h},\mathbf{a}) \;\propto\; \prod_{k=1}^{K}\left[L(\theta \mid D_{hk})^{a_k}\right] \;\times\; \pi_0(\theta) \qquad \text{FOR } k=1,\ldots,K \qquad (3)$$

Data and statistical model

The data: As an illustration, a Bayesian analysis was performed on the data from an equine clinical trial (Higler et al., 2014). In this RCT, treatment effect of oral supplementation of Glucosamine (GS) and Chondroitin Sulphate (CS) on stiffness in aged horses was assessed. A total of 24 horses and ponies with a mean age of 29 years were involved in a 3-month treatment period, where 12 were randomised into the treatment group and 12 into the placebo control group. Change in stride length from pre- to post-treatment was the primary outcome variable, and clinical improvement of stride length was expected. Assessment of treatment effect (denoted *T*) was obtained by comparing the mean difference of the primary outcome variable (i.e. change in stride length) between the treatment and the control group.

Eight historical studies with a theoretically comparable research question were initially collected based on the references in Higler et al. (2014). Characteristics and findings of the current trial as well as the historical studies are displayed in Table 1 showing the varying study characteristics and findings. For instance, not all studies were carried out in horses, but also in dogs and humans. Most studies were RCTs except for one Bayesian network meta-analysis. Furthermore, drugs used for the treated participants varied between studies and the treatment effect was evaluated by various primary outcomes. Note that in Table 1, for outcomes such as stride length, clinical improvement corresponds to a positive *T* value, while for outcomes such as pain intensity, clinical improvement corresponds to a negative *T* value since an effective treatment would reduce pain intensity. Before inclusion in the power prior approach, all scores were recoded such that clinical improvement always corresponds to a positive mean difference between the treatment and the control group.

Table 1. Relevant study characteristics of the current study and eight historical studies, where T refers to the mean difference between the treatment and control and the scaled used.

Year	Author	Size	Species	Design	Drugs	Outcome	T (scale)	95% CI of T
2014	Higler	24	horse	trial	GS&CS	stride length	0.5 cm	[-1.3, 2.3]
2010	Wandel	3803	human	meta-analysis	GS&CS	pain intensity	-0.5 [0-10]	[-0.9, 0.0][a]
2009	Rozendaal	222	human	trial	GS	pain scores	-1.4 [0-100]	[-6.7, 3.8]
2008	Sawitzke	572	human	trial	GS&CS	joint space width	0.028 mm	[-0.214, 0.271]
2006	Forsyth	20	horse	trial	GS&CS	stride length	13 cm	-[b]
2006	McCarthy	35	dog	trial	GS&CS	lameness scores	1.1 [1-5]	-
2003	White	30	horse	trial	GS&CS	stride length	23.9 cm	-
2002	Clayton	8	horse	trial	GS	velocity	-1 cm/s	-
2000	Rindone	98	human	trial	GS	pain intensity	-0.1 [0-10]	-

GS = Glucosamine, CS= Chondroitin Sulphate.

[a] This meta-analysis provided a 95% credible interval, not confidence interval.

[b] When a certain statistic is not reported in the study, it is denoted as "-".

The statistical model: Since different studies used different outcome variables, all primary data were standardised before being entered in the analysis. For the historical studies, individual data points were not available but could be simulated if sufficient statistics were reported.

The standardised data within each study, the current as well as the historical, were assumed to be normally distributed in both the treatment and the control group:

$$\begin{aligned} y_{ti} &\sim N(\mu_t,\ \sigma_t^2) \qquad \text{for } i = 1,\ldots,n_t, \\ y_{cj} &\sim N(\mu_c,\ \sigma_c^2) \qquad \text{for } j = 1,\ldots,n_c. \end{aligned} \tag{4}$$

In (4), y_{ti} and y_{cj} refer to the standardised change in the outcome variable before and after treatment of the *i*th subject of the treatment and the *j*th subject of the control group respectively; and n_t and n_c represent the sample sizes of the treatment and the control group respectively.

The parameter of main interest is the standardised treatment effect τ, expressed as the standardised mean difference between the two groups, that is, $\tau = \mu_t - \mu_c$.

Weight elicitation and defining *a*

Weight elicitation: An equine specialist and a methodologist were asked to assign and motivate a study-specific weight for each historical study. The elicitation was carried out independently and there was no exchange in opinion between the experts. Both experts were allowed to discuss the weights with their colleagues as long as they remained responsible for the total weighting process of all historical studies. The experts were first personally approached, next contacted via email.

Both experts were free to decide which criteria to use for the scoring. They were, however, asked to explicitly ignore the results found in each study, such as the effect size or the significance value. The equine scientist was asked to weight each study regarding the clinical relevance, the methodologist regarding the methodological quality. In the end, two sets of 8 weights were obtained: one set based on the clinical relevance and the other on the methodological quality. The elicited weights were the basis for the final values of the weight parameter *a*.

The constant-sum scaling method (Durek & Baker, 1956) was employed as the elicitation method where a total of 100 points was to be distributed among the eight studies. In contrast to simple ranking, this method gives numerical scale values which imply the relative importance or the ratio relationships of the historical studies. A more relevant study to the research question at hand or a higher quality study was supposed to get a higher weight, and vice versa. In addition, exclusion of the historical study from the prior was possible by assignment of an 0.

Defining the weight parameter *a*: As previously mentioned, a weight equivalent to 1 means full inclusion of the data. The current study therefore always receives weight 1. In our analysis, we chose to let the sum of all weights for the historical studies (either clinical or methodological) be equivalent to 1 as well. The final values for the weight parameter *a* were hence the original weights elicited by experts proportional to the total assigned points (i.e. 100).

Statistical analysis

Calculation of the power prior: To illustrate how the power prior is computed we will simplify the notations by omitting the subscripts for group (treatment and control), study (in case of multiple historical studies), and weight (for the two sets of weights). Since the two groups are independent, the same prior specification can be applied to each group separately. Also we will start with the situation that only one historical study and one weight is of interest. At the end of this section we will address how this can easily be extended to multiple historical studies.

The initial priors were specified as the conjugate prior for assumed normally distributed data with unknown mean and variance. Conjugate priors result in posterior distributions with the same functional form and similar properties as the prior. This is convenient in both computation and interpretation (Gelman et al., 2008). In other words, the initial prior, the power prior, and the posterior all have the same distributions but with different hyper parameters.

The hyper parameters of the initial prior are denoted μ_0 , σ_0^2 and ν_0 , leading to:

$$\begin{aligned} \pi_0(\mu \mid \sigma^2) &\sim N\left(\mu_0, \sigma^2 / \nu_0\right) \\ \pi_0(\sigma^2) &\sim Inv-\chi^2\left(\nu_0,\ \sigma_0^2\right) \end{aligned} \qquad (5)$$

By setting the prior sample size ν_0= 0.1, the initial prior is low-informative. The values for μ_0 and σ_0^2 are then relatively unimportant and were set at 0 and 1, respectively.

Updating the initial prior with one historical study will change the hyper parameters of the distributions presented in (5). Let n_E denote the effective sample size of the historical data, computed as $n_E = n_h \cdot a$ where n_h refers to the original sample size of the historical data and a refers to the weight at hand. Further, let $\bar{y}$ denote the sample mean and s^2 the sample variance of the historical data. The updated values for the hyper parameters (denoted with subscript *n*) are then computed as (Gelman et al., 2008):

$$\nu_n = \nu_0 + n_E$$

$$\mu_n = \frac{\nu_0}{\nu_n}\mu_0 + \frac{n_E}{\nu_n}\bar{y} \tag{6}$$

$$\sigma_n^2 = \frac{\nu_0\sigma_0^2 + (n_E - a)\cdot s^2 + \frac{\nu_0 \cdot n_E}{\nu_n}(\bar{y} - \mu_0)^2}{\nu_n}$$

Slightly abusing notations, we can also use (6) to update the power prior obtained after inclusion of the first historical study D_{h1}, with data from a second historical study D_{h2}. The current values for (ν_n, μ_n σ_n^2) after inclusion of D_{h1} are used as the new (ν_0, μ_0 σ_0^2) in (6) for updating with information from study D_{h2}. This provides new values for (ν_n, μ_n σ_n^2) that define the power prior after incorporation of both historical studies. In a similar way, the third, fourth,…, until *K*th historical study can be included as well.

By applying this process to both groups (treatment and control) and for both sets of weights (clinical and methodological), two power priors were obtained. The two power priors contained either clinically or methodologically weighted information from all historical studies.

Sampling of the posterior: The discounted historical evidence contained in the power prior was updated in the light of new evidence from the current trial, providing posterior estimates for the model parameters μ_t, μ_c, σ_t^2 and σ_c^2. Furthermore, posterior estimates for the standardised treatment effect τ can easily be obtained with the MCMC sampling approach. In each iteration, a value for μ_t as well as μ_c is sampled and therefore also a value for $\tau = \mu_t - \mu_c$. With the resulting sample from the posterior of τ, all estimates of interest are available. Statistical inference on the clinical treatment effect was made on the basis of the posterior mean and variance of τ, as well as the 95% credible interval. The posterior estimates resulting from the power priors based on the clinical relevance were compared to the results based on the methodological quality weights.

The power prior was calculated analytically using the program R, while the Bayesian analysis of the current trial combined with the resulting power prior was carried out in OpenBUGS version 3.2.2. For each model, the first 10,000 iterations were discarded as the burn-in phase, and the following 10,000 were used for posterior inference. Convergence of the MCMC chains was monitored by visual inspection of the trace plots of the parameters of interest.

RESULTS

The weight

An overview of the expert elicited weights can be seen in Table 2. Table 2 reveals that both sets of weights were not equally distributed among the historical studies, reflecting the variable degrees of informativeness of the historical studies on the current trial. The clinical relevance weight was slightly more evenly divided among the studies than the methodological quality weight, possibly indicating more difference in the study qualities than in clinical relevance. Clinical relevance and methodological quality were expected to be two different types of study characteristics with different criteria for inclusion of historical evidence. However, both experts used outcome assessment and sample size as arguments in their weight assignment.

Table 2. An overview of the weights assigned by experts with their summarised motivation.

Study	Equine specialist			Methodologist
	Motivation	Score		Motivation
Wandel	n=3803; human; the used principle is correct	14	0	meta-analysis, not comparable to other studies
Rozendaal	n=222; human; subjective scoring	12	30	properly executed
Sawitzke	n=572; human/veteran; subjective scoring	14	30	properly executed
Forsyth	n=20; horse; small control group	22	15	treatment duration short; study design not optimal
McCarthy	n=35; dog; no negative control	8	2	control group not optimal; lacked sufficient power
White	n=30; horse; IM application	4	8	lacked a predetermined non-inferiority margin
Clayton	n=8; horse; small sample size	16	5	small sample size; results unclear
Rindone	n=98; human; only GS; subjective scoring	10	10	treatment duration short; study design not optimal

The ordering between the two sets of weights showed some resemblance in their tendency for the high and the low weights, with the exception of the meta-analysis. The meta-analysis received 0 points from the methodologist with the motivation that it was not comparable to primary evidence and would be difficult to aggregate as a single study into the power prior. The highest methodological weights were assigned to two human trials because they were properly executed. These two studies also had larger sample sizes than the other historical studies, resulting in relative large impact on the methodological power prior and the subsequent posterior estimates.

The data

Only four out of the eight historical studies were used for the power prior specification. They were from Rozendaal et al. (2009), Sawitzke et al. (2008), Forsyth et al. (2006), and Rindone et al. (2000). The meta-analysis was quantitatively difficult to summarise as a single study, and was therefore removed. The other three studies were all excluded because they lacked numerically reported sample means and variances. Table 3 lists the standardised statistics used for specification of the power prior. The last two columns contain the clinical and methodological weights, computed from and proportional to the elicited weights for the four studies and summing up to 1.

Table 3. The sample size (n), the sample mean ($\bar{y}$) and standard deviation (s) after standardisation, the clinical weight (a_c) and the methodological weight (a_m) for the power prior specification.

Author	Outcome	Species	n_t	n_c	$\bar{y}_t$	$\bar{y}_c$	s_t	s_c	a_c	a_m
Higler (current)	stride length	horse	12	12	0.029	-0.029	0.980	1.062	1	1
Rozendaal	pain scores	human	111	111	0.070	-0.070	0.842	1.135	0.207	0.353
Sawitzke	joint space width	human	59	70	0.011	-0.009	1.037	0.975	0.241	0.353
Forsyth	stride length	horse	15	5	0.468	-1.405	0.599	0.450	0.379	0.176
Rindone	pain intensity	human	49	49	-0.018	0.018	1.092	0.910	0.173	0.118

The standardised group means show that the average change of the outcome variable was higher in the treatment than in the control group for the current trial as well as the first three historical studies listed in Table 3. Among the three historical studies, the study from Forsyth et al. (2006) showed the largest difference between the treatment group and the control group.

Posterior inference

Table 4. Posterior estimates based on the current trial combined with the uninformative prior, the clinically weighted power prior (PP) and the methodologically weighted power prior.

	posterior mean τ	posterior variance τ	95% credible interval
Current trial + uninformative prior	0.056	0.189	[-0.799, 0.911]
Current trial + PP based on a_c	0.146	0.032	[-0.207, 0.497]
Current trial + PP based on a_m	0.108	0.024	[-0.200, 0.418]

Proper convergence of the MCMC chains was observed for all chains, allowing assessment of the posterior estimates. Table 4 shows the posterior estimates of the standardised treatment effect conditional on (1) using an uninformative prior (no historical evidence included), (2) inclusion of historical evidence weighted by the equine specialist and (3) inclusion of historical evidence weighted by the methodologist.

All posterior results shown in Table 4 indicated no clinical treatment effect since the 95% credible intervals all contained 0. This supported the original conclusion from the current trial where no significant difference was found on stiffness in old horses between treatment and control group, after 3 months oral supplementation of GS & CS. However, the effect of the inclusion of historical evidence can be seen by looking at the posterior means and variances. The mean has shifted towards a larger value, revealing that when including historical studies with a positive treatment effect, the effect estimate will become larger. The posterior variance decreased as expected and represents more certainty about the estimates based on the inclusion of more information. The impact of including historical evidence can also be seen from Figure 1, where the power prior based on the clinical weights is plotted with the likelihood of the current data and the resulting posterior.

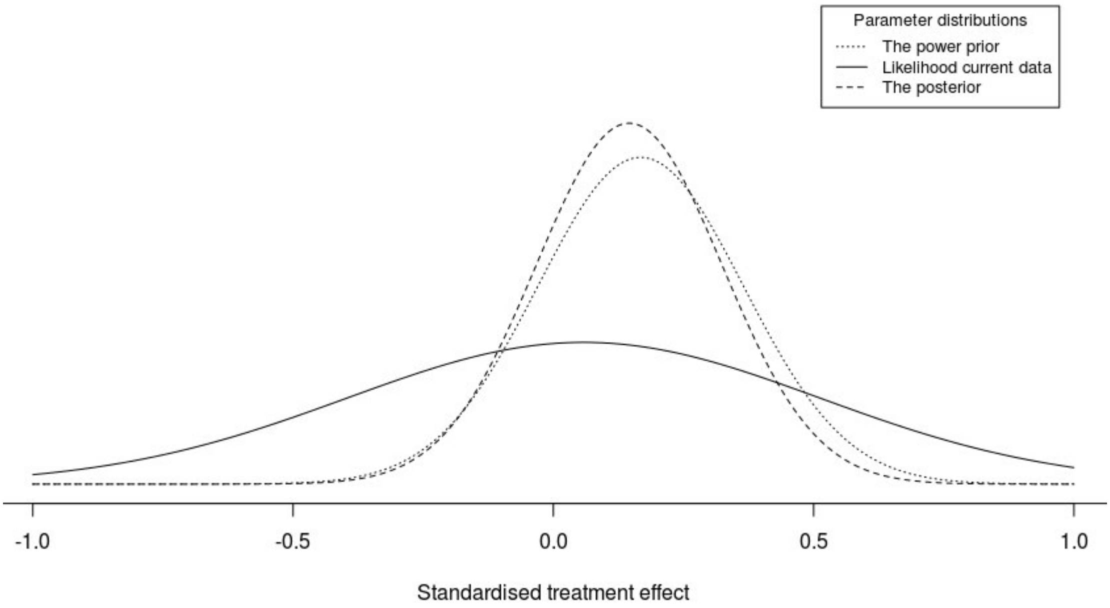


Fig. 1 The power prior based on the clinical weights, the likelihood of the current data and the resulting posterior.

DISCUSSION

In the present study, clinical trial data on treatment effect of oral supplementation of GS&CS on the stiffness in veteran horses (Higler et al., 2014) were analysed with the inclusion of relevant historical evidence in a Bayesian analysis. Results showed no evidence for clinical improvement regardless of the weighting of the historical studies by clinical relevance or methodological quality. It is important to note, however, that the goal of this paper was not the clinical research question, but the investigation of the power prior approach in a veterinary context.

For our proof of principle study, the historical studies were initially selected based on the references used by the current trial. We do not advocate this approach for future clinical applications; a systematic review should be the starting point instead. When studies from different animal species are included in the body of evidence, clinical expert(s) must be consulted to assess the similarity of the pathophysiology of the clinical question. Clinical expertise is also needed to decide which primary outcomes might be seen as equivalent to the current study. In our example, stride length, pain scores and joint space width were all standardised into a single outcome parameter.

Further, studies that report numerical statistics for both intervention groups will be favoured over studies with only, for example, graphical summaries. The reason is that the numerical values are required for the analytical computation of the power prior. In our analysis, three initially selected studies were omitted because sample means and variances were not reported. Also a meta-analysis was excluded in our application because, as the methodologist pointed out, it is hard to compare and weight the importance of a meta-analysis in a set of single studies. However, the incorporation of a meta-analysis into the power prior is worth further investigation, since meta-analyses are generally considered as containing the highest synthesised evidence and thus valuable sources of prior knowledge.

A crucial but difficult component of the power prior approach is the specification of the weight parameter. The weight, or power, of the power prior controls the impact of the historical evidence on the current data analysis and might have significant effect on the conclusions. There are a few aspects regarding the weight parameter that we would like to highlight.

The sample size of a historical study is included in the specification of the power prior through the likelihood function for the historical data. Therefore, the weight as specified by experts should not be based largely on the sample size. However, our elicitation instruction for experts was not clear about this restriction. It turned out that both experts used sample size as an argument when assigning the weights. While in theory it might be desirable to totally exclude sample size when assigning the weight, it is in reality rather difficult to disregard such information. Further investigation is needed to develop possible elicitation strategies, particularly because human studies might generally be larger than veterinary studies.

For two studies with equal weight, the largest sample size study will have a bigger effective sample size and hence more information in the power prior. Special attention may be required when large observational studies are included. Even with moderate or small weights, the effective sample size might be unreasonably large. A solution could be to pre-define a maximum value for the effective sample size, for instance, such that it never exceeds the sample size of the current trial.

In the present study, we adopted the standard conditional power prior approach. The current study was therefore not weighted, and automatically received the weight 1. However, the current study could also be methodologically suboptimal. In such circumstances, one might want to downweight the current study as well. Furthermore, we asked the experts to give a single weight for each historical study, while in fact historical information from the control group could differ in relevance from the treatment group. It might then be appealing to pool, for instance, more data from the control group than from the treatment group into the power prior. Investigation of the use of unequal weights for each intervention group may be worthwhile.

We carried out the statistical analysis independently based on two sets of weights, keeping the clinical relevance and methodological quality separate. Alternative elicitation methods might be explored, such as methods where consensus is met between experts (Rietbergen et al., 2014). Elicitation methods where experts express their uncertainty to each assigned weight are worth exploring as well.

We have applied the power prior method to a simple statistical model for the primary outcome, and used it retrospectively, i.e. the data of the current trial were collected before our application. Further studies might expand the use of this method to more complex models, and explore the prospective use of the power prior approach to design and power a veterinary RCT.

Finally, in our application, the incorporation of historical evidence was done on the basis of the standardised statistics from each historical study. The posterior estimates were therefore standardised as well. For clinical interpretation, it is however important to translate the standardised effect estimate back to the original outcome parameters of the current study to evaluate the treatment effect.

This case study showed that although further research is required, the Bayesian power prior offers a flexible approach to evidence synthesis because different study designs in different species can be utilised. The power prior can be considered an evidence-based prior based on available historical sources while taking the expert knowledge about quality and relevance of these sources into account. In veterinary medicine, due to the scarcity of clinical trials and the variety of species, the pragmatic use of pooling relevant evidence into the prior seems even more beneficial than it is for human medicine. Particularly the potential use of inter-species data could be promising for 'small species' therapies.

In conclusion, historical data provide a valuable source of evidence for the design as well as the analysis of a new study. This paper is a proof of principle study that illustrated the Bayesian power prior method in the veterinary context. Both historical data and expert knowledge were included in the power prior for the analysis of an equine RCT. Weighting the historical studies was the key part of the power prior approach and weight assignment needs further investigation, particularly related to cross-species information.

REFERENCES

Berry, S.M., Carlin, B.P., Lee, J.J. and Mueller, P. (2011). Bayesian Adaptive Methods for Clinical Trials. Chapman & Hall/CRC, Boca Raton, FL

Chen, M.H. and Ibrahim, J.G. (2006). The relationship between the power prior and hierarchical models. Bayesian Analysis 1, 551–574

Clayton, H.M., Almeida, P.E., Prades, M., Brown, J., Tessier, C. and Lanovaz, J.L. (2002). Double-Blind Study of the Effects of an Oral Supplement Intended to Support Joint Health in Horses with Tarsal Degenerative Joint Disease. Proceedings of the Annual Convention of the AAEP 48, 314-317

Cockcroft, P.D. and Holmes, M.A. (2003). Handbook of Evidence-Based Veterinary Medicine. Blackwell Publishing, Ltd, Oxford

Dudek, F.J. and Baker, K.E. (1956). The Constant-sum Method Applied to Scaling Subjective Dimensions. American Journal of Psychology 69, 616-624

Forsyth, R.K., Brigden, C.V. and Northrop, A.J. (2006). Double blind investigation of the effects of oral supplementation of combined glucosamine hydrochloride (GHCL) and chondroitin sulphate (CS) on stride characteristics of veteran horses. Equine vet. J. Suppl. 36, 622-625

Gelman, A., Carlin, J.B., Stern, H.S. and Rubin, D.B. (2008). Bayesian Data Analysis 2nd Edition, Chapman & Hall/CRC, New York

Greenhouse, J.B. and Wasserman, L. (1995). Robust Bayesian methods for monitoring clinical trials. Statistics in Medicine 14, 1379-1391

Higler, M.H., Brommer, H., L'Ami, J.J., De Grauw, J.C., Nielen, M., Van Weeren, P.R., Laverty, S., Barneveld, A. and Back, W. (2014). The effects of three-month oral supplementation with a nutraceutical and exercise on the locomotor pattern of aged horses. Equine Vet J. 46, 611-617

Hobbs, B.P., Carlin, B.P., and Sargent, D.J. (2012). Commensurate priors for incorporating historical information in clinical trials using general and generalized linear models. Bayesian Analysis 7, 1–36

Ibrahim J.G., and Chen, M.H. (2000). Power prior distributions for regression models. Statistical Science 15, 46–60

McCarthy, G., O'Donovan, J., Jones, B., McAllister, H., Seed, M. and Mooney, C. (2007). Randomised double blind, positive-controlled trial to assess the efficacy of glucosamine / chondroitin sulfate for the treatment of dogs with osteoarthritis. Vet. J. 174, 54-61

Neuenschwander, B., Branson, M. and Spiegelhalter, D.J. (2009). A note on the power prior. Statistics in Medicine 28, 3562-3566

Neuenschwander, B., Capkun-Niggli, G., Branson, M. and Spiegelhalter, D. (2010). Summarizing historical information on controls in clinical trials. Clinical Trials 7, 5–18

Rietbergen, C., Klugkist, I., Janssen, K.J.M., Moons, K.G.M. and Hoijtink, H.J.A. (2011). Incorporation of historical data in the analysis of randomized therapeutic trials. Contemporary Clinical Trials 32, 848-855

Rietbergen, C., Groenwold, R.H.H., Hoijtink, H.J.A., Moons, K.G.M., and Klugkist, I. (2014). Expert Elicitation of Study Weights for Bayesian Analysis and Meta-Analysis. Journal of Mixed Methods Research, published online before print

Rindone, J.P., Hiller, D., Collacott, E., Nordhaugen, N., and Arriola, G. (2000). Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. Western Journal of Medicine 172, 91-94

Rozendaal, R.M., Uitterlinden, E.J., van Osch, G.J., Garling, E.H., Willemsen, S.P., Ginai, A.Z., Verhaar, J.A., Weinans, H., Koes, B.W. and Bierma-Zeinstra, S.M. (2009). Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. Osteoarthritis Cartilage 17, 427-432

Sawitzke, A.D., Shi, H., Finco, M.F., Dunlop, D.D., Bingham, C.O. 3rd, Harris, C.L., Singer, N.G., Bradley, J.D., Silver, D., Jackson, C.G., Lane, N.E., Oddis, C.V., Wolfe, F., Lisse, J., Furst, D.E., Reda, D.J., Moskowitz, R.W., Williams, H.J. and Clegg, D.O. (2008). The Effect of Glucosamine and/or Chondroitin Sulfate on the Progression of Knee Osteoarthritis: A Report from the Glucosamine/Chondroitin Arthritis Intervention Trial. Arthritis Rheum. 58, 3183-3191

Spiegelhalter, D.J., Abram, K.R. and Myles, J.P. (2004). Bayesian approaches to clinical trials and health-care evaluation. John Wiley & Sons, Ltd, Chichester

Toft, N., Innocent, G., Gettinby, G. and Reid, S. (2007). Assessing the convergence of Markov Chain Monte Carlo methods: An example from evaluation of diagnostic tests in absence of a gold standard. Preventive Veterinary Medicine 79, 244-256

Wandel, S., Jüni, P., Tendal, B., Nüesch, E., Villiger, P.M., Welton, N.J., Reichenbach, S. and Trelle, S. (2010). Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 341, c4675

White, G.W., Stites, T., Jones, E.W., and Jordan, S. (2003). Efficacy of Intramuscular Chondroitin Sulfate and Compounded Acetyl-d-Glucosamine in a Positive Controlled Study of Equine Carpitis. Journal of Equine Veterinary Science 23, 295-300

SOCIO-CULTURAL ANALYSIS

APPLYING PARTICIPATORY APPROACHES IN THE EVALUATION OF SURVEILLANCE SYSTEMS: A PILOT STUDY ON SWINE FEVERS IN CORSICA

C. CALBA*, N. ANTOINE-MOUSSIAUX, F. CHARRIER, P. HENDRIKX, C. SAEGERMAN, M. PEYRE AND F.L. GOUTARD

SUMMARY

Regular and relevant evaluations of surveillance systems are critical to improve their performance and limit their costs. Due to the complexity of these systems, and to the context variability in which they are implemented, there is a need to develop flexible evaluation tools. In this frame, participatory tools were developed and implemented to assess the acceptability of the swine fevers surveillance system in Corsica (France). Individual interviews and focus groups were implemented with representatives at every level of the system. Diagraming and scoring tools were used to assess all the elements behind the acceptability definition. Results highlighted a medium acceptability of the system for farmers and hunters; and a good one for the other representatives (e.g. private veterinarian, local laboratory). The data collected using such an approach allowed provision of relevant recommendations based on the Corsican context that can be implemented to improve the current surveillance system.

INTRODUCTION

Even though the need for effective surveillance systems has long been recognised, in most countries investments are decreasing due to budget constraints, leading to an increase in international pressure to improve the efficiency of these systems (Drewe et al., 2012). Therefore, regular and relevant evaluations of these systems are critical to improve their performance and limit their costs (Shahab, 2009). According to the World Health Organisation (WHO), evaluation refers to ‘the systematic and objective assessment of the relevance, adequacy, progress, efficiency, effectiveness and impact of a course of actions, in relation to objectives and taking into account the resources and facilities that have been deployed’ (WHO, undated). Applied to surveillance, this includes the assessment of a series of evaluation attributes such as sensitivity, acceptability and timeliness, using qualitative, semi-quantitative or quantitative methods and tools (Drewe et al., 2012).

The complexity of surveillance systems, and the context variability in which they are implemented, entail the need for flexible evaluation tools, able to take into account every stakeholders’ opinions. This could be achieved by using flexible and adaptable methods based on participatory approaches within the evaluation process. Participatory approaches refer to a range of methods and tools that enable stakeholders, depending on their degree of participation in the process, to play an active role in the definition and in the analysis of the problems they may encounter, and in their solution (Johnson et al., 2004; Peyre et al., 2014;

---

* Clémentine Calba, Centre de Coopération International pour la Recherche Agronomique et le Développement (CIRAD), Campus International de Baillarguet, TA C 22/E, 34398 Montpellier Cedex 5, France. Email: clementine.calba@cirad.fr

Pretty, 1995; Pretty et al., 1995). By taking into consideration stakeholders' perception, needs and expectations, these approaches could lead to a better understanding of the system (Hoischen-Taubner et al., 2014).

Participatory tools were developed and applied during a pilot study designed to evaluate some of the attributes of the surveillance system of Classical Swine Fever (CSF) and African Swine Fever (ASF) in Corsica (France). This system is coordinated by the General Directorate of Food (DGAL) under the supervision of the French Ministry of Agriculture, Agribusiness and Forest (MAAF). Originally the system was designed to detect CSF, and indirectly ASF. However due to the increasing occurrence of ASF in Eastern Europe these last years (Costard et al., 2013; Sánchez-Vizcaíno et al., 2013; Torre et al., 2013), and its endemic situation in Northern Sardinia (European Commission, 2011; Mur et al., 2014), in conjunction with the increase risk of its introduction, spread and maintenance in Corsica, the current system mainly targets ASF (Desvaux et al., 2014). The objective of this surveillance system is to early detect both diseases using (i) post-mortem surveillance in slaughterhouses (active surveillance), and (ii) the mandatory notification of suspected cases by farmers and private veterinarians (passive surveillance).

In Corsica, pig breeding is mainly based on traditional forest-pastoral system (outdoor free-range breeding), which mobilises resources and involves transhumance summer practices (Casabianca et al., 1989). Also, there are a reduced number of rural private veterinarians in the island (personal communication). It is thus impossible to regularly assess the health of every animal, meaning that the system relies on stakeholders' willingness to report suspicions (Sawford, 2011). The decision to report a suspected event is a critical function of an emerging infectious disease surveillance system (Tsai et al., 2009). In order to limit the under-reporting of suspected cases and to identify the best ways to improve the current surveillance system, it is crucial to assess stakeholders' willingness to participate in this system (Bronner et al., 2014). The acceptability of the surveillance system reveals important perception factors and sociological aspects due to the fact that reporting an outbreak may be conflicting economic, cultural, and/or political incentives (Tsai et al., 2009; Valeeva and Backus, 2007). This evaluation attribute has been defined as the 'willingness of persons and organisations to participate in the surveillance system' (Drewe et al., 2012), and refers to the degree to which each of these users is involved in the surveillance (Hoinville et al., 2013). Even though it has been listed by the Centre for Diseases Control and prevention (CDC) as one of the most important factor for the quality of surveillance (German et al., 2001), having indirect impact on the quality of other evaluation attributes such as sensitivity or timeliness (Peyre et al., 2014), there are still issues related to the way to evaluate it (Auer et al., 2011).

These are the reasons why acceptability of the swine fevers surveillance in Corsica appeared to be a relevant case study for the implementation of participatory methods and tools in an evaluation frame.

MATERIALS AND METHODS

Targeted population

The objective of the field interviews was to meet representatives at every level of the surveillance system. Farmers and hunters, who are in the front line of the passive surveillance, represent level 1. Private veterinarians, the GDS animal health groupings

(*Groupements de Défense Sanitaire*, association of farmers addressing health issues, recognised in an official capacity under French law (Bronner et al., 2014)), local laboratories, or wildlife organisation (for example hunters' federations), that are contacted in case of suspicion on a farm, or in the wild animal population by farmers or hunters, represent level 2. Then the Veterinary Services, at local, regional, and national levels, to whom any suspicion has to be declared and who are in charge of implementing sanitary politics represent level 3.

Participants were selected according to their role in the surveillance system and to their availability, and were interviewed through focus groups or individual interviews. Focus groups are designed to expose a group of people to some common stimulus (Pahl-Wostl, 2002). They are particularly important to assess complex issues through the discussions and the social processes analyses (Pahl-Wostl, 2002). The objective was to implement focus groups with (i) ten farmers (two groups of five participants), (ii) five hunters (one group) for level 1; (iii) five private veterinarians (one group), and (iv) three GDS technicians (one group) for level 2. For other stakeholders, the objective was to implement individual interviews with one representative from each local laboratories (two in Corsica), and one representative of wildlife organisation for level 2; two representatives of Veterinary Services at local level, and one at regional level for level 3.

This work was implemented between April and June 2014. Interviews were conducted by a team of two to three evaluators: one was in charge of leading the discussion, and the other(s) one(s) in charge of observing participants' behaviour and taking notes. All of the interviews were recorded with the participants consent and were subsequently transcribed to text format.

Evaluation process

Acceptability is relevant to different aspects of surveillance system (Auer et al., 2011). It first refers to the acceptance by the actors of the system objective and to the way it is operating. The acceptance of the way the system is operating refers to (i) the role of each actor and the representation of its own utility, (ii) the consequences of the flow of information for each actor, (iii) the perception by each actor of its own role relative to other actors', and (iv) the relations between stakeholders. Another essential element of acceptability is the trust, devoted to the system as a whole but also devoted to each other stakeholders involved in it.

These elements were measured using a combination of participatory diagraming and scoring tools, which were developed and adapted to this specific context.

(1) Relational diagrams, developed to identify professional networks and interactions between stakeholders. Participants' status or organisation was placed in the middle of a flip chart. Then facilitators asked them to list the stakeholders they have interactions with, and to describe these interactions (i.e. frequency and reciprocity).

(2) Flow diagrams, developed to assess participants' knowledge about the flow of information following swine disease suspicion and to identify the different pathways where this information can circulate. The implementation of these diagrams started with a representation of stakeholders from level 1 (i.e. farmers or hunters), asking the participants how the information usually flows within the system. Once the diagram was considered completed by the participants, proportional piling (Catley and Admassu, 2003; Catley et al., 2012; Jost et al., 2007) was performed to quantify the level of trust they had in the system, and on the other stakeholders involved. Next facilitators asked the participants to divide 100

counters into two parts, one representing their confidence in the system and the other the non-confidence. The counters allocated to confidence were then used to specify confidence level with the actors and organisations represented on the diagram.

(3) Impact diagrams, to assess both positive and negative impacts of a specific event and to document the consequences as experienced directly and indirectly by project beneficiaries (Kariuki and Njuki, 2013). In this study, the specific event was an ASF suspicion in Corsica. Facilitators asked the participants to list and explain the positive and negative impacts of a suspicion in their own work, organisation and relations. Proportional piling was then implemented on the diagram by first dividing the 100 counters over positive and negative impacts according to their weights, and then by splitting the counters across the identified impacts to assess their probability of occurrence.

Data analysis

Each element of acceptability was assessed through the analysis of the diagrams and discussions as stated in Table 1. The acceptability of the surveillance system objective was assessed using the qualitative data collected during the elaboration of the impact diagrams (i.e. discussions). The acceptability of the operation of the system was done using all three diagrams (relation diagrams, flow diagrams, and impact diagrams) and using the qualitative data collected during their drawing. The trust allocated to the system as a whole, and to other stakeholders' was analysed on the basis of the proportional piling implemented on flow diagrams, and by analysing the qualitative data collected during its implementation.

RESULTS

Focus groups and individual interviews of representatives from each level of the swine fevers surveillance system in Corsica were implemented in the field. The analysis of diagrams, proportional piling and the data generated through the discussions during these interviews allowed to assess the acceptability's elements previously identified. Nonetheless, the 'perception by each actor of its own role relative to other actors' could not be assessed using the collected data, and thus it has been left out from the present analysis.

Interviews

A total of 16 actors were interviewed, of which 3 were women and 13 were men. Three focus groups were held: one with 3 farmers, one with 3 representatives from the GDS (including one woman), and another one with 2 representatives of the Veterinary Services at regional level (including one woman). Eight individual interviews were implemented: 2 farmers/hunters, 3 hunters, one private veterinarian, one representative from the local laboratory, and one representative of the Veterinary Services at local level (woman). Focus groups lasted between 2 and 3 hours; individual interviews an average 2 hours.

Acceptability of the objective of the surveillance system

The objective of the swine fevers surveillance system in Corsica was only known for level 1 by farmers (and farmers/hunters), which represented 5 out of the total 8 participants interviewed. All participants from levels 2 and 3 knew about the objective. Participants of all levels agreed on a need for early detection for these specific diseases. Nonetheless, they highlighted the fact that according to them post-mortem surveillance at slaughterhouses and passive surveillance would not be enough to reach the objective of early detection. Furthermore, they stated that once the disease is detected in pigs, it is already too late. Consequently, to avoid the introduction of the diseases, ports surveillance and awareness campaigns for tourists should be strengthened.

Table 1. Participatory methods and tools used to assess acceptability's elements

Acceptability's elements	Associated questions	Associated participatory methods and tools
Objective	Are stakeholders *satisfied* by the objective of the system?	Impact diagram
Operation	-	-
Role of each actor and representation of its own utility	Are stakeholders *satisfied* with their duty?	Flow diagram
Consequences of information flow	Are stakeholders *satisfied* with the consequences of information flow?	Impact diagram associated with proportional piling
Perception by each actor of its own role relative to other actors'	How do stakeholders perceive their own role in the system in comparison with other stakeholders' role?	Flow diagram
Relations between stakeholders	Are stakeholders *satisfied* with the relations they have with other stakeholders?	Relational diagram
Trust	Do stakeholders know about the system?	-
In the system	Do stakeholders trust the system to fulfil its surveillance objective(s)?	Flow diagram associated with proportional piling
In the other stakeholders involved in the system	Do stakeholders trust the other stakeholders to fulfil their role in the system?	Flow diagram associated with proportional piling

Acceptability of the operation of the surveillance system

Level 1: Most participants from the first level (6/8) were clear about their role in the system and they accepted it, including the reporting of any suspicion. Nonetheless, 2 hunters did not have a clear understanding of their role in the system: they were not aware of ASF threats and of what to do in case of suspicion.

Issues on the constraints linked to the reporting were highlighted and differed between farmers and hunters. The 3 hunters did not identify any consequences following a suspicion due to the fact that they never experienced an ASF epidemic. For all farmers, the consequences of a suspicion were not well accepted because of regulatory restrictions to be implemented on the farm (i.e. animals have to be penned), leading to an increase of feed costs. In addition, even if ASF is a non-zoonotic disease, consumer confidence in the product could be affected, causing damages on the entire sector. However, they anticipated that in case of suspicion in Corsica, farmers would come together to face the problem; which would perhaps enhance collective efforts and contribute in improving the organisation of the sector.

Participants were not satisfied with the relations they have with other stakeholders. All farmers felt isolated and 'completely abandoned' by animal health services (either by private veterinarians, GDS and Veterinary Services) (Fig. 1). Indeed, only 3 out of the 6 farmers interviewed acknowledged being regularly in contact with a private veterinarian, including one having a personal relationship with his private veterinarian. They commented more than once that 'relations with vet correspond to the minimum requirement'[1], and found it regrettable that '90% of the information are going through farmers'[1]. Most of the hunters (4 out the 5 interviewees, including 2 farmers/hunters) had a very poor network having relations only among hunters.

Level 2: Participants from level 2 were satisfied about their role, except for a few points. The private veterinarian highlighted the fact that in case of suspicion 'it is impossible to comply with safety standards imposed by emergency plans'[2]. The local laboratory stated that 'the perception of each other's roles in the system is not clear'[3]. GDS technicians told about the difficulties of being a moderator between Veterinary Services and farmers.

Regarding the consequences of the information flow, they highlighted that an ASF suspicion would cause an increase and disorganisation of their workload, leading to a decrease in the surveillance of other diseases, even if it could spur an increase of contacts and collaborations.

They were satisfied about the relations they have with other stakeholders. Nonetheless both the private veterinarian and the GDS technicians complained about the relations with the Veterinary Services at local level. Given that they are not always well given the needed information from the Veterinary Services. However they highlighted that it was mostly due to human constraints. Although they are aware about the potential important role of wildlife in the spread of the disease, they complained about the lack of collaboration between wildlife and animal health.

Level 3: Veterinary Services were satisfied about their role in the system and about the consequences of the flow of information. They stated that a suspicion 'could bring feedback, this would allow testing the system and to raise stakeholders' awareness'[4]; and could increase contacts and collaborations between organisations. As they represent the French State in the region, they stated the hypothesis that a crisis in Corsica would increase consideration from superior authorities in Paris, who would perhaps allocate them more resources. Nonetheless,

---

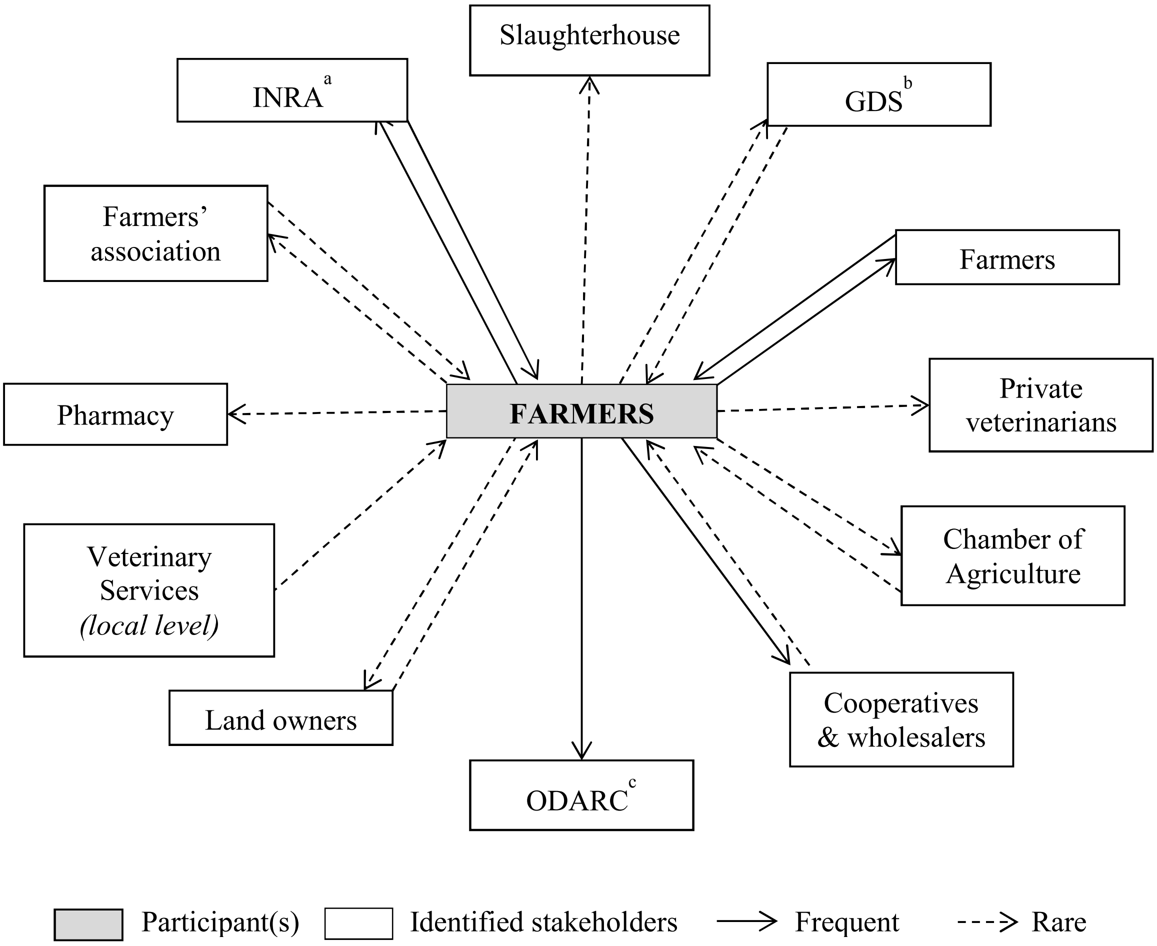
[1] Focus group with farmers, 28th May 2014

[2] Individual interview with a private veterinarian, 6th June 2014

[3] Individual interview with a local laboratory, 3th June 2014

[4] Individual interview with Veterinary Services at the local level, 12th June 2014

they stated that a suspicion would also cause an increase and disorganisation of their workload. They were satisfied about their relations with the other stakeholders involved in the system, even if there was some lack of direct contacts with level 1.



a. INRA: National Research Institute; b. GDS: Health Defense Group; c. ODARC: Office of Agricultural and Rural Development in Corsica

Fig. 1 Relational diagram resulting from a focus group implemented with three farmers

Trust devoted to the surveillance system and to other stakeholders

For level 1, the trust allocated to the system was low and ranged from 15% to 56%. One hunter stated that ‘they will listen in case of problem, but I am not sure there will be action’[5]. The two other hunters did not know about the organisation and the operation of the system, thus they could not draw the flow diagram. The other participants showed hesitation in drawing the surveillance system scheme. The time taken to do the exercise and the associated discussions showed that these actors did not know the system well outside their farm environment. Four farmers did not completely trust other farmers because ‘some of them will hide it, at least initially’[6]; and did not trust Veterinary Services at the local level because of

---

[5] Individual interview with a hunter, 4th June 2014

[6] Focus group with farmers, 28th May 2014

budget constraints, and at the national level because ‘for them Corsica is just a drop of water regarding the whole French territory’[6]. Two farmers/hunters did not completely trust hunters either because of their lack of awareness, and did not trust wildlife organisations because the relations between them are minimal.

For level 2, the trust devoted to the system as a whole was about 37%. All participants agreed that there were problems with the local laboratories due to budget and human constraints, and to the difficulties to send some samples to mainland France. GDS representatives stated that they did not trust all private veterinarians because ‘they are not interested in the pig sector’[7]; even the private veterinarian highlighted that most of them never saw clinical signs of the disease, and might thus miss a suspicious case. They agreed that ‘the critical point is the farmers’[7], because ‘they will call at the last moment *[in case of suspicion]*, they will even tend to hide it’[7].

For level 3, the trust devoted to the system as a whole was about 40%. Here again, local laboratories were identified as a critical point in the system, because of the same reasons stated by level 2. There was a lack of trust regarding farmers, especially due to the specificities of the dominant farming system (free-ranging). Indeed, farmers do not see their animals every day and can therefore take some time to notice that some animals are missing.

DISCUSSION

Acceptability of the swine fevers surveillance system in Corsica

Results from focus groups and individual interviews showed variations in the acceptability of the system between the different levels.

The acceptability was medium for level 1. Most of their relations were only shared with stakeholders of the same level. There were lacks of interactions with levels 2 and 3. Farmers felt isolated and abandoned by animal health services. This is due to the fact that GDS lacks human resources to be able to visit every farm during the year. Also, most of the private veterinarians in Corsica do not work with pigs. Their services are thus limited and expensive. Moreover farmers were afraid of ASF. They were aware of the presence of the disease in Sardinia, and the complexity of dealing with this sort of infectious disease without any preventive means. They felt helpless regarding the protection of their animals, even if they provide or receive the information related to a suspicion. Hunters did not know about the surveillance system and about the disease. Even though Veterinary Services implemented awareness campaigns in early 2014, in collaboration with hunters’ federations, their knowledge regarding their role in the system as well as the importance of wildlife in diseases transmission was limited. This limited knowledge might result from limitation in the campaign or because the hunters involved in this pilot study did not take part in the campaigns. Only one hunter spoke about these campaigns, explaining that they raised more fear about the disease instead of giving knowledge and recommendations on the behaviour to adopt in case of disease suspicion. This hunter had more relations with hunters’ federation then the other interviewees, highlighting the needs to strengthen the interactions between hunters and wildlife organisations.

---

[7] Focus group with GDS representatives, 23th May 2014

The acceptability was good for levels 2 and 3. The main problem identified was related to the limited trust given to the system, and more specifically to the low trust given to level 1 and to local laboratories. This correlate with the finding that farmers felt isolated and left alone by animal health services who rely on them to report these diseases.

All participants knew about the early detection objective of the surveillance system and were satisfied with it. Nevertheless, they all agreed that the ways of achieving that aim were not consistent with the objective in mind. Stakeholders expect the Veterinary Services at national level to develop surveillance at ports and to implement awareness campaigns, especially for tourists coming from Sardinia.

Feedback on the method

The visualisation tools helped the stakeholders to discuss their perception of the surveillance system. They allowed collection of more information related to the context in which surveillance is implemented, and related to the environment in which stakeholders operate. Limitations of the current system were highlighted thanks to the involvement of representative from all levels. Also, several solutions for its improvement emerged during the discussions. In order for these solutions to be acceptable for all the levels it would be necessary to organise a feedback meeting gathering all participants involved.

Only few participants were involved in this study, and thus some points of view may be missing. Nonetheless, qualitative approaches rely on ‘purposive sampling’ to maximise the diversity of the data collected (i.e. perceptions and point of views) (Bronner et al., 2014). The quality of the sample is thus considered as more important than the sample size in such approaches (Côte and Turgeon, 2002). Participants were selected in order to reach this diversity, and to reach the theoretical saturation of the data (Côte and Turgeon, 2002). Indeed, saturation has become the gold standard for health science research (Guest et al., 2006). It refers to the point at which no new information is observed in the data (Guest et al., 2006). This standard for qualitative research has not been reach during this pilot study because of time constraints, and due to the lack of availability of some stakeholders. Some stakeholders, especially private veterinarians, did not have time to joining these meetings. Moreover, participants from all levels were selected according to their availability, but also to their willingness to be part of the study. This means that mostly people with an interest related to animal health were involved. As this was a pilot study, biases on the way to formulate the questions and to guide stakeholders may have also occurred.

CONCLUSION

Although acceptability represents an important concern in the evaluation process, limitations exists regarding how this attribute should be considered and evaluated (Auer et al., 2011). The participatory approaches developed in this study allowed to assess all the elements behind the acceptability definition. Indeed this study confirmed previous work which showed that participatory methods and tools play an important role in helping researchers and decision makers to reconnect with farmers, and to gain a better understanding of diseases from a local perspective (Catley et al., 2012). Since the information from all levels is critical for effective disease surveillance (Tsai et al., 2009), the data collected using such an approach allowed to provide relevant recommendations based on the Corsican context that can be implemented to improve the current surveillance system.

ACKNOWLEDGEMENTS

This work was performed under the framework of RISKSUR project funded by the European Union Seventh Framework Programme (FP7 / 2007-2013) under grant agreement n°310806. We thank Dr Casabianca (LRDE research unit Director, INRA Corte), Oscar Maestrini (INRA Corte), and all participants for their implication in this work. We are grateful to Juana Bianchini for reviewing the English.

REFERENCES

Auer, A.M., Dobmeier, T.M., Haglund, B.J. and Tillgren, P. (2011). The relevance of WHO injury surveillance guidelines for evaluation: learning from the Aboriginal Community-Centered Injury Surveillance System (ACCISS) and two institution-based systems. BMC Public Health 11, 744

Bronner, A., Hénaux, V., Fortané, N., Hendrikx, P. and Calavas, D. (2014). Why do farmers and veterinarians not report all bovine abortions, as requested by the clinical brucellosis surveillance system in France? BMC Vet. Res. 10, 93

Casabianca, F., Picard, P., Sapin, J., Gauthier, J. and Vallée, M., (1989). Contribution à l'épidémiologie des maladies virales en élevage porcin extensif. Application à la lutte contre le maladie d'Aujeszky en Région Corse. Journées Recherches Porcines En France 21, 153-160

Catley, A. and Admassu, B. (2003). Using participatory epidemiology to assess the impact of livestock diseases. In FAO-OIE-AU/IBAR-IAEA Consultative Group Meeting on Contagious Bovine Pleuropneumonia in Africa (Rome, Italy)

Catley, A., Alders, R.G. and Wood, J.L. (2012). Participatory epidemiology: approaches, methods, experiences. Vet. J. 191, 151-160

Costard, S., Mur, L., Lubroth, J., Sanchez-Vizcaino, J. and Pfeiffer, D. (2013). Epidemiology of African swine fever virus. Virus Res. 173, 191-197

Côte, L. and Turgeon, J. (2002). Comment lire de façon critique les articles de recherche qualitative en médecine. Pédagogie médicale 3, 81-90

Desvaux, S. Le Potier, M.F., Bourry, O., Hutet, E., Rose, N., Anjoubault, G., Havet, P., Clément, T. and Marcé, C. (2014). Peste porcine africaine: étude sérologique dans les abattoirs en Corse durant l'hiver 2014. Bulletin Epidemiologique 63, 19

Drewe, J., Hoinville, L., Cook, A., Floyd, T. and Stärk, K. (2012). Evaluation of animal and public health surveillance systems: a systematic review. Epidemiol. Infect. 140, 575-590

European Commission (2011). Commission Implementing Decision of 15 December 2011 amending Decision 2005/363/ EC concerning animal health protection measures against African swine fever in Sardinia (Italy)

German, R.R., Lee, L., Horan, J., Milstein, R., Pertowski, C. and Waller, M. (2001). Updated guidelines for evaluating public health surveillance systems. In MMWR Recommendations and Reports (Center for Disease Control and Prevention (CDC)), 1-35

Guest, G., Bunce, A. and Johnson, L. (2006). How many interviews are enough? An experiment with data saturation and variability. Field methods 18, 59-82

Hoinville, L., Alban, L., Drewe, J., Gibbens, J., Gustafson, L., Häsler, B., Saegerman, C., Salman, M. and Stärk, K. (2013). Proposed terms and concepts for describing and evaluating animal-health surveillance systems. Prev. Vet. Med. 112, 1-12

Hoischen-Taubner, S., Bielecke, A. and Sundrum, A. (2014). Different perspectives on animal health and implications for communication between stakeholders. In: The 11th European IFSA Symposium, Berlin

Johnson, N., Lilja, N., Ashby, J.A. and Garcia, J.A. (2004). The practice of participatory research and gender analysis in natural resource management. In: Natural Resources Forum, 189-200

Jost, C., Mariner, J., Roeder, P., Sawitri, E. and Macgregor-Skinner, G. (2007). Participatory epidemiology in disease surveillance and research. Rev. Off. Int. Epizoot. 26, 537-549

Kariuki, J. and Njuki, J. (2013). Using participatory impact diagrams to evaluate a community development project in Kenya. Dev Pract 23, 90-106

Mur, L., Atzeni, M., Martínez-López, B., Feliziani, F., Rolesu, S. and Sanchez-Vizcaino, J. (2014). Thirty-Five-Year Presence of African Swine Fever in Sardinia: History, Evolution and Risk Factors for Disease Maintenance. Transbound Emerg Dis, 1-13

Pahl-Wostl, C. (2002). Participative and stakeholder-based policy design, evaluation and modeling processes. Integrated assessment 3, 3-14

Peyre, M., Hoinville, L., Haesler, B., Lindberg, A., Bisdorff, B., Dorea, F., Wahlström, H., Frössling, J., Calba, C., Grosbois, V. and Goutard, F. (2014). Network analysis of surveillance system evaluation attributes: a way towards improvement of the evaluation process. In International Conference on Animal Health Surveillance (ICAHS) (La havane, Cuba)

Pretty, J.N. (1995). Participatory learning for sustainable agriculture. World development 23, 1247-1263

Pretty, J.N., Guijt, I., Thompson, J. and Scoones, I. (1995). Participatory learning and action: A trainer's guide. London: IIED, 270 p

Sánchez-Vizcaíno, J.M., Mur, L. and Martínez-López, B. (2013). African swine fever (ASF): Five years around Europe. Vet. Microbiol. 165, 45-50

Sawford, K.E. (2011). Animal health surveillance for early detection of emerging infectious disease risks. University of Calgary, Calgary, Alberta

Shahab, S. (2009). Finding value in the evaluation of public health syndromic surveillance systems from a policy perspective. K. u. Search Canada, Alberta Health Services, 24 p

Torre, A.D.L., Bosch, J., Iglesias, I., Muñoz, M., Mur, L., Martínez-López, B., Martínez, M. and Sánchez-Vizcaíno, J. (2013). Assessing the Risk of African Swine Fever Introduction into the European Union by Wild Boar. Transbound Emerg Dis, 1-8

Tsai, P., Scott, K.A., Pappaioanou, M., Gonzalez, M.C. and Keusch, G.T. (2009). Sustaining global surveillance and response to emerging zoonotic diseases. National Academies Press, Washington, 338 p

Valeeva, N. and Backus, G. (2007). Incentive Systems under ex post Moral Hazard to Control Outbreaks of Classical Swine Fever in the Netherlands. In: American Agricultural Economics Association, Portland, USA, 18 p

World Health Organisation (WHO). Health systems strengthening – Glossary (http://www.who.int/healthsystems/hss_glossary/en/index4.html). Accessed 15 December 2014

PREVENTIVE SERVICES OFFERED BY VETERINARIANS ON SHEEP FARMS IN THE UK: OPINIONS AND DRIVERS OF PROACTIVENESS

C. BELLET*, J. WOODNUTT, L.E. GREEN AND J. KALER

SUMMARY

Recent independent UK government reports and studies highlighted the importance, but lack of, flock health preventive services provided by veterinarians on sheep farms. To better understand veterinarians' opinions and drivers for their current practices, qualitative interviews were used to construct belief statements. A postal questionnaire was designed with these belief statements, demographic information and questions on veterinarians' current services and sent to 515 sheep practices registered with the RCVS in England and Wales in 2012. Qualitative data was analysed by thematic analysis, and exploratory factor analysis with heuristic approaches was conducted on the respondents' belief statements to identify common factors of veterinarian beliefs. Veterinarians' belief statements reduced to three main factors: their motivation for proactiveness, their perceived capability of offering preventive services and their perceived opportunity to deliver these services. These factors significantly influenced the time veterinarians spent in an advisory role with increasing time with each factor.

INTRODUCTION

Along with market competitiveness, the evolution of EU agricultural subsidy schemes and the overall public health pressures, the expectations and needs of producers with regards to animal health and welfare have evolved (AHDB, 2013). The demand towards health advisors has shift not only to disease prevention, rather than treatment, but also towards nutrition, genetic selection and productivity, integrating divergent interests. Veterinarians are as a consequence requested to implement innovative animal health and welfare monitoring programs along with action plans, not only considering disease epidemiology, specific farm business' economy and public health, but also farmers' individuality, perceptions and decision-making (LeBlanc et al., 2006; Lowe, 2009).

Since 2004, the Department for Environment Food and Rural Affairs (DEFRA) has been developing strategies, such as the Farm Health Planning Initiative, to improve animal health and welfare within the UK. Although one of the main aspects of those preventive strategies is the development of close partnership between farmers and veterinarians to facilitate and improve the implementation of good preventive practices on farms (DEFRA, 2004; Osmond, 2009), there is, to date, no evidence of coverage and sustainability of proactive management on sheep farms in the UK. Quite the reverse, recent surveys showed that sheep farms were the most predominant farm businesses not receiving any veterinarians' visits to discuss or implement flock health plans, with only 20% of sheep farmers declaring having all-year-

---

* Camille Bellet, The School of Veterinary Medicine and Science, The University of Nottingham, Sutton Bonington Campus, Sutton Bonington, Leicestershire, LE12 5RD, UK. Email : camille.bellet@nottingham.ac.uk

round contact with their veterinarians and 67% contacting them exclusively for emergencies (ADAS, 2008; DEFRA, 2013).

A recent study of English sheep farmers (Kaler & Green, 2013) suggested that although farmers believed their veterinarians to be the most useful source of new information (i.e. an unrecognised disease) they also considered inconsistent service, lack of expertise of sheep farming, high turnover and concern about independence of advice as key barriers to using veterinarians proactively. There is, to date, no information on veterinarians' beliefs about the services that they offer to their sheep clients. Because the perception of both farmers and veterinarians is crucial to guarantee an efficient and proactive relationship and fulfil both parties' objectives in the improvement of sheep health and welfare, there is a need to better understand the views of veterinarians on the services they offer to sheep farmers.

There are numerous psychosocial theories that have been developed in human health to explain the behavioural process and change various health behaviours (Sutton, 2001; Michie et al., 2014) and there is considerable overlap between the theories. The use of these theories to understand behaviour is relatively new in veterinary science and most of studies to date have focused on farmer behaviour (Ellis-Iversen et al., 2010; Garforth et al., 2013). To understand behaviour and to develop a behavioural intervention, the most crucial step is to not to limit oneself to a single theory but to identify which constructs are most relevant to the behaviour concerned in a particular population and environment (Michie et al., 2014).

The aim of the current study was to use psychosocial approaches to better understand UK veterinarians' opinions of, and drivers for, an advisory role on sheep farms in order to propose new behaviour change interventions that might increase and promote flock health preventive management on sheep farms in the UK.

MATERIALS AND METHODS

In order to investigate veterinarians' perceptions of and drivers for the advisory role they play on sheep farms, three analyses were conducted. First, a qualitative analysis of 12 UK veterinarians' interviews was conducted to identify their main beliefs and barriers for having a proactive advisory role on sheep farms. Second, based on these results, belief statements were formed. These statements were included in a postal questionnaire, sent to a wider sample of 515 UK veterinarians, and an exploratory factor analysis was conducted to explore underlying psychological constructs/factors of veterinarians' beliefs. Third, beta regression modelling was undertaken to examine the influences of each of the resulting factors on the time veterinarians spent offering preventive services to their sheep clients. This proceedings paper focuses on the qualitative and exploratory factor analyses.

Study esign

Interviews: In the first part of the study 12 face-to-face semi-structured interviews with sheep veterinarians (selected using a snowballing technique) were conducted by JK. The discussion guide covered areas around: current contact with sheep farmers, services offered and views on how these were received and perception of the veterinarian's expertise. The interview schedule was pilot tested on 2 veterinarians. Interviews lasted for 60 to 90 minutes, were audio-recorded and transcribed.

Postal questionnaires: A list of RCVS-registered practices was used to choose the sample. From the 4642 practices on the list, any that did not register treating sheep were discarded. Practices registered as ‘branch practices’ or ‘supporting practices’ were also discarded to avoid contacting the same veterinarian twice, and those with an address in any region not in England and Wales were also discarded. This resulted in 515 veterinary practices selected for the postal questionnaire.

Based on themes identified by veterinarians during the interviews thirty belief statements related to veterinarians preventive services were formed. The belief statement scores were collected using a five-point Likert-based scale with descriptors from 1 to 5: ‘strongly agree’, ‘agree’, ‘neither agree nor disagree’, ‘disagree’, ‘strongly disagree’. Veterinarians were asked to provide the proportion of their current time they spent in an advisory role along with general demographic data and practice characteristics. The questionnaire was pilot tested and sent by post with a cover letter and a prepaid envelope; postal reminders including a copy of the questionnaire were sent within twelve working days of no response from the practice and an additional two weeks period was given for the respondents to reply.

Qualitative analysis

Thematic analysis (Braun and Clarke, 2006) was used relying on the constant comparative method (Maykut and Morehouse, 1994) to examine the perceptions of veterinarians on the advisory role they play for their sheep clients. A first step consisted of reading and re-reading transcripts in order to familiarise the analyst with the content. Interesting features of the data were then systematically generated using general non-overlapping codes across the dataset. Further sub-themes were generated after reviewing the codes. Comparisons within and between categories in relation with the research questions were done and main veterinarians behavioural beliefs were identified. The qualitative analysis was managed using NVivo 9.0 (QSR International) software.

Quantitative analysis

Data from the questionnaire were coded, checked and entered into a database (Microsoft Access, 2010). The data were analysed using STATA 12.1 (STATA Inc., Texas, USA). A first stage descriptive analysis was conducted to summarise the data. An exploratory factor analysis was then performed using the belief statement variables, in order to explore which of the veterinarians’ belief statement loaded together and then to understand their relationship to the identified core dimension. Statement variables were standardised prior to the analysis and the appropriateness of its resulting correlation matrix was checked. Kaiser-Mayer-Olkin (KMO) test of sampling adequacy was conducted for both the entire correlation matrix and each variable individually (weighted value > 0.5). Bartlett test of Sphericity (weighted p value for $\chi 2 < 0.05$), indicating the strength of association among variables was conducted (Ferguson and Cox, 1993). In order to avoid any violation of distributional assumptions, the estimation of factor loadings was made with the iterated principal factor method. Both the scree test and parallel analysis using eigenvalues from the reduced correlation matrix were used to determine the number of factors. An oblique factor rotation (promax) was performed, to allow correlation between factors (Fabrigar et al., 1999; Costello and Osborne, 2005). Factor loadings greater than ± 0.3 were considered and statement variables with low reliability (i.e. high uniqueness) were discarded from the analysis (Fabrigar et al., 1999). Complex variables (i.e. loading on two or more factors) were avoided, either excluding the item from the analysis or, in the case of large discrepancy (>0.2), considering the highest loading variable (Ferguson and Cox, 1993). A minimum criteria of four items per factor was retained (Fabrigar et al., 1999). Finally, for model diagnostics, the resulting sets of items per factor were examined for internal consistency, using both Cronbach's alpha and inter-item covariance (Cronbach, 1951; Tavakol and Dennick, 2011).

RESULTS

Qualitative analysis

Only some key themes from qualitative analysis are presented here.

Reactive services: Veterinarians perceived a problem with the contact they currently had with farmers. The veterinarians used phrases such as "a 'fire-brigade' service" and "only after several sheep have died", showing an awareness of the nature of the contact. Most veterinarians had negative emotions towards this type of contact, indicating that they were not happy with their current situation, for example declaring:

"I think as a practice we find that we've got a lot of sheep on our books but we very rarely see them. I think you'd probably find that around a lot of the country, I don't think we're unique in that but it's something that's been niggling at myself and one of the other vets a bit recently that we've not got enough contact with our sheep farmers"

Knowledge and expertise: The beliefs by veterinarians on knowledge and expertise were expressed in two ways: a) there was a general feeling among the veterinarians about their own lack of sheep expertise that hindered them to have a more proactive role; and, b) veterinarians believed that sheep farmers did not trust in the veterinarians knowledge and expertise on areas related to sheep farming.

The two quotes below are given as for examples:

"I think we've not necessarily enough knowledge to really supply the farmer with something that he really thinks 'wow that was really useful, I didn't know that'."

"I think they (sheep farmers) probably think that generally we've got the same knowledge level as they've got <chuckles> or slightly more or slightly skewed towards the medicine side but I don't know that most of them aren't aware of what else we can offer them."

Sheep farmers: There were general feelings among veterinarians that their sheep clients are just not prepared to pay for the services. For example this quote below highlights this:

"We do have trouble getting the farmers to pay for education. So they will pay for you to go and see a sick ewe but they don't want to pay you to educate them to prevent them getting a sick ewe, do you see what I mean?"

Most of those interviewed were ready to assume that farmers would not want to pay without really asking them. This was identified by one vet as being a problem, as shown in the following quote:

"I think the reason it's hard is, and I'm myself really to blame here, is assuming farmers won't pay for it and that's exactly the same as trying to charge them for coming to meetings, is we assume that farmers, you know for so long they've got it for free or … yeah so it's possibly a lack of self-confidence and lack of trying."

Quantitative analysis

A total of 162 out of 515 questionnaires were received, representing a response rate of 31%. Fifteen questionnaires were returned empty or with apologies for not having been completed due to the practice no longer treating sheep, resulting in 147 questionnaires included in the analysis.

Demographic characteristics of the respondents: The majority of the veterinarians had at least five (76%) years of professional experience with 60% having ten or more years of experience. The majority of vets graduated from UK universities; the Royal Veterinary College (24%), Liverpool (18%), Bristol (16%), Edinburgh (14%) and Glasgow (10%). A further 10% of the veterinarians graduated from abroad.

Current veterinarians sheep services: The median number of sheep clients the veterinarians had in their practice was 53 (IQR 20-130). A total of 78% (114/147) of the veterinarians reported spending time in an advisory role with their sheep clients with a median of 20% of their work time spent on it (IQR 5-50). Ninety-six per cent of the veterinarians reported providing services to their clients by phone, of which only 4% were prepared to ask their clients to pay a fee for advice offered by telephone. Approximately 40% of the veterinarians reported attending Continual Professional Development (CPD) courses covering sheep-related topics in 2012.

Belief statement scoring and Exploratory Factor Analysis (EFA): Of the 147 veterinarians who answered the questionnaire, 26 had ten sheep clients or fewer and were removed from the exploratory factor analysis. The suitability of the belief statements for factor analysis was also assessed, based on: (1) the overall Kaiser-Meyer-Oklin value, which was meritorious (KMO=0.81), with no items having an individual sampling adequacy of less than 0.5, and (2) the Bartlett's Test of Sphericity, which was statistically significant $\chi 2 = 644.3$ (df = 153, $p < 0.001$), supporting the factorability of the resulting items correlation matrix (Kaiser, 1974; Ferguson and Cox, 1993).

The initial Iterated Principal Factor Analysis (IPFA) on the belief statements after inspection of scree plot, parallel analysis, considering factor loadings revealed the three factor solution with eigenvalues exceeding 1.0 (5.02, 1.64, 1.30). This three factor solutions accounted for 65.1% of the total variance of the veterinarians' belief statements'. The factors were: 'motivation' (with 10 items), 'capability' (with 4 items) and 'opportunity' (4 items). The factor loadings for three-factor solution, items for the factors along with measures of internal consistency and mean scores of the given items are presented in Table 1. There were positive correlations between factors: r=0.4 between factor 1 and 2; r=0.3 between factor 2 and 3 and r=0.2 between factor 1 and 3. All factors presented a good internal consistency taking into account both its number of items and the inter-item covariance measure (Cronbach, 1951; Tavakol and Dennick, 2011).

Within factor 1 'motivation', about 19-24% of the veterinarians either "agreed" or "strongly agreed" that their sheep clients were aware or prepared to pay for their services or that veterinarians themselves had enough marketing skills to promote their services. Veterinarians also believed that they were not the primary source of advice to their sheep clients with only 24% either "agreeing" or "strongly agreeing" to this. The majority of veterinarians "agreed" or "strongly agreed" (65-75%) that they provided a good service to their sheep clients and that their boss/colleagues and sheep clients were happy with the

Table 1. Exploratory factor analysis of UK veterinarians’ belief statements regarding their advisory role on sheep farms (Only loadings > 0.30 are displayed)

		Exploratory Factor Analysis		
Items	Scores Mean ± SD	Factor 1 “Motivation”	Factor 2 “Capability”	Factor 3 “Opportunity”
I think I provide good services to my clients	2.18 ± 0.77	0.608		
I see my clients often enough	4.10 ± 0.94	0.642		
I think I offer sufficient preventive advices	2.69 ± 0.89	0.517		
I think I am my clients’ primary source of advice	3.17 ± 0.99	0.557		
My boss/colleagues are happy with my services	1.97 ± 0.72	0.667		
My clients are happy with my services	2.18 ± 0.74	0.635		
My clients wish to use the services I could offer	2.40 ± 0.86	0.442		
My clients are prepared to pay my services	3.26 ± 1.09	0.429		
My clients are aware about services I could offer	2.77 ± 1.00	0.425		
I have enough marketing skills to encourage it	3.12 ± 0.93	0.411		
I believe I know enough my clients’ needs	2.48 ± 1.16		0.534	
My clients are interested about additional services	2.66 ± 1.08		0.495	
I have enough sheep health expertise to provide it	2.14 ± 0.93		0.578	
I know enough about non-vet sheep enterprise	2.60 ± 1.12		0.700	
These services could provide additional incomes	2.05 ± 1.02			0.385
What my boss/colleague think is important	2.40 ± 1.09			0.387
What my clients think is important	1.40 ± 0.56			0.494
I would prefer external consultants providing it	4.54 ± 0.76			-0.671
Cronbach’s alpha		0.82	0.70	0.60
Average Inter-item covariance		0.30	0.40	0.20

services they offered but disagreed (81%) that they were seeing their sheep clients often enough.

In factor 2 ‘capability’, approximately 70% veterinarians “agreed” or “strongly agreed” having sheep health expertise and about 46-50% believed in knowing enough about their clients’ needs, having knowledge about non-veterinary sheep enterprise issues and that their clients were interested in the additional services they could offer.

Within factor 3 ‘opportunity’, the majority of the veterinarians “agreed’ or “strongly agreed” that what their sheep clients (97%) or boss/colleagues (58%) think was important to them and that proactive services could provide additional income to the practice (74%). There was a general disagreement (92% either “disagreeing” or “strongly disagreeing”) between veterinarians that they would prefer external consultants to provide these services to the sheep clients.

DISCUSSION

To authors’ knowledge, this is the first paper exploring veterinarians’ behavioural process and beliefs towards a proactive role on sheep farms. Exploratory factor analysis in the current study generated three factors underpinning the measured veterinarians’ beliefs. These factors gave a strong description of the underlying data, with good internal consistency of the factors. Given these factors mapped perfectly to the three behaviour components, proposed by the COM-B system (‘Motivation’ ‘Capability’, and ‘Opportunity’; Michie et al., 2011), that influence a behaviour, it confirms the usefulness of the data inductive approach used in the current study. These factors are discussed below in context of this framework.

The first factor included items related to ‘motivation’ of veterinarians. Motivation includes automatic and reflective brain processes that lead to one’s engagement with the behaviour (Michie et al., 2011). Items included in factor 1 demonstrated both the automatic (e.g. ‘my clients/boss or colleagues are happy with my services’) and reflective motivation (e.g. ‘I think I am my clients’ primary source of advice or my clients are prepared to pay for services’) among veterinarians. It was interesting that this factor included items corresponding to reflective evaluation by veterinarians of their own actions (e.g. ‘I see my sheep clients enough’) and also their sheep clients (e.g. ‘my sheep are prepared to pay the services I could offer’) suggesting associations between these two set of motivations. This was confirmed by the fact that most veterinarians generally did not believe they had enough marketing skills or were seeing their sheep clients enough, and that their clients wish to use their services or were aware/ prepared to pay for the services. These results confirm the veterinarians’ views expressed in the qualitative interviews in the current study and sheep farmers’ opinions of their veterinarians in study by Kaler and Green (2013). This suggests that changing veterinarians’ reflective motivation on how they believe sheep clients perceive their services would possibly influence their motivation towards their own actions. Despite the fact most veterinarians believed they did not see their sheep clients enough, they believed they were providing good services and their sheep clients were happy with their services. This is an example of cognitive bias (Burke, 2006) where there is disparity between associated beliefs. Motivations have been often linked to behaviour and various studies have demonstrated that farmers’ motivations (e.g. their perceptions of control of mastitis; Jansen et al., 2009) and outcome perception of having biosecurity measures on farm (Gunn et al., 2008) are linked to their behaviour (i.e. effective mastitis control and action to improve biosecurity respectively).

Items in factor 2 demonstrated veterinarians' awareness of their 'capability' to engage in the advisory role. Capability has been defined as a person's physical skill/strength or psychological knowledge to engage in the behaviour (Michie et al., 2011). The items in this factor demonstrated measures related to psychological capability, for example knowing enough about client needs, having enough overall sheep expertise or knowledge about non-veterinary sheep enterprise. The veterinarians' lack of knowledge of sheep enterprise was highlighted both by sheep farmers (Kaler and Green, 2013) and by veterinarians in the current qualitative analysis as the key barrier for farmers to use veterinarians proactively. The findings from the quantitative study suggest that only half of the veterinarians agreed knowing about non-veterinary sheep enterprise issues or their sheep clients' needs. However, given 80% of the veterinarians declared not seeing their sheep clients enough it is hard to see how this psychological capability of veterinarians engaging in proactive role could be developed without finding more novel ways of building the effective communication between sheep farmers and veterinarians.

The third factor included items related to opportunity. Opportunity relates to factors either physical (time, resources, environment or 'affordance') or social (interpersonal influences, social norms) that lie outside the control of an individual, which facilitates or prompt the behaviour (Michie et al., 2011). This factor in the current study included both physical opportunity (for example in terms of source of additional income and external consultants as competitors) and social opportunity (importance of what boss/colleagues or sheep clients opinions). Sheep farmers have highlighted that there is lack of availability of routine flock health plans or models demonstrating benefits to them and veterinarians should be instigators of this (Kaler and Green, 2013). The results from the current study suggest that most veterinarians are aware of having to make the opportunity as it could provide them additional income and they would not prefer external consultants to provide the services. Since majority of veterinarians also viewed their boss/colleagues and sheep clients' views important, the support from them could prove beneficial towards promoting these opportunities.

Behaviours are complex and often involve interplay of various factors. Motivations, capabilities and opportunities are correlated and influenced by behaviour itself (Michie et al., 2011). Results from the current study also indicate this as these three factors were correlated and significantly (results not shown) influenced the veterinarians' current behaviour (i.e. the percentage time they spent in an advisory role).

Although it is acknowledged that the Exploratory Factor Analysis used in the current study was driven by the set of items included and that additional factors not identified may exist, the factor model proposed in the current study provided: a) better understanding to consolidate beliefs among veterinarians on their advisory role on sheep farms; b) identified how those beliefs were correlated; and, c) helped to generate hypotheses about underlying processes of behaviour change.

ACKNOWLEDGEMENTS

The work was funded by BBSRC-IIP award and as a part of a student project at SVMS, University of Nottingham. We would like to especially thank all the veterinarians who agreed to participate in this study.

REFERENCES

ADAS (2008). Flock Health Planning in the West Middlands. A report for DEFRA FFG

AHDB (2013). The Impact of CAP Reform on Direct Payments to Farms in the UK and Other Member States

Braun, V. and Clarke, V. (2006). Using thematic analysis in psychology. Qual Res Psychol 3, 77-101

Burke, A.S. (2006). Improving Prosecutorial Decision Making: Some Lessons of Cognitive Science. William & Mary Law Review 47, 1587-1633

Costello, A.B. and Osborne, J.W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Pract Ass Res Eval 10, 1-9

Cronbach, L.J. (1951). Coefficient alpha and the internal structure of tests. Psychometrika 16, 297-334

DEFRA (2004). Delivering the Animal Health and Welfare Strategy in England. Implementation Plan 2004

DEFRA (2013). Animal Health and Welfare Practices on Farm 2011/12, England. National Statistics

Ellis-Iversen, J., Cook, A.J.C., Watson, E., Nielen, M., Larkin, L., Wooldridge, M. and Hogeveen, H. (2010). Perceptions, circumstances and motivators that influence implementation of zoonotic control programs on cattle farms. Prev Vet Med 93, 276-285

Fabrigar, L.R., Wegener, D.T., MacCallum, R.C. and Strahan, E.J. (1999). Evaluating the use of exploratory factor analysis in psychological research. Psychol Meth 4, 272-299

Ferguson, E. and Cox, T. (1993). Exploratory factor analysis: a users' guide. Int J Sel Assess 1, 84-94

Garforth, C.J., Bailey, A.P. and Tranter, R.B. (2013). Farmers' attitudes to disease risk management in England: a comparative analysis of sheep and pig farmers. Prev Vet Med 110, 456-466

Gunn, G.J., Heffernan, C., Hall, M., McLeod, A. and Hovi, M. (2008). Measuring and comparing constraints to improved biosecurity amongst GB farmers, veterinarians and the auxiliary industries. Prev Vet Med 84, 310-323

Jansen, J., van den Borne, B.H., Renes, R.J., van Schaik, G., Lam, T.J. and Leeuwis, C. (2009). Explaining mastitis incidence in Dutch dairy farming: the influence of farmers' attitudes and behaviour. Prev Vet Med 92, 210-223

Kaiser, H. (1974). An index of factorial simplicity. Psychometrika 39, 31-36

Kaler, J. and Green, L.E. (2013). Sheep farmer opinions on the current and future role of veterinarians in flock health management on sheep farms: a qualitative study. Prev Vet Med 112, 370-377

LeBlanc, S.J., Lissemore, K.D., Kelton, D.F., Duffield, T.F. and Leslie, K.E. (2006). Major advances in disease prevention in dairy cattle. J Dairy Sci 89, 1267-1279

Lowe, P. (2009). Unlocking potential. A report on veterinary expertise in food animal production

Maykut, P. and Morehouse, R. (1994). Beginning Qualitative Research: A Philosophic and Practical Guide. The Falmer Press, London, 195p

Michie, S., van Stralen, M.M. and West, R. (2011). The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 6, 42

Michie, S., West, R., Campbell, R., Brown, J. and Gainforth, H. (2014). ABC of Behaviour Change Theories: An Essential Resource for Researchers, Policy Makers and Practitioners. 499p

Osmond, J. (2009). Defra Farm Health Planning Initiative. Review Of Pump-Priming Expenditure. IHPC

Sutton, S. (2001). Health Behavior: Psychosocial Theories. Int Encycl Soc Behav Sci, 6499-6506

Tavakol, M. and Dennick, R. (2011). Making sense of Cronbach's alpha. Int J Med Educ 2, 53-55

ENDEMICITY OF ZOONOTIC DISEASES OF PORCINE ORIGIN IN LAO PEOPLE'S DEMOCRATIC REPUBLIC: IDENTIFYING SOCIO-CULTURAL RISK FACTORS THROUGH MULTIPLE CORRESPONDENCE ANALYSIS

H.R. HOLT[*], P. INTHAVONG, K. BOUALAM, K. BLASZAK, C. KEOKAMPHE, V. SOMOULAY, P. DÜRR, K. GRAHAM, J. ALLEN, S. BLACKSELL, F. UNGER, D. GRACE, S. ALONSO, D. PFEIFFER AND J. GILBERT

SUMMARY

The aim of this study was to identify potential risk factors for human infection with zoonotic diseases of porcine origin in Lao PDR. Multiple correspondence analysis was performed on data collected during a large cross-sectional study regarding pig contact, consumption of pork products, hygiene and sanitation. Cluster analysis was then conducted to aggregate individuals into relatively homogeneous subgroups. The analysis identified three distinct profiles: cluster 1 had low pig contact and good hygiene practices and were used as the baseline category for subsequent risk factor analysis. Individuals' in cluster 2 were more likely to have occupational pig contact (handling and slaughtering pigs) and had increased odds of testing seropositive for hepatitis E and Japanese encephalitis. Cluster 3 had poorer sanitation and hygiene and had increased odds of testing seropositive for hepatitis E and cysticercosis/taeniasis. The results of this study could be used to conduct risk-based surveillance and control activities.

INTRODUCTION

Public health in Lao PDR in relation to pig production

In Lao People's Democratic Republic (Lao PDR) co-habitation with livestock is common; even in urban households and households where livestock rearing is not a major source of income (Somphou et al., 2008). Pigs are increasingly important as a source of income and food security and are kept by up to 75% of rural households, with smallholder pig production accounting for more than 80% of the total pig production (FAO 2008). There is an increasing demand for pig meat, and in 2007 pork was the 2nd most consumed meat in the country (Huynh et al., 2006). There is a resulting risk of the Laotian population being exposed to zoonotic pathogens either via direct contact with pigs or indirectly via vectors or consumption of unsafe products e.g. raw or undercooked pork, raw pig's blood, fermented pork sausage or contaminated crops.

In Lao PDR funding for healthcare and veterinary services is lacking, resulting in poor access to health care, low diagnostic capabilities and virtually non-existent surveillance and control of zoonotic diseases (Willingham et al., 2010). Disease is therefore likely to remain unreported, diseases which are relatively straight forward to control remain endemic and

---

[*] Hannah Holt, The Royal Veterinary College, London. Email: hholt@rvc.ac.uk

human and animal health services are overwhelmed by disease outbreaks (Barennes et al., 2008).

The aim of this study was to identify risk factors for human infection of important zoonotic diseases of porcine origin, with a focus on unsafe practices. Diseases selected were hepatitis E, Japanese encephalitis and taeniasis/cysticercosis. Two of the 17 provinces of Lao PDR were selected as the study populations. Luang Prabang Province, situated in the North of Lao PDR is an upland Province, and the lowland Savannakhet Province was selected from the South of the country. Savannakhet has an increasing number of commercial pig systems near the Thai border (Phengsavanh et al., 2011) and Luang Prabang has a large market for pigs which are sourced from all districts in Luang Prabang as well as other Provinces, and are then sold directly or via slaughter traders and middlemen.

Overview of the selected diseases

Zoonotic diseases selected for inclusion in the study were hepatitis E, Japanese encephalitis and taeniasis/cysticercosis. Hepatitis E is primarily a water-borne disease causing acute hepatitis; transmission is faecal-oral and drinking contaminated water is responsible for most epidemics. The disease is also zoonotic, with consumption of undercooked contaminated meat and shellfish documented as additional transmission routes (Meng, 2010). It is also considered an occupational hazard for slaughterhouse workers, pig farmers and veterinarians (Meng et al., 2002). Japanese encephalitis is a vector borne disease transmitted by Culex spp. mosquitos and is a major cause of morbidity and mortality in humans (van den Hurk et al., 2009). The transmission cycle involves wading birds, pigs and humans. Epidemics occur after amplification of JEV in immunologically naïve pigs close to human populations; most notably near rice paddies during the rainy season.

Taenia solium causes taeniasis and cysticercosis; considered one of the most important diseases in Southeast Asia and a neglected zoonotic disease (Willingham et al., 2010). Cysticercosis is caused by ingestion of the larval stage of the tapeworm, usually from food or water contaminated with human faeces, and taeniasis is caused by infection of the adult tapeworm in contaminated meat (Ito et al., 2003). Cysticercosis causes significant morbidity and mortality in humans and can lead to neuro-cysticercosis; the leading cause of epilepsy in the region.

Multiple correspondence analysis

An individuals' risk of becoming infected with zoonotic disease is influenced by a large number of variables, many of which are interrelated. Correlation between these variables can make it difficult to perform risk factor analysis using traditional regression methods, particularly for pathogens with a very low or high prevalence. Multiple correspondence analysis (MCA) is a multivariable technique used for data exploration (similar to factor analysis or principal components analysis) which allows complex patterns in a dataset of categorical variables to be identified (Greenacre & Blasius, 2006, Abdi & Valentin, 2007). Briefly, MCA provides a graphical representation describing the relationships between categories of variables and without assuming an underlying distribution to the data (Abdi & Valentin, 2007).

MCA can be used to reduce the number of variables to be analysed by creating uncorrelated synthetic dimensions which describe the variation in the data (Greenacre & Blasius, 2006). The coordinates of each individual can be calculated on the dimensions derived from the MCA to obtain quantitative values and cluster analysis can be performed on these coordinates (Greenacre & Blasius, 2006). In the current study, MCA was utilised to identify general patterns of individuals' exposures and hierarchical clustering analysis (HCA) was then used to identify and describe typologies of individuals in terms of their hygiene and sanitation, pig contact and pork consumption habits (Costard et al., 2009, Husson et al., 2010).

MATERIALS AND METHODS

Selection of the study population and sampling

Thirty-villages were randomly selected from each Province with probability proportional to size; however in the Northern Province (Luang Prabang) only 29 were successfully recruited. In each village, permission to conduct the study was sought from the village leaders and a village-wide meeting was held to recruit participants. Fifteen households in the village were then selected using simple random sampling and enrolled in the study if they gave their informed consent; within each chosen household one family member over the age of five was randomly blood sampled.

A questionnaire was then administered to the chosen household member or, when necessary, their parent or guardian. The questionnaire gathered information on general characteristics (gender, age, ethnicity, education and household size), hygiene practices, pig contact, and consumption habits with respect to water sources and pig products. The questionnaire contained both household-level variables e.g. presence of pigs in the household as well as individual-level e.g. their duties in terms of pig husbandry.

Serological survey of pathogens

All laboratory testing was performed in Lao PDR at the National Animal Health Laboratory, Ministry of Agriculture or the National Centre for Laboratory and Epidemiology, Ministry of Health. Blood samples were collected in plain vacutainers and serum extracted for analysis. Samples were refrigerated and then placed on ice until arrival at the laboratory where they were frozen at -20oC before analysis. All questionnaire and serological data was entered and stored in a SurVET database (www.quest.survet.net).

Human serum samples were tested for presence of antibodies against Hepatitis E virus (HEV) using the HEV ELISA 4.0 (MP Diagnostics, Singapore); for Japanese Encephalitis (JE) antibodies and ratio of JE to Dengue antibodies using the JE-Dengue IgM Combo ELISA Test E-JED01C (Panbio, France); and for Taenia and Cysticercosis antibodies using the EITB test kit supplied from CDC, Georgia USA.

Statistical analysis

Multiple correspondence analysis (MCA) was performed on the data collected from the survey, incorporating potential risk factors for human infection with zoonotic diseases. This included information collected on water sources, toilet access, pork consumption, food preparation habits (including consumption of fermented sausage and pigs' blood) and contact with pigs (i.e. presence of pigs in the household, involvement in pig husbandry and participation in pig slaughtering). Ethnicity, gender, age group and education level were included as supplementary variables, this means they did not influence the calculation of the dimensions but were still projected on them.

The coordinates of each individual were calculated on dimensions created from the MCA which explained at least 10% of the variation in the dataset. HCA using Ward's criteria for linkage was then performed on individuals' coordinates of the selected dimensions to aggregate individuals into relatively homogeneous subgroups (clusters). The aim of which was to maximise intra-cluster correlation and inter-cluster variance. The analysis was performed in R 3.0.1 using the package FactoMineR.

Risk factor analysis

Associations between cluster membership and testing seropositive for certain zoonotic pathogens were investigated using logistic regression models with random-effects in order to control for correlation within villages and potential confounding effects of age and gender. The outcome for each model was serological status for each pathogen, the exposure of interest being which cluster the individual belonged to. Age and gender were also included in the models as fixed effects to control for potential confounding of these variables; gender was subsequently removed from any models were it was associated with the outcome with a *p*-value > 0.05. Village was included as a random-effect to control for the correlation of humans within villages. The analysis was also performed in R 3.0.1, using the package lme4.

RESULTS

The Cluster analysis was performed using the first three dimensions which explained 49.8% of the total variation; and not less than 12% individually. The coordinates of the variables on the two dimensions explaining the largest percentage of the variance (inertia) are graphically represented in Fig. 1. The coordinates are defined by the squared correlation ratio between the dimension and the variable. Variables with higher values contribute more to the construction of the dimensions and close proximity of variables in two-dimensional space indicates high correlation.

The profiles of each cluster are described in Table 1; most people were classified as Cluster 1 (51.1%). This cluster appeared to have the best hygiene practices with most people having toilet access (86.1%), washing their hands after using the toilet (92.5%), using protected water sources (90.4%) and boiling water before consumption (92.1%). In terms of pig contact; most had no pigs in the household (83.0%) and did not handle or slaughter pigs (>95%). This cluster was mainly Lao Loum (Lao Tai) the predominant ethnic group in Lao PDR. This cluster was used as the baseline for risk factor analysis.

People in cluster 2 were mostly male, Khmu (Lao Theung), and Hmong (Lao Soung) ethnicities (in addition to some Lao Loum) and from the Northern Province. Most people in this cluster were involved with slaughtering (83.7%), handled offal and/or raw meat (99.6%), consumed raw pigs' blood (76.4%) and were more likely to have pigs in the household compared to cluster 1 (36.0%). Around half had access to toilets (56.2%) and used protected water sources (51.1%), although most washed their hands after using the toilet (83.1%) and boiled water before consumption (87.1%).

Table 1. Description of the clusters

Variable	Cluster 1 N=458	Cluster 2 N=185	Cluster 3 N=252
Sanitation & drinking water			
Use toilets	86.1%	56.2%	7.2%
Always wash hands after using the toilet	92.5%	83.1%	38.1%
Use protected water source	90.4%	51.1%	65.3%
Boil water before consumption	92.1%	87.1%	33.1%
Contact with pigs			
Pigs in the household	17.0%	36.0%	64.0%
Handle pigs	3.3%	39.3%	19.1%
Slaughter pigs	5.4%	83.7%	15.4%
Pig products			
Drink raw pigs' blood	10.6%	76.4%	23.3%
Consume fermented pork sausage	57.0%	29.8%	51.3%
Handle offal/raw meat	88.6%	99.4%	71.2%

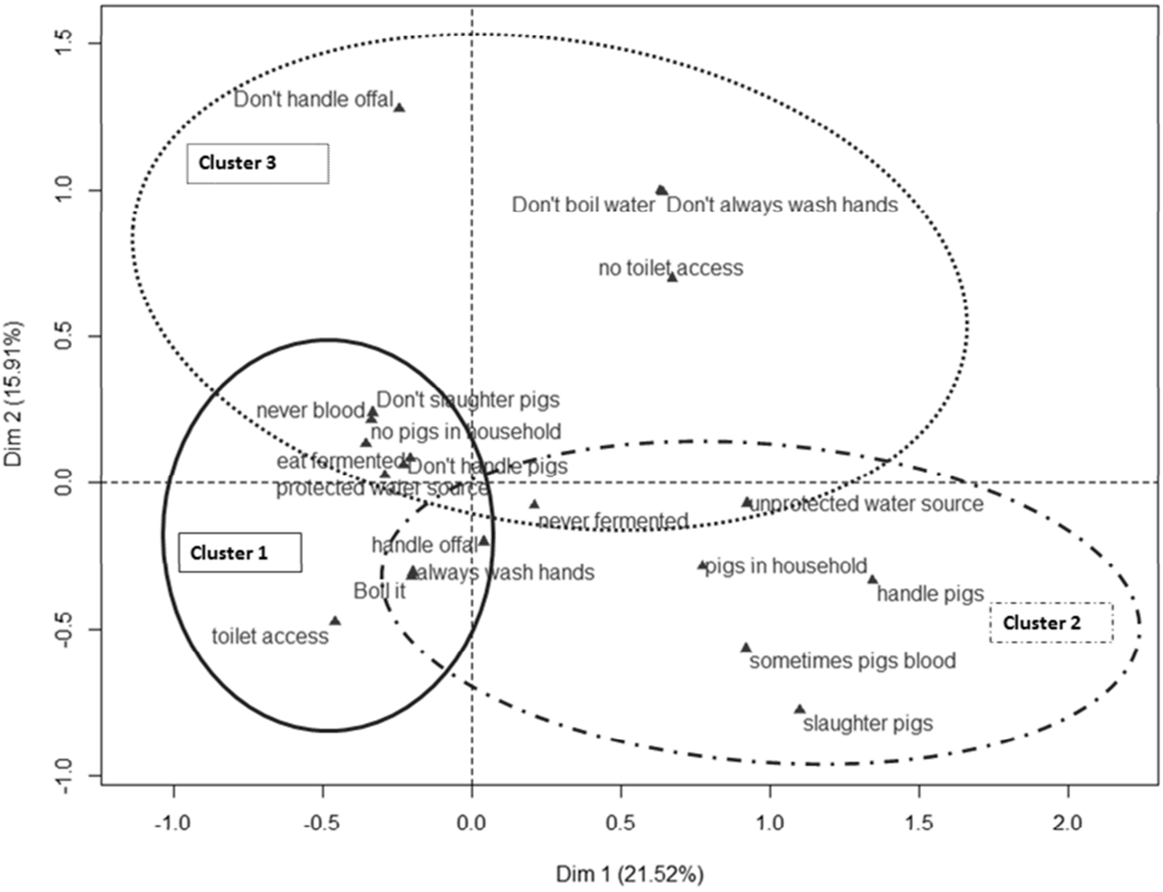


Fig. 1 Coordinate of the variables on the different dimensions

Cluster 3, which were mainly from the Southern Province appeared to have the most risky hygienic practices; although 65.3% used protected water sources; very few used toilets and only a third boiled their water before consumption, in addition most people did not always wash their hands after using the toilet (61.9%). This cluster appeared to have the lowest level of education with 42.4% having no schooling; they were mainly Lao Loum, with Khmu ethnic group also present. Although occupational pig contact was lower than cluster 2 they were more likely to have pigs in the household.

Risk factor analysis

In total 895 people were studied; in some cases, results for particular samples were not available due to problems with the sample (i.e. not enough serum) or inconclusive test results and these were classified as missing (<10% for any pathogen). For the analysis, the odds of testing seropositive for the various pathogens for people in cluster 2 and 3 were compared to the odds of testing seropositive in cluster 1 (protected water sources, boiled water, good hygiene practices and relatively low pig contact), as intuitively this cluster should have the lowest risk of most zoonotic diseases. People in cluster 2 (higher pig contact: particularly slaughtering, handled offal/raw meat, more likely to drink raw pigs' blood with moderate hygiene practices) and people in cluster 3 (unprotected water sources, poorer hygiene practices, pigs) were more likely to be seropositive for HEV, compared to cluster 1. Cluster 2 (high pig contact) were more likely to test seropositive for Japanese encephalitis and cluster 3 (poor hygiene) were more likely to test seropositive for *Taenia* spp. and cysticercosis.

DISCUSSION

The MCA and cluster analysis identified three typologies (or clusters) of individuals in terms of hygiene, pig contact and consumption of high-risk pig products. Cluster 1 was used as the baseline for risk factor analysis as it contained individuals with relatively safe hygiene practices and low pig contact. This cluster was mainly Lao Loum who are the predominant ethnic group in Lao PDR; they are less likely to raise pigs and have more political influence in the country (Phengsavanh and Stür 2006, IFAD 2012). Hmong, and to a lesser extent Khmu, are politically marginalised ethnic groups more likely to experience poverty and suffer reduced infrastructure including access to healthcare services (IFAD 2012).

Cluster 2 and 3 had increased odds of testing seropositive for HEV. The main transmission route for hepatitis E is consumption of contaminated water and both these clusters were more likely to use unprotected water sources; with few people in cluster 3 boiling water before consumption (Kumar et al., 2013). Genotypes 3 and 4 of the virus are also considered zoonotic; cluster 2 were mostly male, and more likely to have direct pig contact (slaughtering and handling pigs) and cluster 3 were most likely to have pigs in the household. The risk of exposure has previously been demonstrated to be higher in those with occupational contact with pigs (Drobeniuc et al., 2001, Meng et al., 2002). In addition, transmission is also thought to occur via raw or undercooked pig products and cluster 2 were most likely to drink raw pig's blood (Meng 2010). However, the importance of HEV as a zoonotic disease has not been fully characterised and routes of transmission from pigs to humans are not fully understood (Meng 2010).

People in cluster 2 were most likely to be seropositive for JEV for which pigs are the amplifying host (van den Hurk et al., 2009). Per capita pig density has previously been reported to be higher in the Northern mountainous region of Lao PDR in areas inhabited by

Khmu or Hmong ethnicities (Phengsavanh and Stür 2006). In the current study, the number of pigs per pig-owning household was higher ($p<0.001$) in the Northern Province to which most people in cluster 2 belonged. In addition pigs in this Province were more likely to test IgM positive for JEV, which indicates recent infection. The disease is a major public health concern due to its' high mortality and morbidity, particularly in young children.

Cluster 3 had the highest risk of *Taenia* spp./cysticercosis (Ito et al., 2003); around 50% of the cluster consumed fermented sausage which may lead to ingestion of the tapeworm (taeniasis). However, this was a similar figure to cluster 1 which had a lower risk of testing seropositive for *Taenia* spp. Following faecal shedding in humans; eggs are ingested by both pigs and humans through consumption of contaminated vegetation or water. Cluster 3 were most likely to practice open defecation and were predominantly from the Southern Province where more than half of pigs sampled were tethered or free-grazed; compared to the Northern province where 90.6% were housed. It may be that the *Taenia* spp. lifecycle is only maintained in areas in areas practicing open defecation and in places where pigs are not kept in zero grazing systems (Conlan et al., 2008). Cysticercosis should be a priority disease in the Lao PDR; infection can lead to neuro-cysticercosis; the leading cause of epilepsy in the region (Willingham et al., 2010).

In order to reduce the zoonotic disease burden in Lao PDR an integrated approach is needed including disease surveillance, educational campaigns and community mobilisation (Bardosh et al., 2014). Cost-effective and appropriate interventions should then aim to reduce prevalence of the disease in livestock and mitigate human exposure. Meat inspection is recommended for the control of certain zoonoses including cysticercosis (FAO 2005), however, due to limited and inconsistent funding for veterinary and public health services, a lack of data on the supply chain of pigs in Lao PDR and informal slaughter practices this is unlikely to be practical in this setting (Conlan et al., 2008).

Campaigns are needed to increase awareness of zoonotic diseases in individuals and communities, strengthen communication between health workers, veterinarians and livestock owners and promote behavioural changes. Simple changes such as hand washing with soap and water after certain activities, not practicing open defecation and altering consumption habits may significantly reduce zoonotic disease transmission in Lao PDR (Owen 2005, Willingham et al., 2010), many of the risk behaviours are socio-cultural and any campaigns would need to be developed in consultation with local stakeholders to promote community participation and ensure a design appropriate for the setting.

The results of this study provide evidence to support the efficient application of scarce resources through targeting risk-based surveillance and control initiatives at those most vulnerable. For example in the case of cysticercosis, villages practicing open defecation, particularly with high levels of pigs in free range scavenger systems could be targeted for control. Following this work an intervention campaign was launched in a hyper-endemic village combining Mass Drug Administration in humans, vaccination and anti-helminthic treatment in pigs, and educational campaigns to increase community awareness and knowledge of the risk of zoonotic diseases and preventive measures. The results to date are promising, however, prior to interventions there was almost two years of trust-building work in the community (Bardosh et al., 2014).

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Vladamir Grosbois (CIRAD) for his advice regarding multiple correspondence analysis.

REFERENCES

Abdi, H. and Valentin, D. (2007). Multiple correspondence analysis. Encyclopedia of measurement and statistics. 651-657

Bardosh, K., Inthavong, P., Xayaheuang, S. and Okello, A.L. (2014). Controlling parasites, understanding practices: The biosocial complexity of a One Health intervention for neglected zoonotic helminths in northern Lao PDR. Soc. Sci. Med. 120, 215-223

Barennes, H., Sayasone, S., Odermatt, P., de Bruyne, A., Hongsakhone, S., Newton, P.N., Vongphrachanh, P., Martinez-Aussel, B., Strobel, M. and Dupouy-Camet, J. (2008). A major trichinellosis outbreak suggesting a high endemicity of Trichinella infection in northern Laos. Am. J. Trop. Med. and Hyg. 78, 40-44

Conlan, J., Khounsy, S., Inthavong, P., Fenwick, S., Blacksell, S. and Thompson, R.C.A (2008). A review of taeniasis and cysticercosis in the Lao People's Democratic Republic. Parasitol. Int. 57, 252-255

Costard, S., Porphyre, V., Messad, S., Rakotondrahanta, S., Vidon, H., Roger, F and Pfeiffer, D.U. (2009). Multivariate analysis of management and biosecurity practices in smallholder pig farms in Madagascar. Prev. Vet. Med. 92, 199-209

Drobeniuc, J., Favorov, M.O., Shapiro, C.N., Bell, B.P. Mast, E.E., Dadu, A., Culver, D., Iarovoi, P., Robertson, B.H. and Margolis, H.S. (2001). Hepatitis E Virus Antibody Prevalence among Persons Who Work with Swine. J. Infect. Dis 184, 1594-1597

FAO (2005). Control of hazards of public health and animal health importance through ante- and postmortem meat inspection: Working Group on Animal Production Food Safety http://www.oie.int/doc/ged/D2914.PDF

FAO (2008). Regional data exchange system (RDES) on Food and Agricultural Statistics in Asia and the Pacific. http://www.fao.org/nr/water/aquastat/countries_regions/lao/index.stm

Greenacre, M. and Blasius, J. (2006). Multiple correspondence analysis and related methods. CRC Press

Husson, F., Josse, J. and Pages, J. (2010). Principal component methods - hierarchical clustering - partitional clustering: why would we need to choose for visualizing data. Applied Mathematics Department http://factominer.free.fr/docs/HCPC_husson_josse.pdf

Huynh, T.T.T., Aarnink, A.J.A., Drucker, A. and Verstegen, M.W.A. (2006). Pig production in Cambodia, Laos, Philippines, and Vietnam: a review. AJAD 3, 69-90

IFAD (2012). Country Technical Note on Indigenous People’s Issues - Lao People's Democratic Republic. http://www.ifad.org/english/indigenous/pub/documents/tnotes/laos.pdf

Ito, A., Nakao, M and Wandra, T. (2003). Human taeniasis and cysticercosis in Asia. Lancet 362, 1918-1920

Kumar, S., Subhadra, S., Singh, B. and Panda, B.K. (2013). Hepatitis E virus: the current scenario. Int. J. Infect. Dis. 17, 228-233

Meng, X. J. (2010). Hepatitis E virus: animal reservoirs and zoonotic risk. Vet. Microbiol. 140, 256-265

Meng, X. J., Wiseman, B., Elvinger, F., Guenette, D.K., Toth, T.E., Engle, R.E., Emerson, S.U. and Purcell, R.H. (2002). Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. J. Clin. Microbiol. 40, 117-122

Owen, I.L. (2005). Parasitic zoonoses in Papua New Guinea. J. Helminthol. 79, 1-14

Phengsavanh, P., Ogle, B., Stür, W., Frankow-Lindberg, B.E. and Lindberg, J.E. (2011). Smallholder pig rearing systems in northern Lao PDR. Asian-Australas. J. Anim. Sci. 24, 867-874

Phengsavanh, P. and Stür W. (2006). The use and potential of supplementing village pigs with Stylosanthes guianensis in Lao PDR. Proceeding of a Workshop on forages for Pigs and Rabbits, Phnom Penh.

Somphou, P., Takano, T. and Nakamura, K. (2008). Cohabitation with farm animals in urban households with and without occupational farm work: associations between participation in educational activities and good hygiene practices in at-risk households cohabiting with farm animals. Environ. Health and Prev. Med. 13, 322-331

van den Hurk, A.F., Ritchie, S.A. and Mackenzie, J.S. (2009). Ecology and Geographical Expansion of Japanese Encephalitis Virus. Annu. Rev. Entomol. 54, 17-35.

Willingham, I., Lee, A., Wu, H., Conlan, J. and Satrija, F. (2010). Chapter 9: Combating Taenia solium Cysticercosis in Southeast Asia: An Opportunity for Improving Human Health and Livestock Production. Adv. Parasitol. Academic Press. 72, 235-266

ANALYSIS OF SURVEILLANCE DATA

A BOOSTING APPROACH FOR SYNDROMIC SURVEILLANCE: THE EXAMPLE OF RESPIRATORY DISEASE IN SMALL ANIMAL PRACTICES IN THE UK

F. SANCHEZ-VIZCAINO[*], E. WALDMANN, P.H. JONES, S. DAWSON, R.M. GASKELL, T. MENACERE, P-J.M. NOBLE, S. REYNOLDS AND A.D. RADFORD

SUMMARY

In companion animals, the increasing availability of electronic health records is creating new challenges for analysing large datasets. Boosting is a convenient method for variable selection and model estimation in these data situations. To demonstrate the utility of this method, a mixed effects boosted logistic regression model was developed to model the presentation of respiratory disease in dogs and cats attending veterinary practices in the UK. In addition, descriptive statistics were used to characterise respiratory disease consultations in UK small animal practices. Data from 71,141 consultations was collected from 20 veterinary practices between March and August 2014. In addition, 627 respiratory questionnaires were gathered from 55 practices. Presentation for respiratory disease comprised 1.5% of dog and 2.4% of cat consultations. The final model included: age, time between consultations, species, presence of a respiratory consultation in the previous six days, insurance and microchipping status and several two-way interactions.

INTRODUCTION

Although reliable estimates are not published, it is likely that the use of electronic health records (EHR) is becoming standard practice in companion animal medicine in developed countries. This evolution in the collection of individual patient results from traditional paper medical record to EHR implies an ability to collect information on a larger and more complex scale. Certainly, disparate data sets offer an opportunity to improve health by providing insights into the causes and outcomes of disease and enhanced disease prediction and prevention (Khoury & Ioannidis, 2014). However, massive data sets also provide analytical challenges beyond handling high number of observations. A risk inherent in the statistical analysis of large data sets is that very many correlated potential covariates may be identified (Peters & Buntrock, 2014).

Using a classical variable selection approach like forward or backward selection via the AIC or considering the p-values as indicators for variable selection can lead to over-fitted models and estimation problems due to collinearity of covariates (Mayr, 2014). Component-wise gradient boosting (Breiman, 1998; Breiman, 1999; Friedman et al., 2000; Friedman, 2001) is a convenient and robust method for variable selection and model estimation in these data situations (Hofner et al., 2014). However, it represents a very novel methodological approach for data analysis in veterinary epidemiology. Thus, the implementation of this method was illustrated here by developing a mixed effects logistic regression model using

---

[*] Fernando Sánchez-Vizcaíno, University of Liverpool, Institute of Infection and Global Health, Leahurst Campus, Chester High Road, Neston, Wirral, CH64 7TE, UK. Email: fsvb@liv.ac.uk

boosting for variable selection to model the presentation of respiratory disease in dogs and cats attending veterinary practices in the UK.

Respiratory disease is a common cause for presentation of companion animals to UK veterinary surgeons. Despite this, there are few national statistics regarding its frequency, the main signs seen in different species, the diagnostic approach to these cases or even the risk factors for disease susceptibility; a prerequisite for the development of evidence-based medicine. Hence, SAVSNET (Small Animal Veterinary Surveillance Network) electronic health data gathered from participating veterinary practices was used here to profile the presentation, diagnostic approach and to identify risk factors for dogs and cats presenting with respiratory signs to UK small animal practices.

MATERIALS AND METHODS

Data collection

Population study data was collected electronically in near real-time by SAVSNET from 20 veterinary practices (with a combined total of 40 premises) using a compatible version of practice management software (Robovet, Vetsolutions, Edinburgh feature pack 17). Data was gathered between March and August 2014 and included animal signalment (the animal's medical history including species, breed, sex, neutering status, date of birth, vaccination history, weight, insurance and microchipping status), clinical free text and owner's post-code.

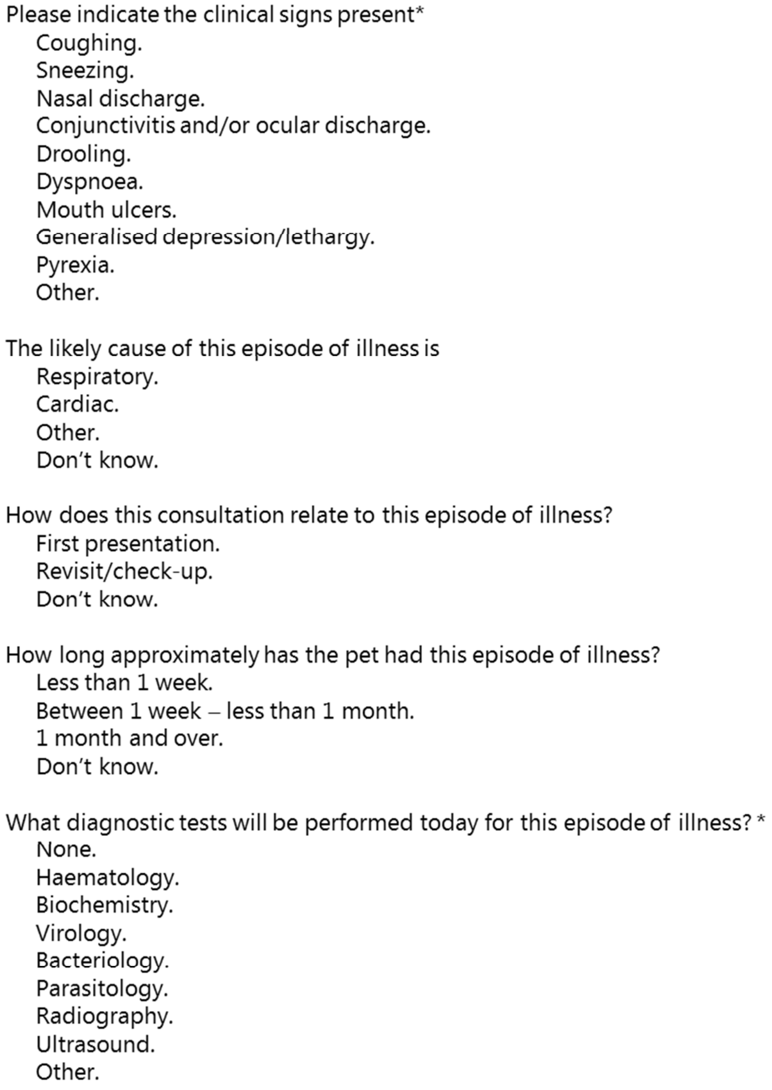
The SAVSNET system also collected additional information on the presentation of respiratory disease by appending a short, context-specific respiratory questionnaire after approximately 25% of routine respiratory consultations (Fig. 1). SAVSNET respiratory questionnaire responses assessed here were collected from 55 practices (with a combined total of 91 premises) between January and August 2014.

Data were excluded if the client had opted out of SAVSNET study participation.

Statistical analysis

A multivariable mixed effects logistic regression model, incorporating veterinary practices as a random effect, was used to model the presentation of respiratory disease (as a binary dependent variable) in dogs and cats attending veterinary practices. Animals were classified as presenting with respiratory disease if, based on a veterinary opinion, the main reason for the consultation was due to signs associated with conditions affecting the upper and / or lower respiratory tract. Multiple visits of individual animals to participating veterinary practices for both healthy and sick animal consultations were included in the analysis. Component-wise gradient boosting was used for parameter estimation (Breiman, 1998; Breiman, 1999; Friedman et al., 2000; Friedman, 2001). This approach has the advantage of automatically selecting variables. Instead of maximizing the likelihood of the assumed error distribution, it minimizes the resulting loss function by a steepest decent algorithm. The model was fitted using the R package "mboost". A cross-validation approach was conducted to choose the number of boosting iterations.

The explanatory variables considered in the analysis were: species, pedigree status (i.e. whether the animal was purebred or crossbred), age, sex, neutering status, whether or not the consultation was the first one during the study period (RANK), time between consultations per animal (TC), whether or not there was a respiratory consultation in the previous six days (PR6), insurance and microchipping status. Relevant two-way interactions were included in the model, such as species by age, sex by species, sex by age, PR6 by species, PR6 by TC, PR6 by age, TC by RANK, neutering by age, neutering by sex and insuring by age. Continuous variables were centred and modelled using splines. TC was also squared root transformed in order to improve the fit of the model.



Please indicate the clinical signs present*
- Coughing.
- Sneezing.
- Nasal discharge.
- Conjunctivitis and/or ocular discharge.
- Drooling.
- Dyspnoea.
- Mouth ulcers.
- Generalised depression/lethargy.
- Pyrexia.
- Other.

The likely cause of this episode of illness is
- Respiratory.
- Cardiac.
- Other.
- Don't know.

How does this consultation relate to this episode of illness?
- First presentation.
- Revisit/check-up.
- Don't know.

How long approximately has the pet had this episode of illness?
- Less than 1 week.
- Between 1 week – less than 1 month.
- 1 month and over.
- Don't know.

What diagnostic tests will be performed today for this episode of illness? *
- None.
- Haematology.
- Biochemistry.
- Virology.
- Bacteriology.
- Parasitology.
- Radiography.
- Ultrasound.
- Other.

Fig. 1 Questions presented to the veterinary surgeon on completion of approximately 25% of respiratory consultations. *Questions where multiple answers were allowed.

Descriptive statistics were used to describe the main results obtained from the respiratory questionnaires. Specifically, they illustrate the similarities and differences between clinical signs reported, likely cause, type of consultation (i.e. first presentation or revisit/check-up), duration of illness and diagnostic tests requested for cases of respiratory disease in dogs and cats. When more than one questionnaire was completed for the same animal, data from the first questionnaire only were used. Questionnaires where species of animal was not recorded were discarded.

RESULTS

Characteristics of study population

Individual consultation records (including repeat consultations for the same animal) in the database totalled 71,141 consultations from 20 veterinary practices. Of these, 52,896 consultations (74.3%) were from dogs, 14,750 (20.7%) from cats, 1,284 (1.8%) from rabbits, 1,615 (2.3%) were from other species and there were 596 consultations where the species was not noted. Presentation for respiratory disease comprised 1.5% of canine consultations and 2.4% of feline consultations. Data analysed on a single visit per animal basis, provided a total of 44,461 unique records. Of these, 31,712 (71.3%) animals were dogs, 10,219 (23%) were cats, 929 (2.1%) were rabbits, 1,223 (2.7%) were other species and there were 378 animals where the species was not noted.

Risk factors for the presentation of respiratory disease

The standard deviation of the random effects for practices was 0.25. The final model included the continuous variables: age, TC, the categorical variables: species, pedigree status, PR6, microchipping status, insurance status and the 2-way interactions: species by age, PR6 by species, PR6 by age and PR6 by TC (Table 1).

The odds of dogs and cats presenting with respiratory disease in a typical veterinary practice (RD) – i.e. with a random effect of zero for practice, were impacted by the species, with a reduced risk for dogs (Table 1). Crossbred animals were less likely to present with respiratory disease in a typical veterinary practice than purebred animals (Table 1).

An effect of age on RD was found, with an increase in risk each year for the first 3 years, followed by a slight reduction every year for the next 4 years and an increase again every year for the next six years when the risk started to decrease again (Fig. 2). There was an interaction between age and species and between age and PR6. In short, the effect of age on RD was slightly higher in dogs than in cats for animals older than approximately 11 years of age (Fig. 2). In PR6-positive animals the effect of age was higher for approximately the first 6.25 years and lower for other years (Fig. 2).

Figure 3 shows the effect of TC as well as its interaction with PR6. Briefly, PR6-positive animals were 2.2 times more likely to present with respiratory disease for a one-unit increase in TC within the six days since the last consultation than PR6-negative animals.

PR6-positive animals were 100.4 times more likely to present with respiratory disease in a typical veterinary practice than PR6-negative animals. This relationship between RD and PR6 was complex due to an interaction between PR6 and species and the mentioned interaction between PR6 and age / TC. In short, the effect of PR6 on RD was 2.2 times lower in dogs than in cats.

Microchipped animals and insured animals were less likely to present with respiratory disease in a typical veterinary practice than, respectively, animals not microchipped and animals not insured (Table 1).

Table 1. Odds ratios of fixed effects from the final multivariable mixed effects logistic regression model of the probability of presenting with respiratory disease in dogs and cats attending veterinary practices.

Variable	Beta value	Odds ratio
Species		
Cat		Reference
Dog	-0.089021	0.9148264
Pedigree status		
Purebred		Reference
Crossbred	-0.2178484	0.8042474
Age	Continuous	
Species by age		
Cat, age		Reference
Dog, age	0.0065792	1.006601
TC[a]	Continuous	
PR6[b]		
No		Reference
Yes	4.608992	100.3829
PR6 by species		
PR6 negative, cat		Reference
PR6 negative, dog		Reference
PR6 positive, cat		Reference
PR6 positive, dog	-0.7905962	0.4535743
PR6 by age		
PR6 negative, age		Reference
PR6 positive, age	-0.071945	0.930582
PR6 by TC		
PR6 negative, TC		Reference
PR6 positive, TC	0.7968538	2.21855
Microchipping status		
No		Reference
Yes	-0.1427418	0.8669779
Insuring status		
No		Reference
Yes	-0.1013695	0.9035991

[a] TC: time between consultations per animal

[b] PR6: presence of a respiratory consultation in the previous six days

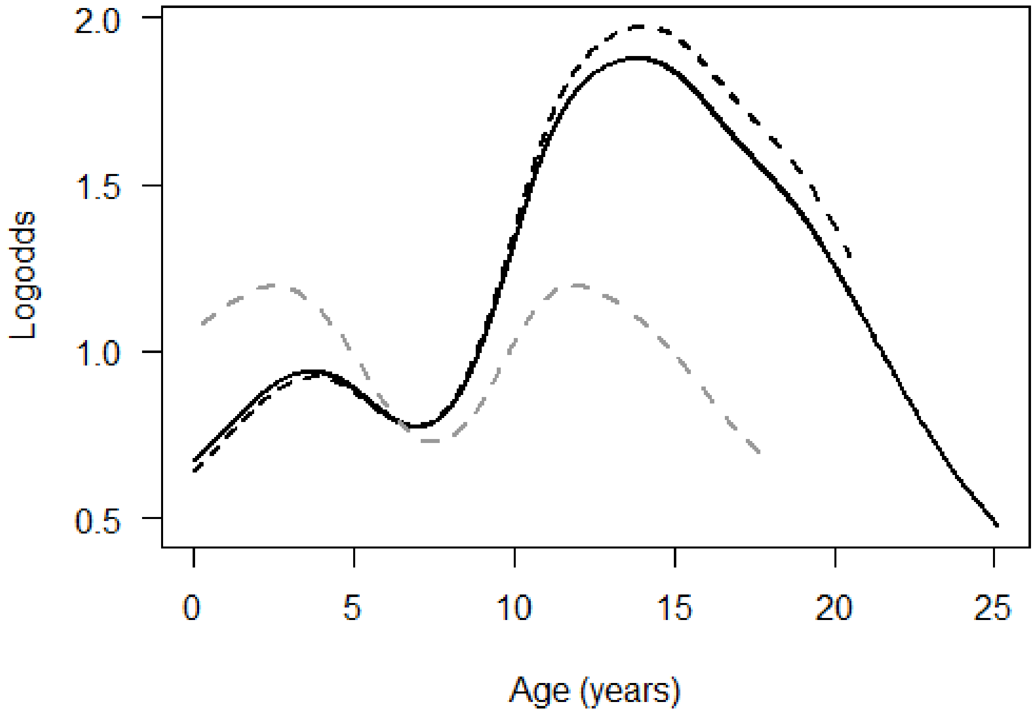


Fig. 2 Log-odds of dogs and cats presenting with respiratory disease in a typical veterinary practice by age. Black solid, black dashed and grey dashed lines depict respectively the impact of age in cats (reference), dogs and in animals that have presented for a respiratory consultation in the previous six days, keeping other model covariates constant.

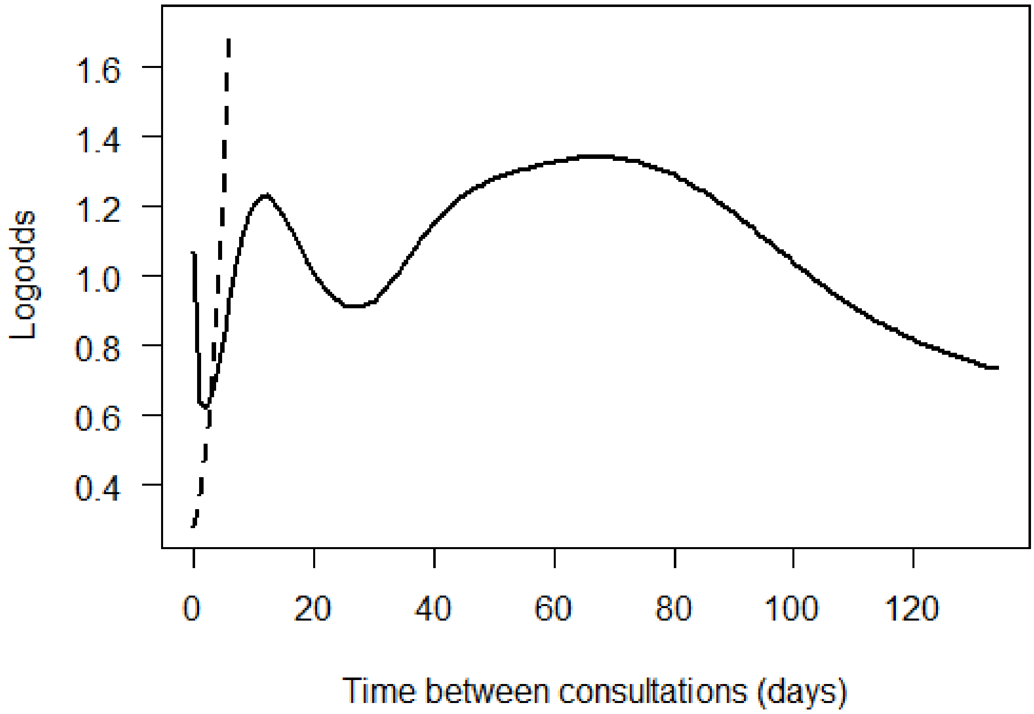


Fig. 3 Log-odds of dogs and cats presenting with respiratory disease in a typical veterinary practice by time between consultations (TC) keeping constant other model covariates (black solid line). The black dashed line depicts the impact of TC in animals that have presented for a respiratory consultation in the previous six days, keeping constant other model covariates.

Main results of the respiratory questionnaire

In total, responses to 627 respiratory questionnaires were collected from 55 practices. Four questionnaires where species of the animal was not recorded were discarded. Subsequently, data were analysed on a single questionnaire per animal basis, providing a total of 591 unique questionnaires. Of these, 371 (62.8%) questionnaires were from dogs, 185 (31.3%) from cats, 14 (2.4%) from rodents, 12 (2%) from rabbits and 9 (1.5%) from birds.

In dogs, the most frequent respiratory sign reported was coughing (68.2% of consultations), whilst in cats it was sneezing (43.2%) (Table 2).

Table 2. Summary of respiratory clinical signs in dogs and cats presenting with respiratory disease to veterinary practices in the UK. Percentage of dogs and cats presenting with a specific clinical sign was calculated based on a total number of 371 dogs and 185 cats. The same animal could present with more than one clinical sign per consultation.

Clinical signs	No. (%) of dogs	No. (%) of cats
Coughing	253 (68.2)	45 (24.3)
Sneezing	41 (11.1)	80 (43.2)
Nasal discharge	25 (6.7)	61 (33)
Conjunctivitis	16 (4.3)	38 (20.5)
Drooling	4 (1.1)	2 (1.1)
Dyspnoea	71 (19.1)	45 (24.3)
Mouth ulcers	2 (0.5)	2 (1.1)
Lethargy	16 (4.3)	27 (14.6)
Pyrexia	13 (3.5)	10 (5.4)
Other	36 (9.7)	20 (10.8)

In most dogs (70.6%) and cats (84.3%) the likely cause of the respiratory disease had a respiratory origin. A cardiac cause and other causes were believed in 16.4% of dogs and 10.8% of cats and 7.8% of dogs and 3.2% of cats, respectively.

More than half (54.4%) of dogs and 45.4% of cats that presented with respiratory disease had attended a veterinary surgeon only once in relation to this episode of illness. The type of presentation was unknown in 2.7% of dogs and 3.8% of cats.

A high proportion of dogs (50.9%) and cats (47%) with respiratory disease presented with a history of illness over the previous six days. Animals with a history of respiratory related illness over the previous week and less than 1 month represented 21.3% of dogs and 22.2% of cats. Animals with a history of illness in the previous month or longer than one month ago, represented 26.1% of dogs and 29.2% of cats.

Diagnostic tests were planned to be performed in 17.3% of cases with respiratory disease (96/556; 18.6% for dogs; 14.6% for cats). Radiography, serum biochemistry and haematology were the most common tests planned to be used in 4.3% of dogs and 4.9% of cats, 3.5% of dogs and 3.8% of cats and 3.2% of dogs and 4.3% of cats, respectively.

DISCUSSION

To the best of the authors' knowledge, this is the first time that a mixed effects boosted logistic regression model has been used in veterinary syndromic surveillance to identify risk factors associated with a syndrome of interest. Specifically, the study here identifies risk factors for respiratory disease susceptibility in dogs and cats attending veterinary practices in the UK. In addition, this study uses a coordinated syndromic surveillance system to characterise the consultations presenting with respiratory disease in small animal practices in the UK. These results are a prerequisite for supporting the development of evidence-based medicine.

In companion animal medicine, the increasing availability of electronic health records is bringing new challenges for large-scale data management, processing and analysing. Thus, this expansion of EHR should take advantage of the new progress in statistical methodology to increase the value of clinical data for improving healthcare.

A key issue in statistical research is the development of algorithms for model building and variable selection (Hastie et al., 2009). This issue becomes even more relevant in large data sets with large numbers of covariates, as occurs with EHR, where statistical techniques are necessary to select the appropriate modelling alternative for each of the covariates and deal with estimation problems due to collinearity of explanatory variables. In these data situations, classical techniques for model building and variable selection (such as generalized linear modelling with stepwise selection) are known to be unreliable or might even be biased (Hofner et al., 2014; Mayr et al., 2014). To address these situations, component-wise gradient boosting (Breiman, 1998; Breiman, 1999; Friedman et al., 2000; Friedman, 2001) can be used. This is a machine learning method for optimizing variable selection and prediction accuracy and for obtaining statistical model estimates via gradient descent techniques. However, to the best of the authors' knowledge, this method has only been implemented in veterinary epidemiology in the development of a likelihood survival scoring system for hospitalised equine neonates (Dembek et al., 2014). The authors have noted, however, that in this earlier study boosting was only used for variable selection from a data set with large number of covariates but small sample sizes. Hence, to demonstrate the usefulness of this method for variable selection and parameter estimates from large complex veterinary data, here a model-based boosting approach was conducted for modelling the presentation of respiratory disease in dogs and cats attending veterinary practices in the UK.

The current study indicated that cats have higher risk for presenting with respiratory disease than dogs. Only speculation can be made on the cause of this, but cats arguably have more known respiratory infections which are less well controlled by vaccination because of strain variability and complex carrier states, epitomised by feline calicivirus (FCV) (Radford et al., 2009) and feline herpesvirus (FeHV-1) (Thiry et al., 2009). The prevalence of respiratory disease consultations in dogs (1.5%) that attended UK veterinary practices was lower than that reported in an England-based study. Within the work, O'Neill et al. (2014) reported that 7.0% (95% CI 6.2 – 7.9) of dogs seen for primary-care at veterinary practices in England showed signs of respiratory disease. This difference could be due to differences in the sampling population; respiratory infection was calculated based on a single visit per animal basis and for dogs attending only for primary-care in O'Neill et al. (2014), whilst the results presented in this study were calculated on a consultation basis, taking into account both healthy and sick animal consultations. Furthermore, the previous study was based on data collected on dogs attending veterinary practices across central and south-eastern England, whilst the data assessed in the current study were gathered from practices distributed around England, Wales and Scotland. Consequently, variation in the prevalence of respiratory disease in dogs between both studies could be also due, at least in part, to geographical differences in disease prevalence.

Results revealed that crossbred dogs and cats are less likely to present with respiratory disease at veterinary practices than purebred animals. This was not unexpected as some purebreds are generally considered to be prone to respiratory problems, possibly as a result of their conformation (Roedler et al., 2013). However, it is of note that purebred and crossbred categories comprise heterogeneous amalgamations of size, shape and genetics. Merging this variation into single categories may have masked important effects related to specific conformational, physiological or behavioural features. Many breeds and breed crosses were represented in the data set but also many were represented by only a few individuals, limiting further breed analysis. With ongoing data collection through SAVSNET, substantially larger datasets will become available, allowing for higher resolution analysis of the breed-related disease risk factors.

In both dogs and cats, RD was higher in animals between 9-21 years of age (Fig. 2). Infectious respiratory disease is generally considered to be more prevalent in young animals, whilst non-infectious causes of respiratory disease such as tumours are more prevalent in aged animals. Understanding the precise aetiologies underlying this syndrome, as well as the impact age has on the likelihood of an animal with respiratory disease presenting to the vet will be necessary to understand this finding more fully. Interestingly, in old PR6-positive animals the effect of age on RD was much less important than in old PR6-negative animals of similar ages (Fig. 2).

The covariate PR6 had the biggest effect on RD. Thus, animals attending veterinary practices that in the six previous days had attended for a respiratory consultation, were at much higher risks of presenting again with the condition than animals that never presented or had presented with respiratory disease longer than six days ago. This result could be related to a general acute presentation of respiratory disease in dogs and cats, as was reflected in the results of the questionnaire, with a high proportion of animals presenting with a short history of illness. The effect of PR6 was lower in dogs than in cats, which might indicate that dogs get more acute respiratory disease than cats. This result seems to be reinforced by findings obtained from the questionnaire, which suggest that cats presenting with respiratory disease more frequently need to attend the veterinary surgeon for a follow up consultation. Interestingly, in PR6-positive animals the risk of presenting with respiratory disease was increasing every day, within the six days since the last consultation, at a higher rate than in PR6-negative animals (Fig. 3). The explanation for this effect is not immediately obvious, but it could be related to differences in the attitudes of animal owners; some might prefer to wait a few days and see if the animal gets better before presenting their pets to veterinary practices again.

The most frequent signs presented in respiratory consultations included coughing in dogs and sneezing in cats. Coughing as a syndrome is suggestive of tracheal and bronchial disease, often associated with "kennel cough" syndrome in dogs, and attributed to a variety of pathogens notably *Bordetella bronchiseptica* (Mochizuki et al., 2008). In contrast in cats, respiratory disease is more frequently associated with viral infections that have a predilection for oronasal and ocular tissues, particularly FCV and FeHV-1, and possibly explaining the high frequency of sneezing reported for this species.

The main drawback of the boosting method is that it does not yield uncertainty estimates, such as the standard deviation. The latter are less necessary than in classical models, as the algorithm itself conducts the variable selection. The authors have noted, however, that by the time the manuscript was finished a new function had been implemented in the R package "mboost" to calculate point-wise confidence intervals for the parameter estimates using a bootstrap method. This is a reflection in itself of the fast evolution of this novel method.

A novel method in veterinary epidemiology for analysing large complex data has been implemented here to identify risk factors associated with respiratory disease in dogs and cats attending UK veterinary practices. In addition, electronic health records, including questionnaire responses, were used to profile the presentation and diagnostic approaches for dogs and cats presenting with respiratory signs to UK small animal practices. Future studies establishing the spatio-temporal baseline for the occurrence of respiratory disease in companion animals and determining outcome measures associated with specific diagnostic and therapeutic approaches would augment the current results and contribute to influence clinical decision-making in practice.

ACKNOWLEDGEMENTS

Since October 2012, SAVSNET Ltd. has been a registered Charity (No. 1149531) supported by The British Small Animal Veterinary Association (BSAVA) and the University of Liverpool. The authors are extremely grateful to the 55 practices that participated in this study, and to our colleagues at Vet Solutions without whose dedicated help and support, collection of these data would not be possible.

REFERENCES

Breiman, L. (1998). Arcing classifiers. Ann Stat 26, 801-849

Breiman, L. (1999). Prediction games and arcing algorithms. Neural Comput 11, 1493-1517

Dembek, K.A., Hurcombe, S.D., Frazer, M.L., Morresey, P.R. and Toribio, R.E. (2014). Development of a likelihood of survival scoring system for hospitalized equine neonates using generalized boosted regression modeling. PLoS ONE 9, e109212

Friedman, J.H. (2001). Greedy function approximation: a gradient boosting machine. Ann Stat 29, 1189-1232

Friedman, J., Hastie, T. and Tibshirani, R. (2000). Additive logistic regression: a statistical view of boosting. Ann Stat 28, 337-407.

Hastie, T., Tibshirani, R. and Friedman J. (2009). The Elements of Statistical Learning: Data Mining, Inference, and Prediction. Springer, New York, 2nd edition, 745p.

Hofner, B., Mayr, A., Robinzonov, N. and Schmid, M. (2014). Model-based boosting in R: a hands-on tutorial using the R package mboost. Comput Stat 29, 3-35

Khoury, M.J. and Ioannidis, J.P. (2014). Medicine. Big data meets public health. Science 346, 1054-1055

Mayr, A., Binder, H., Gefeller, O. and Schmid, M. (2014), The Evolution of Boosting Algorithms. From machine learning to statistical modelling. Methods Inf Med 53, 419-427

Mochizuki, M., Yachi, A., Ohshima, T., Ohuchi, A. and Ishida, T. (2008). Etiologic study of upper respiratory infections of household dogs. J Vet Med Sci 70, 563-569

O'Neill, D.G., Church, D.B., McGreevy, P.D., Thomson, P.C. and Brodbelt, D.C. (2014). Prevalence of disorders recorded in dogs attending primary-care veterinary practices in England. PLoS ONE 9, e90501

Peters, S.G. and Buntrock J.D. (2014). Big data and the electronic health record. J Ambul Care Manage 37, 206-210

Radford, A.D., Addie, D., Belák, S., Boucraut-Baralon, C., Egberink, H., Frymus, T., Gruffydd-Jones, T., Hartmann, K., Hosie, M.J., Lloret, A., Lutz, H., Marsillo, F., Pennisi, M.G., Thiry, E., Truyen, U. and Horzinek, M.C. (2009). Feline calicivirus infection. ABCD guidelines on prevention and management. J Feline Med Surg 11, 556-564

Roedler, F.S., Pohl, S. and Oechtering, G.U. (2013). How does severe brachycephaly affect dog's lives? Results of a structured preoperative owner questionnaire. Vet J 198, 606-610

Thiry, E., Addie, D., Belák, S., Boucraut-Baralon, C., Egberink, H., Frymus, T., Gruffydd-Jones, T., Hartmann, K., Hosie, M.J., Lloret, A., Lutz, H., Marsillo, F., Pennisi, M.G., Radford, A.D., Truyen, U. and Horzinek, M.C. (2009). Feline herpesvirus infection. ABCD guidelines on prevention and management. J Feline Med Surg 11, 547-555

EVALUATION OF HEALTH AND PRODUCTION RECORDING OF THE DAIRY CATTLE POPULATION IN GREAT BRITAIN

M. VELASOVA*, J.A. DREWE, J. GIBBONS, M. GREEN AND J. GUITIAN

SUMMARY

Effective surveillance of dairy cattle health is needed to identify new diseases, monitor the level at which current diseases are present and to support optimal disease control. Currently, there is no centralised recording of health and production information for dairy cattle populations in Great Britain. The aim of this project was to evaluate the usefulness of existing dairy cattle health recording systems as a national data resource. Identified recording systems were evaluated using an adaptation of the SERVAL surveillance evaluation framework. The results showed that the quality of recorded information varied between and within the systems depending on factors such as farmers' willingness to report and the quality of recordings made by the individual farmers or people involved in recording and data collection. The use of these data at national level appeared limited due to factors such as low participation, possible disease misclassification, low representativeness and generalizability.

INTRODUCTION

Animal health surveillance has become an important part of veterinary disease control (Doherr and Audige, 2001; O'Neill et al., 2014) and can be defined as "the systematic, continuous or repeated measurement, collection, collation, analysis, interpretation and timely dissemination of animal health and welfare related data from defined populations" (Drewe et al., 2015; Hoinville et al., 2013b). To protect animal and human health, good surveillance needs to be in place to allow appropriate actions to be taken to control any potential risks quickly and effectively (Drewe et al., 2015). The impact of animal disease on production, welfare and public health can be reduced through effective surveillance (Hoinville et al., 2013a). Depending on surveillance objectives, recording systems involved in data collection and recording can use active, passive or risk based approaches (Salman et al., 2003; Stark & Nevel, 2009). Each of them however comes with some limitations. For example, passive surveillance suffers from the issues of under-reporting, selection bias and long term sustainability (Stark & Nevel, 2009; Dorea et al., 2011; O'Neill et al., 2014). Information collected through active surveillance using for example, questionnaire data collection, can be of limited use due to issues such as low response rate, difficulties with data validity and recall bias (O'Neill et al., 2014).

In Great Britain (GB), dairy farming is well established and dairy production significantly contributes to overall agricultural production. It is therefore important that good quality information at national level is collected and available to support and inform continuous improvements in dairy cattle health and production. Currently, dairy cattle health surveillance

---

* Martina Velasova, Veterinary Epidemiology, Economics and Public Health Group, Department of Production and Population Health, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, AL9 7TA. Email: mvelasova@rvc.ac.uk

is carried out through a range of public and private organisations. The organisations involved may include cattle health schemes, government and private laboratories, milk recording companies, breeding and genetics companies. Each of these organisations can provide valuable information for individual farmers. The drawback is that these systems are not centralised, unlike in some other countries (Mork et al., 2010), and the use of the existing information can be constrained by its limited availability or access and therefore the often unknown quality and type of information recorded (Drewe et al., 2014). For these systems to be effective at national level, they should be representative of the whole dairy cattle population (O'Neill et al., 2014). Often limited access to recorded information can result in multiple recording of the same information by various systems. This increases the pressure on the use of more and more limited human and financial resources threatening the sustainability of such systems in the long term (Stark & Nevel, 2009; Dorea et al., 2011; O'Neill et al., 2014).

In GB, there has been lot of effort made to improve recording of dairy cattle health and production information. This can be demonstrated through the implementation of herd health plans by individual farmers (Main and Cartledge, 2000; Sibley, 2000) and through the implementation of strategies for effective surveillance and recording at national level, driven by the government and dairy industry (DEFRA, 2011; NFU, 2011). Despite these efforts, it has been reported that inconsistent standards in recording the same health even by individual farmers, preclude making herd level decisions (Kelton et al., 1998; LeBlanc et al., 2006; Wenz & Giebel, 2012). To maximise the use of existing data for health surveillance at a national level, the ideal data need to be representative of the dairy cattle population, the denominator population needs to be well defined and data must be accurate and reliable. Further, recording systems providing such data need to be sustainable, with limitations to any of these criteria creating biases in the data (Doherr & Audige, 2001; O'Neill et al., 2014). This further highlights the need for data systems to be validated to ensure their objectives are met and that they perform at optimal level (Salman et al., 2003; Stark & Nevel, 2009; Mork et al., 2010; Drewe et al., 2012). Due to factors such as limited access to the information recorded by existing data systems and a lack of literature reporting on the quality and type of data (Stark & Nevel, 2009; Drewe et al., 2014), their use as a national data resource is questionable. The aim of this project was therefore to evaluate the usefulness of existing dairy cattle health recording systems with respect to some important dairy health issues, at national level.

MATERIALS AND METHODS

Important dairy cattle health issues

Fifteen people representing the dairy industry and cattle health experts attended a workshop which was organised in April 2012 by the Royal Veterinary College to identify important health issues and relevant dairy cattle health recording systems that hold such information. During the workshop, the importance of the health issues was considered from the farmers and the industry point of view and included broad areas such as infectious diseases or metabolic conditions. In addition to the data sources identified during the workshop, a further search was carried out using the literature, public domains and later through discussions with colleagues and representatives from industry.

Evaluation protocol

A detailed evaluation protocol (Fig. 1), including a number of predefined criteria, was applied to ensure transparency and to facilitate its use in other settings.

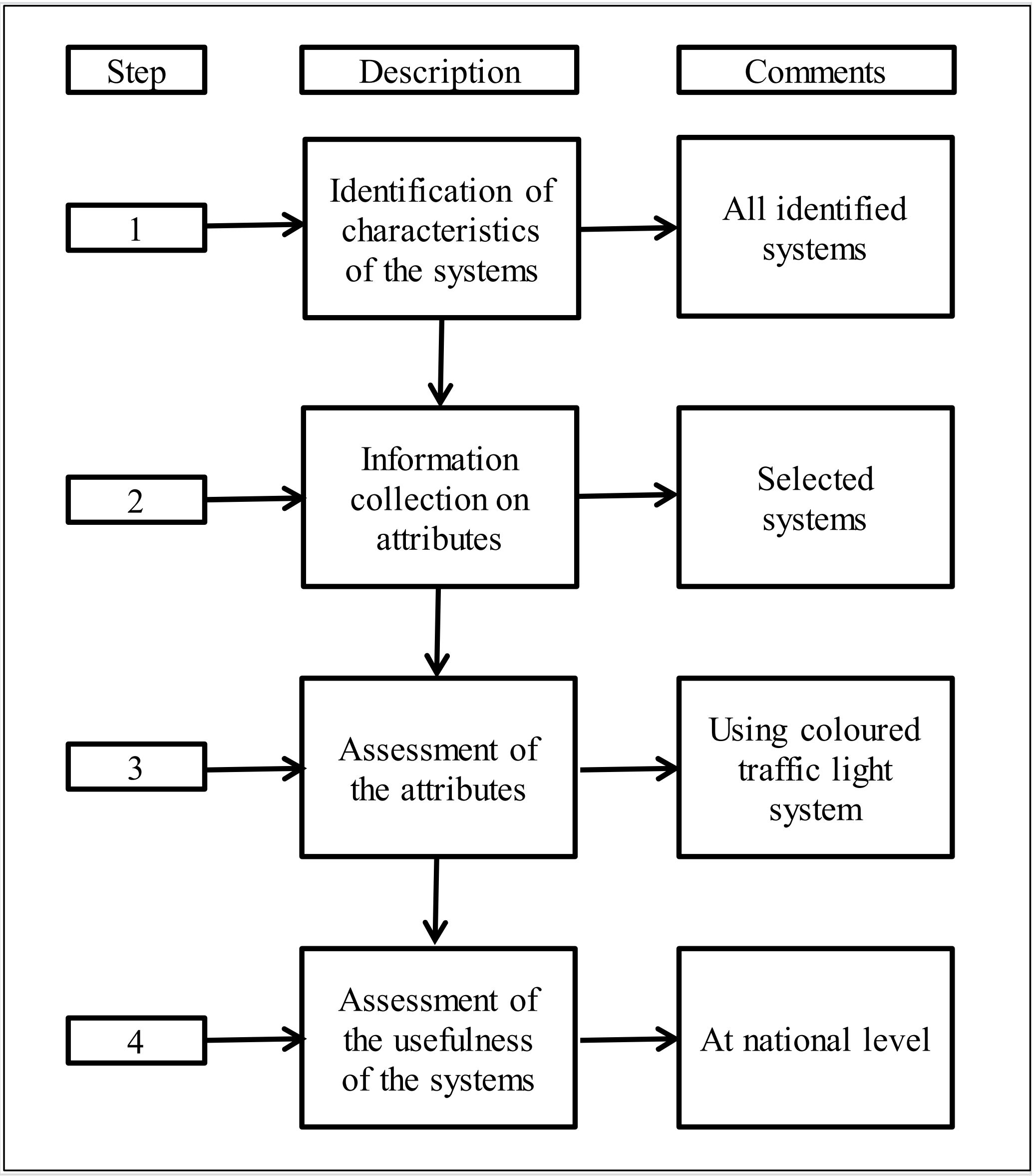


Fig. 1 Schematic illustration of the individual steps included in the evaluation protocol used to assess the usefulness of the relevant dairy cattle health and production recording systems at national level. Description and additional comments for each step are included.

Following the identification of a number of dairy cattle health recording systems, as a first step, all the systems were contacted and a number of their characteristics were established. They included amongst others, the frequency of recording, coverage and type of information recorded. The second step included collection of more detailed information on respective systems and the attributes that were later used for the evaluation. Strict selection criteria were however applied to the relevant systems prior to their inclusion in the second step. For example, the recording systems holding only secondary data were excluded from the full evaluation as it would be difficult to obtain information on attributes such as data collection and recording.

Evaluation of the recording systems

Following the second step, the systems were evaluated using a framework, which was based on the SERVAL surveillance evaluation framework (Drewe et al., 2015). The evaluation was carried out against a set of attributes which included amongst others, for example, data collection, data analysis and stability/sustainability of the recording systems. The individual attributes were assessed using a coloured "traffic light" system, as described in the SERVAL evaluation framework (Drewe et al., 2015). Two assessors were involved in the valuation in order to minimise a bias which could have been introduced by a single assessor and to ensure the validity of the assessment.

Assessment of the usefulness of the recording systems at national level

In order to assess the usefulness of recorded data at national level, individual characteristics of the evaluated systems and attributes such as representativeness, bias (for example: selection bias, misclassification bias) and stability of the recording systems were considered. Based on the outcomes of individual attributes assessment (using a coloured traffic light system), the usefulness of the recorded data at national level was assessed.

RESULTS

Important dairy cattle health issues and relevant recording systems

Conditions identified during the workshop included amongst others: Johne's diseases, bovine viral diarrhoea, salmonellosis, ketosis, milk fever, mastitis and lameness. Subsequently, the identified recording systems represented both private and public organisations such as: government and private laboratories, consulting companies, feed companies, health schemes, pharmaceutical companies and farm assurance schemes.

Evaluation of the recording systems

More than half of the relevant data holders provided the information on their systems as part of the first step of the evaluation. There were great variations between the systems in a number of areas including the geographical coverage, the number of farms and individual cows on which health information was recorded. Initial collection of the information on individual systems showed that both active and passive approaches were used for data collection and the recording of more than one type of information was common.

The majority of the systems recorded health and welfare information on dairy cows and approximately half of them recorded information on reproduction/fertility and on milk production, respectively (Fig. 2).

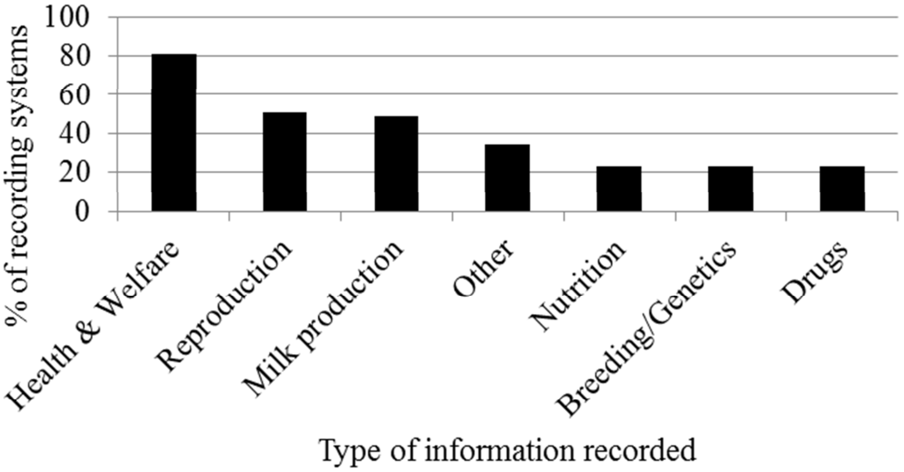


Fig. 2 Frequency of recording of different types of information by the individual recording systems. Presented information was obtained as part of the first step of the evaluation of the recording systems. The category 'Other' includes information such as financial statements, economic health outcome data, biosecurity and pedigree.

Of the systems that provided the information mentioned above, approximately half were eligible for the full evaluation. The use of bespoke databases was common, with most systems focused on individual farmers or producers as the main beneficiaries of the recorded information. Subsequently, only limited analysis of aggregated data was performed by these systems. Flexibility of the recording systems was a strong feature for majority of them. It appeared that the use of recorded data for health surveillance at national level would be constrained by factors such as participation, data quality, commercial value and missing data.

DISCUSSION

To protect animal and human health, effective disease surveillance needs to be well established (Drewe et al., 2015). For dairy cattle health surveillance to be effective, it requires good quality information to be available that is representative of the general dairy population (Doherr & Audige, 2001; O'Neill et al., 2014). This emphasises the need for validation of existing systems (Salman et al., 2003) to ensure that reliable information at national level is collected and available to monitor the frequency at which diseases are currently present, and to support and inform continuous improvements in dairy cattle health and production.

The aim of this study was to evaluate the usefulness of the existing dairy cattle health and production recording systems as a national data resource. Each of the evaluated systems showed some strength (i.e. ability to capture real time information and flexibility of the system) and weaknesses (i.e. low participation, under-reporting and missing data). Such weakness presented the main obstacles to effective use of the existing data for monitoring of disease frequency at national level.

A relatively high number of relevant recording systems relied on the information recorded by individual farmers. This information is prone to human error and misclassification of recorded diagnosis (Osteras et al., 2007) which highlights the need for good quality control being in place to ensure that data are accurate. The influence of the disease situation on individual farms and the different necessary means of their control, impact the completeness and overall quality of farm data (Gilbert et al., 2014). At individual farm level, the use of systems that are simple and easy to use should be prioritised to improve completeness and the quality of data. This would be of direct benefit to farmers.

The majority of the systems indicated recording of more than one type of information (Fig. 2). For example, recording of both cattle health and production information by the same system was common, suggesting a lack of integration of data from various sources and predominant use of primary data. This can put some of the systems at risk of not being sustainable in future due to more and more limited human and financial resources (Stark & Nevel, 2009; Dorea et al., 2011; O'Neill et al., 2014).

Collection of primary data allows better control over the type and quality of information collected and therefore is easier to validate (O'Neill et al., 2014). However, it has been reported that the use of secondary data would be more beneficial for surveillance due to factors such as: better representativeness, reduced bias, lower costs and reduced time associated with data collection (Sorensen et al., 1996; LeBlanc et al., 2006; Stark & Nevel, 2009; O'Neill et al., 2014). Better integration of data from multiple systems would therefore be beneficial as it can increase the denominator population, improve representativeness and thus provide valuable information for monitoring of disease trends at national level. It can further reduce the cost of disease surveillance, and increase the research potential of such data (Sorensen et al., 1996; O'Neill et al., 2014).

Similar to pig health monitoring systems used in England (Stark & Nevel, 2009), in this study, both active and passive approaches were used for data collection from the dairy cattle population. For example, both government and private laboratories used a mostly passive approach for data collection. The main limitation of these systems was under-reporting, difficulty to assess representation of the dairy cattle population and a lack of defined denominator population, which is essential in order to assess the frequency of health conditions at national level. On the other hand, their main strength was the use of valid case definitions which ensures a good diagnostic reliability and is essential for effective data analysis and interpretation (O'Neill et al., 2014). Systems, such as consulting companies used more active approaches for data collection, however they are likely to be biased as farmers' participation was voluntary.

Despite some limitations (i.e. quality of the evaluation depending on the quality of information provided by the data holders), the study results provide an improved knowledge on the usefulness of relevant recording systems as a national data resource. Such a resource could be used to inform current public and dairy industry initiatives to improve efficiency of the existing surveillance and data recording at national level. Some of the remaining challenges that will need to be overcome will include consolidating standards surrounding data recording and better integration of data from the existing systems.

ACKNOWLEDGEMENTS

We thank all the workshop participants for their knowledge and expertise of dairy cattle health and disease surveillance and for their help with identification of important health issues and relevant recording systems. We are grateful to all the respondents and data administrators who provided information on their recording systems; without their help this project would not be possible. The project was funded by DairyCo, a division of the Agriculture and Horticulture Development Board.

REFERENCES

DEFRA (2011). A Review of the implementation of the Veterinary Surveillance Strategy (VSS).www.gov.uk/government/uploads/system/uploads/attachment_data/file/69275/pb13568-vss-review-110204.pdf. Accessed September 12, 2014

Doherr, M.G. and Audige, L. (2001). Monitoring and surveillance for rare health-related events: a review from the veterinary perspective. Philos Trans R Soc Lond B Biol Sci. 356, 1097-1106

Dorea, F.C., Sanchez, J. and Revie, C.W. (2011). Veterinary syndromic surveillance: Current initiatives and potential for development. Prev. Vet. Med. 101, 1-17

Drewe, J.A., Hoinville, L.J., Cook, A.J., Floyd, T. and Stark, K.D. (2012). Evaluation of animal and public health surveillance systems: a systematic review. Epidemiol. Infect. 140, 575-590

Drewe, J.A., Hasler, B., Rushton, J. and Stark, K.D. (2014). Assessing the expenditure distribution of animal health surveillance: the case of Great Britain. Vet. Rec. 174, 16

Drewe, J.A., Hoinville, L.J., Cook, A.J., Floyd, T., Gunn, G. and Stark, K.D. (2015). SERVAL: A New Framework for the Evaluation of Animal Health Surveillance. Transbound Emerg Dis. 62, 33-45

Gilbert, W.H., Hasler, B.N. and Rushton, J. (2014). Influences of farmer and veterinarian behaviour on emerging disease surveillance in England and Wales. Epidemiol. Infect. 142, 172-186

Hoinville, L.J., Alban, L., Drewe, J.A., Gibbens, J.C., Gustafson, L., Hasler, B., Saegerman, C., Salman, M. and Stark, K.D. (2013a). Proposed terms and concepts for describing and evaluating animal-health surveillance systems. Prev. Vet. Med. 112, 1-12

Hoinville, L.J., Alban, L., Drewe, J.A., Gibbens, J.C., Gustafson, L., Häsler, B., Saegerman, C., Salman, M. and Stärk, K.D.C. (2013b). Proposed terms and concepts for describing and evaluating animal-health surveillance systems. Prev. Vet. Med. 112, 1-12

Kelton, D.F., Lissemore, K.D. and Martin, R.E. (1998). Recommendations for recording and calculating the incidence of selected clinical diseases of dairy cattle. J. Dairy Sci. 81, 2502-2509

LeBlanc, S.J., Lissemore, K.D., Kelton, D.F., Duffield, T.F. and Leslie, K.E. (2006). Major advances in disease prevention in dairy cattle. J. Dairy Sci. 89, 1267-1279

Main, D.C.J. and Cartledge, V. (2000). Farm assurance schemes – what is the veterinarian's role? In Pract 22, 335-339

Mork, M., Wolff, C., Lindberg, A., Vagsholm, I. and Egenvall, A. (2010). Validation of a national disease recording system for dairy cattle against veterinary practice records. Prev. Vet. Med. 93, 183 - 192

NFU (2011). Dairy Cow Welfare Strategy. http://www.dairyco.org.uk/technical-information/animal-health-welfare/dairy-cow-welfare-strategy/#.VHcJJ0ZybV0. Accessed June 17, 2014

O'Neill, D., Church, D., McGreevy, P., Thomson, P. and Brodbelt, D. (2014). Approaches to canine health surveillance. Canine Genet Epidemiol 1, 1-13

Osteras, O., Solbu, H., Refsdal, A., Roalkvam, T., Filseth, O. and Minsaas, A. (2007). Results and evaluation of thirty years of health recordings in the Norwegian dairy cattle population. J. Dairy Sci. 90, 4483 - 4497

Salman, M., Stark, K. and Zepeda, C. (2003). Quality assurance applied to animal disease surveillance systems. Rev Sci Tech 22, 689 - 696

Sibley, R.J. (2000). Planning health care on dairy farms. In Pract 22, 405-407

Sorensen, H.T., Sabroe, S. and Olsen, J. (1996). A framework for evaluation of secondary data sources for epidemiological research. Int. J. Epidemiol. 25, 435-442

Stark, K.D. and Nevel, A. (2009). Strengths, weaknesses, opportunities and threats of the pig health monitoring systems used in England. Vet. Rec. 165, 461-465

Wenz, J.R. and Giebel, S.K. (2012). Retrospective evaluation of health event data recording on 50 dairies using Dairy Comp 305. J. Dairy Sci. 95, 4699-4706

PREVALENCE, RISK FACTORS AND SPATIAL ANALYSIS OF LIVER FLUKE INFECTIONS IN DANISH CATTLE HERDS

T. HALASA*, A. OLSEN, R. BØDKER, N. TOFT AND K. FRANKENA

SUMMARY

Fasciola hepatica, a trematode parasite (liver fluke), infects a wide range of host species, including cattle. Fasciolosis is prevalent world-wide and causes economic losses to the livestock industry. Knowledge on prevalence, spatial distribution, and risk factors is needed to investigate the extent of the problem and to explore cost-effective strategies to control the disease. A retrospective study was performed using liver inspection data for the period 2011 to 2013. Spatial analysis was carried out, to investigate whether the infection was driven by local environmental factors. The association between herd level and environmental risk factors and prevalence of *F. hepatica* infection was evaluated. The per annum herd prevalence estimates for fasciolosis increased over the three years from 25.6% in 2011 to 28.4% in 2012 and 29.3% in 2013. Among herd factors, trading with infected herds was a risk factor on large organic dairy and in non-dairy conventional herd type holdings, and presence of environmental factors like streams, wetlands and pastures were significantly associated with the occurrence of fasciolosis.

INTRODUCTION

Liver fluke infection, also known as fasciolosis, is a world-wide prevalent parasitic disease infecting a wide range of host species including cattle, and causes considerable economic loss to the livestock industry (Kaplan, 2001). The disease is regarded as an emerging food-borne zoonosis (Slifko et al, 2000). The geographical distribution of *F. hepatica* is strongly linked to climate and environmental conditions that create a favourable environment for the development of free living fluke stages, and for the growth and reproduction of the intermediate host snail (*G. trunculata*) (Charlier et al., 2011; Relf et al., 2011). Humans become accidental hosts when they ingest contaminated water, aquatic vegetation or consume raw or undercooked liver products.

Infected cattle often suffer from chronic infection which is sub-clinical in nature and therefore animals are left undetected (Kaplan, 2001). In such a case, meat inspection data can serve as an important disease detection tool. However, for fasciolosis, meat inspection has poor sensitivity due to variability in disease detection between abattoirs (Hill et al., 2004). Since the probability of parasite detection is highly associated with severity of infestation, a herd level assessment of geographical areas would facilitate the effective control and implementation of risk based surveillance, taking into account the effect of false negatives.

There is growing evidence that the prevalence of fasciolosis in cattle in Europe is increasing (Sekiya et al., 2013). Despite the substantial economic and animal welfare effects

---

* Tariq Halasa, National Veterinary Institute, Technical University of Denmark, Bülowsvej 27, 1870 Frederiksberg C, Denmark. Email: tahbh@vet.dtu.dk

of the disease, up to date knowledge on its prevalence and risk factors related to its occurrence and distribution in Denmark are scarce. Therefore, the objective of this study was to estimate the prevalence of fasciolosis in the Danish cattle herd population and to identify and quantify potential risk factors at herd level that may help control the disease and improve cattle herd health, performance and welfare and also limit the risk of human liver fluke infection.

MATERIALS AND METHODS

Study design and data

The considered study period was 2011-2013 and all herds that slaughtered at least one bovine in these three years were included.

The ‘abattoir dataset’ included records of all cattle slaughtered in Denmark (n=1,499,417 originating from 19,593 herds). The 19,593 herds represented 82% of all herds registered as active herds during the study period (2011-2013).

The ‘herd information dataset’ held data about the composition (number of animals per age group) of all Danish cattle herds, recorded on the first day of the month since January 2005 (n=2,337,459 records originating from 23,859 herds). From this dataset, a herd-size variable (Small ≤ 30 animals, Medium < 100 animals, Large ≥ 100 animals) was determined by calculating summaries of the total number of animals in the included herds.

The ‘environment dataset’ included quantitative data on land cover within a zone of 500 metres around each farm (n= 22,092 farms) registered in the year 2000 (CORINE land cover vector database, 2000). All the environmental variables were categorized into binary variables, based on their presence or absence on the farms. In total 2,950 herds from the abattoir dataset were missing in the environment dataset.

The ‘trade dataset’ included information about movements of animals between herds and to the abattoirs. This dataset was combined with the abattoir dataset to create a trading with infected herds variable (Yes/No), which described whether or not a herd had traded with infected herds during the study period.

The ‘distance (kilometres) to the nearest positive neighbour for each herd’ dataset was created based on herd identification number, infection status and the geographical coordinates of the herd. This variable was used to adjust for spatial autocorrelation in herd infection status.

The final ‘herd level’ dataset was created by merging all the datasets to include information on 16,626 herds (out of 19,593) that were used for statistical analysis. In total 2,967 records were excluded due to missing information on environmental parameters, herd size or geographical coordinates. For herd level analysis, abattoirs (n=79) were categorized (A-H, Other) based on slaughterhouse preference, where most animals from each herd were sent for slaughter. However, for the herds that could not be categorized in this manner (n=326 herds), the most recently used slaughterhouse was chosen as the preferred slaughterhouse. The herd level dataset included information about farm and herd identification numbers, environmental variables, trade information, abattoir information, infection status, herd size, farm-type, production type, location of the herds (X and Y coordinates) and distance (kilometre) to the nearest positive neighbour for each herd.

Proportion of positive herds

The proportion of positives per annum was determined both at animal and herd level. The herd infection status was classified as positive when one animal from the herd tested positive for *F. hepatica* at the slaughterhouse during the three years, otherwise the herd was considered negative.

Spatial analysis

Spatial analysis was used to explore whether *F. hepatica* infection was clustered in space as this could help identify environmental factors driving infection. Both global and local spatial autocorrelation techniques were used to detect infected and non-infected herd clusters (Getis, 1991). Local mapping techniques were used to identify and map potential clusters.

Global spatial autocorrelation (clustering) of *F. hepatica* positive herds was quantified using two complementary spatial statistical methods; the global Moran's I and general G statistic in ArcGIS 10.1 Spatial Analyst software (Getis, 1991). For these methods, a dataset containing herd identification number, *F. hepatica* herd status (1=positive, 0=negative), and herd coordinates was extracted (n=19,591 observations). For both methods, an inverse Euclidean distance [(1/(Distance)^2] with a threshold value of 5000 meters between two neighbouring herds was selected. The global Moran's I was interpreted using Moran's Index value where an index value close to +1.0 indicated clustering while an index value near -1.0 indicated dispersion. The Z-score and P-value were used to evaluate the significance of Moran's Index. The general G statistic was interpreted relative to its expected value so that when G was larger than the expected value it suggested clustering of positive herds, and when G was smaller than the expected value it indicated clustering of negative herds. The Z test statistic was used for significance testing.

SatScan 9.3 was used for the detection and mapping of statistically significant (95% level) local clusters (Kulldorff, SatScan User Guide). A purely spatial scan statistic with the Bernoulli model was used to simultaneously scan for both high and low rate clusters (positive herds, n= 6,835, negative herds, n=9,791). The SatScan output was run to detect circular clusters on the map by selecting the circular spatial window without overlapping clusters and with a maximum radius of 50% of the population at risk in the settings window. Statistical significance was explored using 999 Monte Carlo replications.

From the SatScan output, relative risk (RR) and P-values were extracted and the clusters were categorized into hot spots ($RR>1.00$, $P\leq0.05$) and cold spots ($RR<1.00$, $P\leq0.05$) and mapped in ArcGIS Spatial Analyst software (version 10.1).

Analysis of risk factors

A risk factor analysis at herd level was performed using logistic regression in SAS (version 9.2). The outcome variable was a binary variable reflecting *F. hepatica* herd status (0= Negative, 1= Positive) during the study period (2011-2013). The predictor variables screened for association with *F. hepatica* infection were the herd level and environmental factors. Herd level factors included farm type (dairy vs. non-dairy), production type (organic vs. conventional), herd size, whether a herd bought animals or not, and whether a herd bought animals from an infected herd. The environmental factors included presence of streams, presence of wetlands, presence of pasture, and presence of cropland.

Herd and environmental categorical variables were first tested for all possible pairwise correlations. If a correlation coefficient was larger than 0.50, then the variable that would be biologically more plausible linked to *F. hepatica* was selected for further modelling. All the selected variables were then fitted into a multivariable model. A backwards-elimination procedure was used to simplify the initial model. Non-significant variables ($P > 0.05$, based on Wald Type III Chi square) were deleted sequentially, beginning with the variable showing the largest P-value. Variables were removed permanently from the model when they were not confounders; confounding was defined as a change in any remaining parameter estimate greater than 20% when compared to the previous model. This process of deleting, refitting and verifying was repeated until all variables in the model were either significant ($P<0.05$) or deemed a confounder. Next, biologically plausible interaction terms were added and retained when significant ($P < 0.05$). Furthermore, to account for the spatial autocorrelation not captured by the environmental variables in the model, the distance to the nearest positive neighbour for each herd was calculated and was treated as a fixed effect during model running, to add a spatial component to the model.

Herd infection status as predicted from the final risk factor model was compared with the observed status using a heat map to assess how well the model matched the observed spatial pattern.

RESULTS

During the study period, the per annum prevalence estimates for fasciolosis at herd level increased ($P< 0.001$, based on Wald Chi square). The estimates during 2011 to 2013 were 25.6% (4,271/16,683), 28.4% (4,506/15,867 herds) and 29.3% (4,492/15,331 herds), respectively.

A significant positive Moran’s I value suggested positive spatial autocorrelation for *F. hepatica* (Moran's I =0.12; Z= 4.39; $P < 0.05$). Additionally, the General G results revealed higher levels of clustering for infected herds than for non-infected herds (General G =0.00001; Z= 5.43; $P < 0.05$). The positive global clustering outcome of both methods suggested spatial autocorrelation of key risk factors.

The results from the circular scan showed that 6,126 herds were situated in hot spots where the RR for *F. hepatica* infection was 1.4; whereas 1,055 herds were situated in cold spots where the RR was 0.6. The plotting of hot spots on a map of Denmark revealed a strong overall spatial trend with a concentration of high RR for *F. hepatica* infection around the North and mid-Jutland region and in the Southern region of Denmark (Fig. 1). Plotting of cold spots revealed low RR for *F. hepatica* infection in the South Jutland, Funen Islands and Zeeland region.

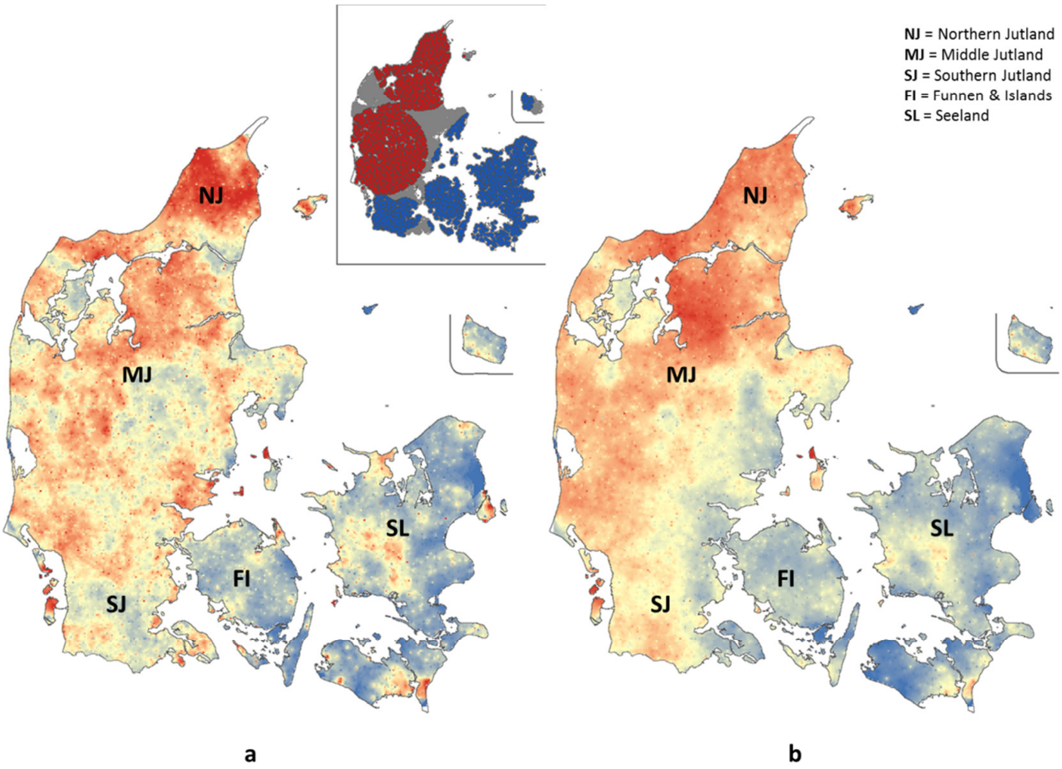


Fig. 1 Heat maps of observed (a) and predicted (b) status of *F. hepatica* infection in cattle herds, where areas coloured in red and blue indicate hot and cold spots. The insert shows a SatScan map of significant spatial local clustering of infected (red) and non-infected (blue) herds.

Buying animals from infected herds was strongly associated with fasciolosis (Table 1). Herd size was also a significant risk factor, in which medium and large herds had a higher risk of infection than small herds (Table 1). However, the effect of herd size was modified by farm type where the probability of being *F. hepatica* positive was high on large organic dairy and organic non-dairy herds (Table 1).

Among environmental variables, cropland, streams, wetlands and pastures showed a significant association with *F. hepatica* infection ($P < 0.05$, Table 1). The presence of streams, pasture and/or wetland increased the risk of fasciolosis in cattle herds (Table 1), however, the presence of croplands showed a negative association with fasciolosis (Table 1).

DISCUSSION

This study was performed to estimate the proportion of animals and herds that tested positive for *F. hepatica* infection at the slaughterhouse over the period 2011-2013. Additionally, risk factors were identified and quantified at herd level and the spatial variation of *F. hepatica* herd level infection in Denmark was explored further.

Table 1. Odds ratios together with the 95% confidence interval (CI) of variables retained in the final model which were associated with the presence of F. hepatica infection in Danish cattle herds, diagnosed by liver inspection during the period 2011 to 2013

Risk factor	Odds ratio (95% CI)
Herd size	
Large vs. small for organic non-dairy farms	6.85 (4.37-10.74)
Large vs. small for organic dairy farms	6.44 (4.38-9.47)
Medium vs. small for organic non-dairy farms	3.22 (1.90-5.48)
Medium vs. small for organic dairy farms	4.88 (3.16-7.55)
Large vs. medium for organic non-dairy farms	2.12 (1.37-3.30)
Large vs. medium for organic dairy farms	1.32 (0.85-2.05)
Large vs. small for conventional non-dairy farms	4.25 (3.18-5.67)
Large vs. small for conventional dairy farms	3.99 (3.43-4.65)
Medium vs. small, for conventional non-dairy farms	1.84 (1.32-2.55)
Medium vs. small, for conventional dairy farms	2.78 (2.52-3.07)
Large vs. medium for conventional non-dairy farms	2.31 (1.91-2.87)
Large vs. medium for conventional dairy farms	1.44 (1.22-1.69)
Herd type	
Organic vs. conventional for herd size small	1.20 (0.90-1.58)
Organic vs. conventional for herd size medium	2.10 (1.47-3.00)
Organic vs. conventional for herd size large	1.93 (1.47-2.54)
Organic vs. conventional for not buying from infected herds	1.20 (0.90-1.58)
Organic vs. conventional for buying from Unknown status	1.10 (0.64-1.88)
Organic vs. conventional for buying from infected herds	0.63 (0.39-1.01)
Production type	
Non-dairy vs. dairy for herd size small	1.23 (0.93-1.63)
Non-dairy vs. dairy for herd size medium	2.16 (1.28-3.64)
Non-dairy vs. dairy for herd size large	1.98 (1.25-3.15)
Buy animals from infected herds	
Yes vs. no for conventional farms	1.98 (1.20-3.24)
Unknown vs. no for conventional farms	0.86 (0.57-1.31)
Yes vs. NA for conventional farms	2.29 (1.27-4.13)
Yes vs. no for organic farms	2.16 (1.91-2.43)
Unknown vs. no for organic farms	1.64 (1.50-1.80)
Yes vs. NA for organic farms	1.31 (1.15-1.51)
Streams (present vs. absent)	1.18 (1.09-1.27)
Pastures (present vs. absent)	1.46 (1.26-1.68)
Wetlands (present vs. absent)	1.37 (1.27-1.47)
Cropland (present vs. absent)	0.42 (0.21-0.84)
Dryland (present vs. absent)	1.08 (1.00-1.16)

During the investigated period, per annum fasciolosis prevalence estimates increased at animal and herd level, confirming that *F. hepatica* infection in Danish herds is a growing problem as elsewhere in Europe (Sekiya et al., 2013). This rise in prevalence in recent years may be attributed to milder temperatures and wetter conditions, which affect the transmission of *F. hepatica* in host snails, thereby exposing grazing livestock to increased levels of infection (Fox et al., 2011; Relf et al., 2011).

Plotting of infected herds revealed a high proportion in North and mid-Jutland and the South East region of Denmark. In these regions, the relative risk for *F. hepatica* infection was high (1.4) and statistically significant ($P<0.05$). Herd density explains the high clustering of positive herds in the mid-Jutland region, where herd density was high (> 0.23 herds per kilometer^2) (Agger et al., 2010). In prevalence studies, herd density has been explored as a potential risk factor, because when herds are situated closer to each other, there is an increased risk of disease transmission between the herds (Ersbøll et al., 2008; Agger et al., 2010). Likewise, herd density can serve as a risk factor for transmission of *F. hepatica* infection, because the population of infected snails can expand and spread to nearby farms, which can consequently result in increased herd level prevalence. Spatial patterns also showed a large local clustering of infected herds in the North Jutland region where herd density is low (<0.07 to 0.23 herds per kilometer^2) suggesting that herd prevalence was not exclusively associated with herd density and that there may be local environmental, meteorological or other risk factors that could be driving the high herd prevalence.

The present study shows that buying cattle from positive herds was a significant risk factor for the presence of *F. hepatica* infection. Furthermore, the probability of being *F. hepatica* positive was high on large (≥ 100 cattle) organic dairy and non-dairy conventional farms when compared to small (< 30 cattle) and medium (≥ 30 < 100) sized farms. Information on transmission of *F. hepatica* infection through movement of animals between herds is currently lacking. However, inclusion of this risk factor is considered important in understanding disease transmission (Ersbøll et al., 2008). Moving an infected animal to an infection-free farm is a risk factor because infected cattle, if left untreated, will contaminate pastures during grazing. The risk of getting infected by trading animals from specifically large herds cannot be directly explained from the data; however, this effect is probably due to some underlying management factors that were not measured in this study.

ACKNOWLEDGEMENTS

We thank Jørgen Nielsen from the Danish Cattle Federation for providing the data for this study. We are grateful to Ms. Birgit Kristensen, DTU, for her help with the use of ArcGIS spatial analyst software. We are also thankful to Dr. Heidi Enemark, DTU and Professor Stig Thamsborg, from University of Copenhagen, for their valuable feedback.

REFERENCES

Agger, J.F., Christoffersen, A., Rattenborg, E., Nielsen, J. and Agerholm, J.S. (2010). Prevalence of *Coxiella burnetii* antibodies in Danish dairy herds. Acta Vet. Scand. 52, 5

Charlier, J., Bennema, S.C., Caron, Y., Counotte, M., Ducheyne, E., Hendrickx, G. and Vercruysse, J. (2011). Towards assessing fine-scale indicators for the spatial transmission risk of *Fasciola hepatica* in cattle. Geospat Health 5, 239-245

Ersbøll, A.K., Kähler, J., Pedersen, N.D., Thamsborg, S.M. and Larsen, M. (2006). Modelling spatial risk Factors for occurrence of *Fasciola hepatica* in Danish cattle: In proceedings of the 11th International Symposium on Veterinary Epidemiology and Economics, Cairns, Australia, Theme 4 - Tools & training for epidemiologists: Short oral presentation session, p 920.

Ersbøll, A.K. and Nielsen, L.R. (2008). The range of influence between cattle herds is of importance for the local spread of *Salmonella* Dublin in Denmark. Prev. Vet. Med. 84, 277-290

Fox, N.J., White, P.C.L., McClean, C.J., Marion, G., Evans, A. and Hutchings, M.R. (2011). Predicting impacts of climate change on *Fasciola hepatica* risk. PloS ONE 6, e16126

Getis, A. (1991). Spatial interaction and spatial autocorrelation: a cross product approach. Environment and Planning. London: PION Limited 1269-1277

Hill, A., Chriel, M., Jensen V.F, Vaarst, M., Stockmarr, A., Bruun, J. and Greiner, M. (2004). Use of existing surveillance data to detect welfare problems in Danish cattle: Report on International EpiLab Project 8- Danish Institute for Food and Veterinary Research (DFVF), Denmark

Kaplan, R.M. (2001). *Fasciola hepatica*: A review of the economic impact in cattle and considerations for control. Vet. Ther., 2, 40-50

Relf, V., Good, B., Hanrahan, J.P., McCarthy, E., Forbes, A.B. and Dewaal, T. (2011). Temporal studies on *Fasciola hepatica* in *Galba truncatula* in the west of Ireland. Vet. Parasitol. 175, 287-292

Sekiya, M., Zintl, A. and Doherty, M.L. (2013). Bulk milk ELISA and the diagnosis of parasite infections in dairy herds: a review. Ir. Vet. J. 3, 66-14

Slifko, T.R., Smith, H.V. and Rose, J.B. (2000). Emerging parasite zoonoses associated with water and food. Int. J. Parasitol. 30, 1379-1393

ZOONOSES AND ANTIBIOTIC RESISTANCE

ENHANCED DECISION-MAKING OF HPAI H5N1 IN DOMESTIC POULTRY IN ASIA: A COMPARISON OF SPATIAL MODELLING METHODS

K.B. STEVENS* AND D.U. PFEIFFER

SUMMARY

Risk maps are one of several information sources for designing risk-based disease surveillance systems. A comparison of three spatial modelling methods – boosted regression trees (BRT), maximum entropy (Maxent) and multicriteria decision analysis (MCDA) – showed how risk maps generated by the three methods all identified known highly pathogenic avian influenza (HPAI) H5N1 hotspots, although predictive accuracy varied between the models (BRT AUC 0.95, Maxent AUC 0.803 and MCDA AUC 0.743. Both the BRT and Maxent models showed density of domestic waterfowl accounted for approximately half of the variation in H5N1 occurrence, followed by proximity to rice-growing areas. Both the BRT and Maxent models showed that the highest probability of H5N1 occurrence was characterized by domestic waterfowl densities of greater than ~800 heads/km^2 and being within ~200 km of areas suitable for rice-growing. All three spatial modelling approaches provide the decision-maker with valuable information upon which to base disease control and surveillance measures.

INTRODUCTION

As financial and personnel resources become increasingly limited, risk-based disease surveillance and control measures provides an opportunity for optimising the use of these finite resources (Stark et al., 2006). Risk maps are one of several information sources for designing risk-based disease surveillance systems; others include estimating the level of disease risk and identifying important risk factors for disease (Pfeiffer et al., 2008a), all of which can be achieved through a range of spatial modelling approaches.

Spatial modelling methods can be divided into data- and knowledge-driven approaches (Pfeiffer et al., 2008b); while data-driven approaches can be further sub-divided based on whether the method requires both disease presence and (pseudo)absence data, presence-background data or presence-only data (Franklin, 2009). However, such methods become less applicable in situations when disease event details are unavailable or if a country has not yet detected a disease incursion; in such instances, knowledge-driven modelling methods (e.g. multicriteria decision analysis (MCDA) (Malczewski, 1999)) use current knowledge regarding the factors associated with disease occurrence as model inputs in order to identify areas suitable for disease occurrence (Pfeiffer et al., 2008b).

It is worth noting that although the terms pseudoabsence and background data are used interchangeably in many publications, they are not in fact equivalent (Peterson et al., 2011);

---

* Kim Stevens, Veterinary Epidemiology, Economics and Public Health Group, Dept. of Production and Population Health, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire, AL9 7TA. Email: kstevens@rvc.ac.uk

pseudoabsence data, an attempt to mimic true absence data, are sampled only from areas where the disease agent has not been detected while background data are sampled from the whole study area thereby attempting to characterize the environmental conditions that exist across the study area (Peterson et al., 2011). However, unless a broadly distributed species is very well sampled, there may be very little actual difference between the results of models based on background or pseudoabsence data (Peterson et al., 2011).

Presence-absence methods, in particular Bayesian and frequentist generalized linear mixed models (GLMM) have generally been the spatial modelling methods of choice and are acknowledged to be highly accurate (Franklin, 2009). However, a comprehensive comparison of 16 modelling methods of over 226 animal species from six regions of the world found that some of the newer methods, such as Maximum Entropy (Maxent) and boosted regression trees (BRT), outperformed the traditional statistical methods with regards to predicting species distribution (Elith et al., 2006). Although other comparative studies have focused on a single region or species, in general they support the improved performance of the novel methods (Segurado & Araujo, 2004, Prasad et al., 2006, Tsoar et al., 2007, Hernandez et al., 2008, Elith & Graham, 2009).

Depending on the type of absence data used to calibrate the model and the modelling method used, different regions of the potentially occupied ecological niche gradient will be modelled (Jimenez-Valverde et al., 2008, Sillero, 2011); simple presence-only methods (e.g. BIOCLIM (Busby, 1986) and HABITAT (Walker & Cocks, 1991)) model a version of the niche that more closely resembles the potential (Jiménez-Valverde et al., 2008) while complex statistical methods (e.g. generalized linear or additive models (GLM or GAM)), calibrated with true absence or pseudoabsence data, will describe something that more closely approximates the occupied niche (Jiménez-Valverde et al., 2008). Between these two situations lies that part of the potential-occupied niche gradient modelled by methods such as Maxent (Phillips & Dudík, 2008, Phillips, 2012) or Genetic Algorithm for Rule-set Production (GARP) (Stockwell & Peters, 1999) that calibrate the model with presence-background data (Jiménez-Valverde et al., 2008).

It is therefore very difficult to compare spatial modelling methods to determine a ‘gold standard’ approach based solely on predictive accuracy. The aim of this study was therefore to compare three spatial modelling methods, each requiring different data inputs – BRT (presence-pseudoabsence), Maxent (presence-background) and MCDA (knowledge-driven) – with a view to determining the usefulness of each approach to decision makers with respect to predictive accuracy, identification of disease risk factors and identification of areas and populations a risk.

MATERIALS AND METHODS

Study area

The study area included all countries in Southern, Eastern and Southeastern Asia as defined by the United Nations Geoscheme (accessed March 2010: http://millenniumindicators.un.org/unsd/methods/m49/m49regin.htm).

Identifying relevant continent-level risk factors

The systematic review published by Gilbert & Pfeiffer (2012) was used to identify continental-level risk factors associated with occurrence of H5N1 in domestic poultry in Asia for use in all spatial models, and to define the relationship between individual risk factors and disease occurrence for the MCDA model. Variables were selected for inclusion in the spatial models provided they met the following criteria: (i) able to be mapped, (ii) the relevant spatial layer was available in the public domain at a sufficiently high resolution to differentiate within-country heterogeneity (i.e. socio-economic factors that are generally reported at country level would not have been included), (iii) reflected broad causal relationships at a continental scale rather than be country-specific (i.e. have been identified to be of importance in more than one country), and to have been (iv) repeatedly identified to be (v) significantly ($p < 0.05$) associated with H5N1 occurrence. Six variables met all these criteria and were also identified by Gilbert & Pfeiffer (2012) as being the most important for H5N1 occurrence namely, density of domestic waterfowl (WfowlDen), chickens (ChickDen) and humans (PopDen) together with proximity to open water (ProxWater), roads (ProxRoads) and areas suitable for rice-growing (ProxRice).

Data collection and generation of spatial risk factor data layers

Spatial risk factor data: The necessary digital spatial data layers were sourced primarily from the public domain. Human population density was obtained from Gridded Population of the World v3 (Center for International Earth Science Information Network (CIESIN), 2005). Chicken and domestic waterfowl densities for the study area were extracted from spatial data layers created, and kindly provided by, Prosser et al. (2011) and van Boekel et al. (2011). Location of open water was extracted from VMap0 Perennial Water Courses (Rivers) of the World and the location of primary and secondary roads (as defined by the was extracted from VMap0 Roads of the World, both available from the Food and Agricultural Organization's (FAO) GeoNetwork website (http://www.fao.org/geonetwork/srv/en/main.home). Location of areas suitable for rice growing were extracted from Suitability for Rain-fed and Irrigated Rice (High Input) available from the GeoNetwork website. For the three 'proximity to' spatial data layers, raster layers showing Euclidean distance to the nearest feature of interest were generated for inclusion in the model and all raster layers were resampled to a resolution of 5 km^2. ArcGIS 9.2 (ESRI. Redlands, CA: Environmental Systems Research Institute) was used for all visualization and manipulation of spatial data.

HPAI H5N1 outbreak data: Locational point data on all confirmed H5N1 outbreaks in domestic poultry in Asia between January 2004 and October 2010 ($n = 10104$) were extracted from FAO's Emergency Prevention Program for Transboundary Animal Diseases (EMPRES-i) database. All duplicate locations were removed from the dataset and when more than one disease point occurred in any $5km^2$ cell, only one was retained per cell leaving a total of 3690 disease points.

Pseudoabsence data: These data were randomly generated within the following constraints to provide a representative sample of the available areas without H5N1 outbreaks in domestic poultry: (i) being > 5.1 km from a disease presence point (i.e. presence and pseudoabsence points could not occur in the same cell), (ii) being > 5.1 km from another pseudoabsence point to ensure that there was never more than one pseudoabsence point per cell and (iii) having a PopDen > 1 head/km2 (i.e. to exclude unpopulated desert and mountainous areas which would be unsuitable for poultry production). Ten thousand points were considered sufficient to represent all environmental conditions in the study area.

Spatial modelling of HPAI H5N1

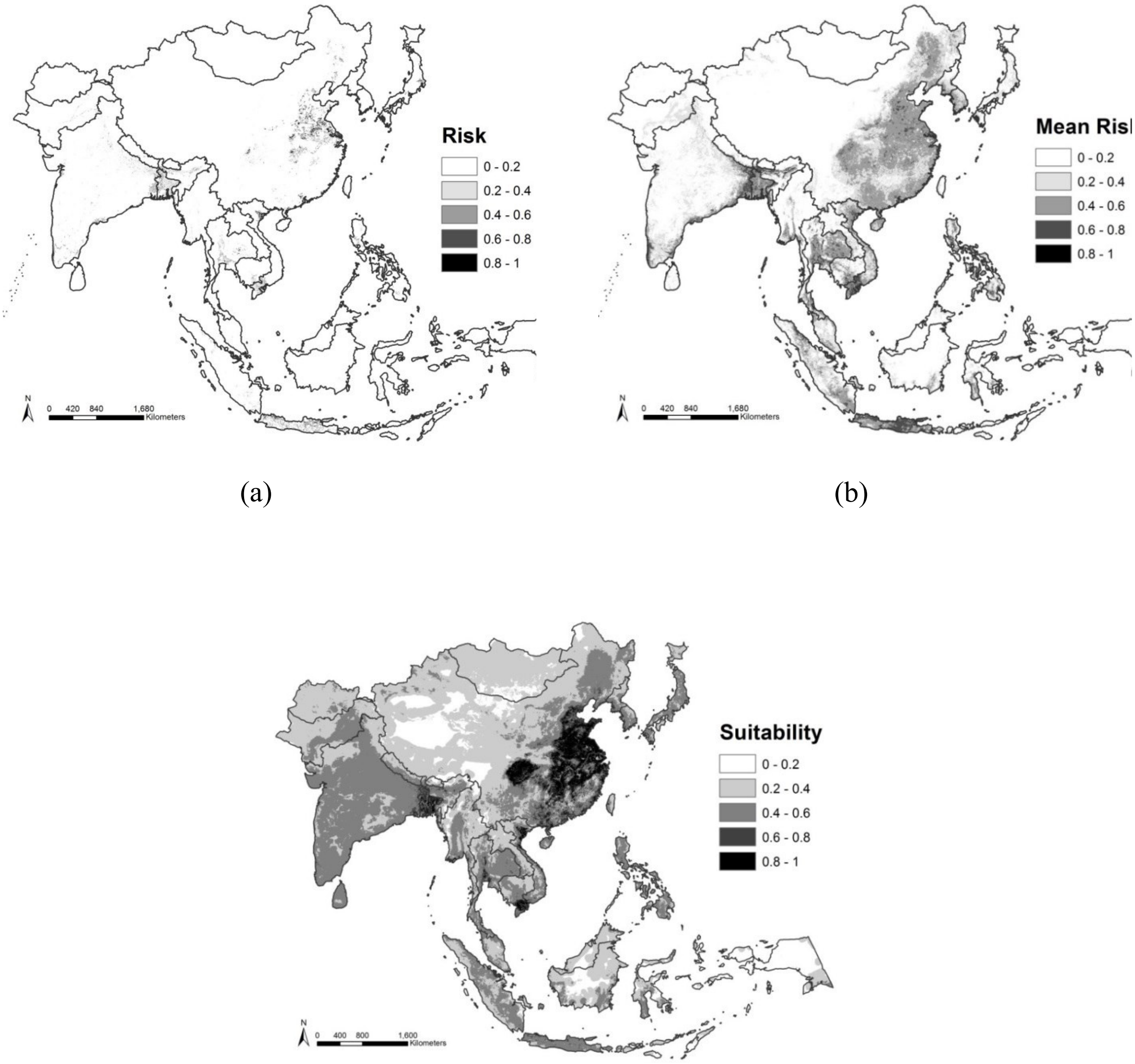
Multicriteria decision analysis (MCDA): Fuzzy membership functions illustrating the hypothesized relationship between each risk factor and H5N1 occurrence were produced from a review of the relevant literature. Risk factor weights were generated using the analytical hierarchy process's (Saaty, 1990) pairwise comparison matrix, and combined with the associated spatial data layers using weighted linear combination to produce a map identifying areas suitable for H5N1 occurrence. Suitability was expressed on a continuous scale ranging from 0 (lowest suitability) to 255 (highest suitability). The IDRISI software's (Clark Labs, Clark University, Worcester MA, USA) RANK module, which applies a simple choice heuristic, was used to rank-order all raster cells and the resulting map was divided by the maximum rank thereby generating a map showing the probability of cells being suitable for H5N1 occurrence, relative to the highest suitability ranking (Eastman, 1997, Malczewski, 2000). The map was validated using the receiver operating characteristic (ROC) curve area under the curve (AUC), against the H5N1 outbreak data and the randomly generated pseudoabsence data (see Stevens et al. (2013) for additional details of the MCDA modelling process).

Maximum Entropy (Maxent): The optimum combination of variables for inclusion in the model was determined using ENMTools' (Warren et al., 2010) model selection procedure and the automated jack-knifing process of Maxent v3.3.3k (Phillips et al., 2006). The 3690 raster cells with H5N1 outbreaks were input as the disease presence localities and background locations (n = 10 196) were randomly generated by the Maxent software. Ten model replicates of that model were run, each using cross-validation and a random partitioning of the training and test data. The resulting raster maps from the ten replicates were averaged to determine the likelihood of H5N1 occurrence in each raster cell relative to the other cells in the study area and the final map was presented using Maxent's logistic output format in order to show probability of disease presence. The permutation importance of each predictor variable to the model was calculated by randomly permuting the values of each variable among the training points and measuring the resulting decrease in training AUC; a large decrease indicated that the model was heavily reliant on that variable. Values were normalized to percentages. Response curves describing the probability of disease presence in relation to the different values of each predictor variable were generated by producing a model using only the variable in question. A ROC curve of sensitivity versus fractional predicted area (i.e. the fraction of the total study area predicted suitable for H5N1) was constructed and the AUC determined as an indicator of the predictive ability of the model. Fractional predicted area was used in the ROC curve instead of the conventional fraction of absences predicted present as no absence data was available (Phillips et al., 2006).

Boosted regression trees (BRT): Based on Huberty's (1994) formula for the optimal partitioning of data, the dataset was divided into training and testing datasets containing observations in the ratio of 69:31. The BRT model was built using the gbm package in R together with the cross-validation stepwise function presented by Elith and co-workers (2008). The model was defined using a tree complexity of 5, learning rate of 0.005 and a bag fraction of 50%. The relative contribution of each variable in predicting the presence/absence of H5N1 was determined, together with the general trends displayed by each variable. Model validity was determined using the test dataset and the ROC AUC.

RESULTS

Mapping the suitability of Asia for occurrence of H5N1 in domestic poultry



(a) (b)

(c)

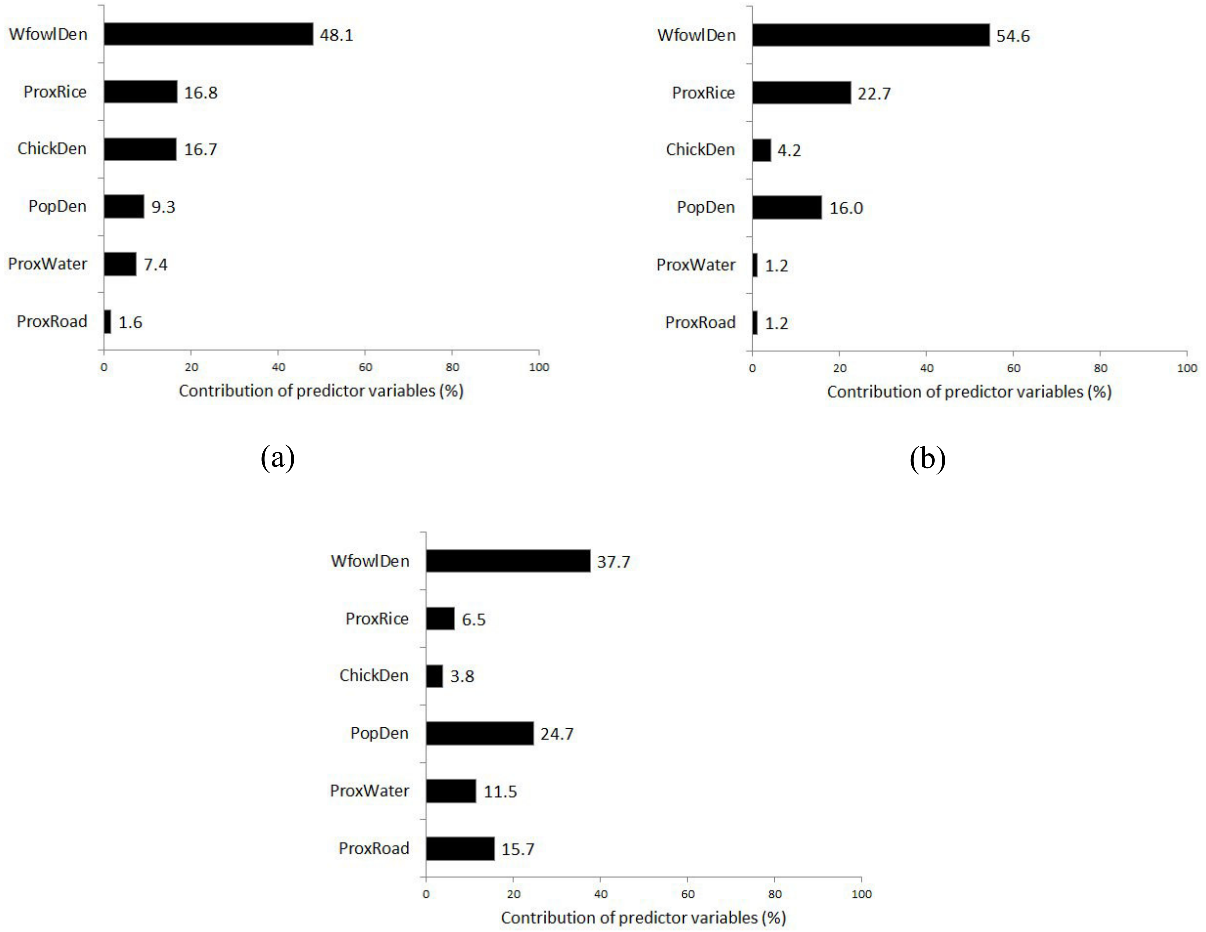
Fig. 1 Map illustrating the probability of highly pathogenic avian influenza (HPAI) H5N1 presence in domestic poultry in Asia as determined by different spatial modelling methods: (a) boosted regression trees (BRT), (b) maximum entropy (Maxent) and (c) multicriteria decision analysis (MCDA)

The risk maps generated by the three modelling methods all identified known H5N1 hotspots – Bangladesh, Java, southern and northern Vietnam - as areas of highest risk for occurrence of H5N1 in domestic poultry (Fig. 1), although in all instances, the BRT model assessed the level of risk in these areas, to be higher than the Maxent model (0.8-1 versus 0.6-0.7).

Despite this difference in order of magnitude, to a large extent the BRT and Maxent risk maps mirrored each other with both showing similar localised areas of high risk. The MCDA map (Fig. 1c), on the other hand, displayed a more diffuse pattern of risk throughout Asia, highlighting India, Sumatra and most of eastern China as areas of moderate risk for H5N1 occurrence.

Predictive accuracy varied between the models with the BRT model having the highest (AUC 0.95) followed by the Maxent (AUC 0.803) and MCDA (AUC 0.743) models.

Risk factors for occurrence of H5N1 in domestic poultry in Asia



(a) (b)

(c)

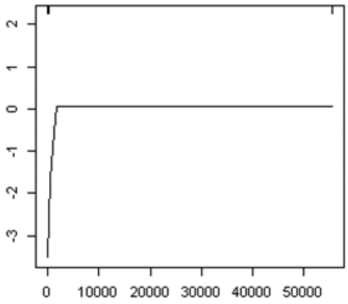
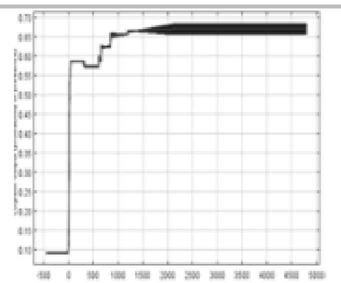
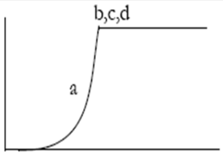
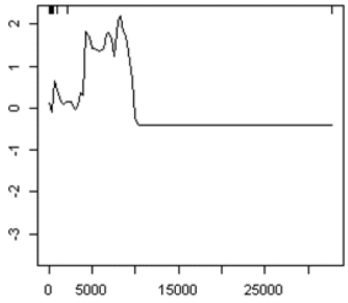
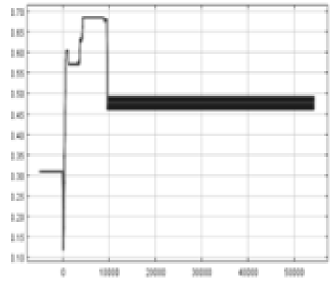
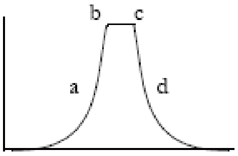
Fig. 2 Percentage contribution of modelled risk factors to occurrence of highly pathogenic avian influenza (HPAI) H5N1 in domestic poultry in Asia as determined by different spatial modelling methods: (a) boosted regression trees (BRT) and (b) maximum entropy (Maxent). (c) Risk factor weights used in the multicriteria decision analysis (MCDA) model as determined by the pairwise comparison method of the analytical hierarchy process

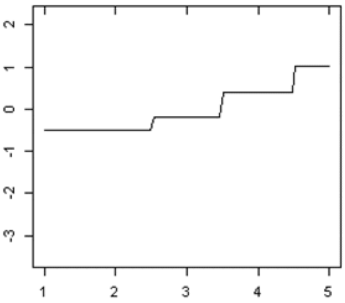
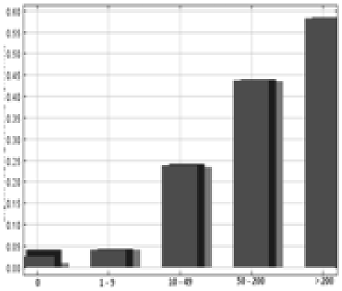
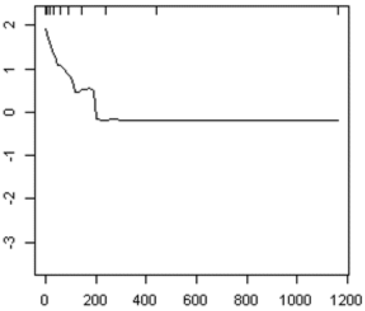
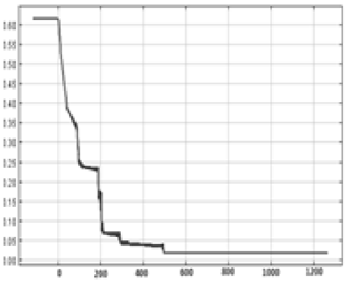
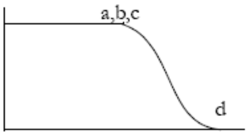
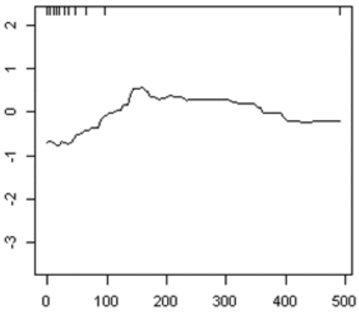
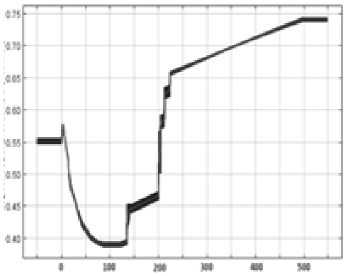
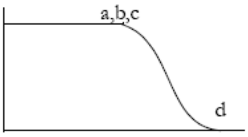
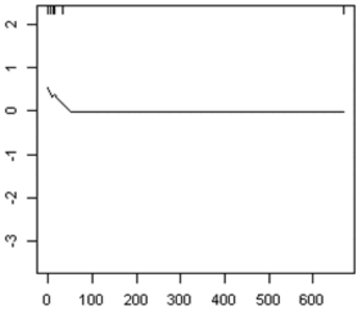
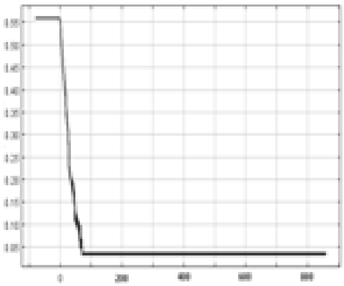
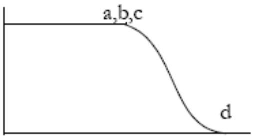
Both the BRT and Maxent models showed density of domestic waterfowl accounted for approximately half the variation in H5N1 occurrence, followed by proximity to rice-growing areas (Fig. 2a and b); together these two risk factors accounted for between two-thirds (BRT) and three-quarters (Maxent) of the variation in H5N1 occurrence. Both models were in agreement that proximity to roads and water contributed very little to H5N1 occurrence but disagreed over whether chicken or human density was the third most important factor determining distribution of occurrence. However, the relative importance of the various risk factors input for the MCDA model (as determined by the pairwise comparison matrix of the analytical hierarchy process) were almost the opposite to those produced by the BRT and Maxent models; although density of domestic waterfowl received the highest weighting, proximity to rice and chicken density received the lowest weightings.

Response curves for the risk factors

Both the BRT and Maxent models showed that the highest probability of H5N1 occurrence was characterized by domestic waterfowl densities of greater than ~800 heads/km^2, high human densities (>200 heads/km^2), medium chicken densities (4000-10 000 heads/km^2), and being within ~60 km of a road, within ~200 km of areas suitable for rice-growing and between 150 and 180 km (BRT) and 220 and 500 km (Maxent) from open water (Table 1).

Table 1. Response curves describing probability of highly pathogenic avian influenza (HPAI) H5N1 presence in relation to the different values of each predictor variable in the final boosted regression trees (BRT) and maximum entropy (Maxent) models together with the fuzzy sets used as inputs in the multicriteria decision analysis (MCDA) model

Risk factors	Spatial modelling method		
	Boosted regression tree (BRT)[a]	Maximum entropy (Maxent)[a,c]	Multicriteria decision analysis (MCDA)[b]
WfowlDen			 a=500, b,c,d= 1000
ChickDen			 a=250, b=500, c=5000, d=10000

Risk factors	Spatial modelling method		
	Boosted regression tree (BRT)[a]	Maximum entropy (Maxent)[a,c]	Multicriteria decision analysis (MCDA)[b]
PopDen			linear
ProxRice			 a,b,c=5, d=10
ProxWater			 a,b,c=5, d=10
ProxRoad			 a,b,c=5, d=60

[a] Response curves produced as <u>outputs</u> from the BRT and Maxent models

[b] Fuzzy membership curves used as <u>inputs</u> for the MCDA model

[c] The Maxent response curves show the averaged response of the ten model.

DISCUSSION

Areas of highest risk for H5N1 occurrence

The risk maps generated by all three methods reliably identified known H5N1 hotspots as high-risk areas. In particular, the BRT and Maxent risk maps mirrored each other with both showing similar localised areas of high risk whereas the MCDA map displayed a more diffuse pattern of risk. Although our models differ to those of previous studies with respect to extent and resolution (Pfeiffer et al., 2007, Fang et al., 2008, Gilbert et al., 2008, Hogerwerf et al., 2010, Martin et al., 2011) which precludes direct comparison (Lobo et al., 2008), in general all three of our models showed good, broad visual agreement with previous studies (Pfeiffer et al., 2007; Gilbert et al., 2008; Martin et al., 2011), in particular in the identification of disease hotspots. However, there was poor visual agreement between this model and that of Fang et al. (2008) whose predictions of high risk areas in mainland China were far more extensive than those of our models. Other studies (Hogerwerf et al., 2010; Martin et al., 2011) limited their study areas to regions suitable for poultry production in order to exclude areas such as the desert regions of Inner Mongolia and Tibet; these areas were all predicted to be high risk for H5N1 occurrence by Fang et al. (2008) even though they do not allow for the maintenance and transmission of H5N1, suggesting that our models more accurately represent the ecological niche of H5N1 than that of Fang et al's (2008) and through their identification of H5N1 hotspots, provide decision markers with a valuable tool for targeting disease control and surveillance measures at areas of highest disease risk.

Unlike the BRT and Maxent risk maps, the MCDA map showed most of India and large parts of eastern China to be moderately to highly suitable for the occurrence of HPAI H5N1, despite these regions having experienced few outbreaks. In China, this discrepancy may be due to a combination of mass vaccination and under-reporting while in India it may be the result of the prevailing semi-arid climate and relatively low domestic waterfowl density (J. Otte, pers. comm.). In addition, WLC allows the low values of one risk factor to be compensated for by high values of another, and although India has a low domestic waterfowl density they have an extensive road network. The risk factor ProxRoad may have therefore contributed largely to India receiving a moderately high suitability rating for HPAI H5N1 occurrence but the low domestic waterfowl density and semi-arid climate preclude a high disease incidence. Furthermore, this suggests that the occurrence of HPAI H5N1 in this part of Asia may be under-reported as the extensive road network, together with its proximity to Bangladesh, implies that the area is likely to have been exposed to the virus yet has few reported outbreaks.

However, while the maps highlight areas that that may be useful for targeted surveillance, it is not sufficient to know only *areas* of highest risk but also which *populations* are at highest risk.

Identification of populations at risk

Both the BRT and Maxent models showed density of domestic waterfowl accounted for approximately half the variation in H5N1 occurrence, followed by proximity to rice-growing areas; together these two risk factors accounted for between two-thirds (BRT) and three-quarters (Maxent) of the variation in H5N1 occurrence. The third factor of importance varied between the models; chicken density (BRT) or human density (Maxent). Although earlier studies have repeatedly shown each of these factors to be independently associated with H5N1 (Gilbert et al., 2006, Pfeiffer et al., 2007, Fang et al., 2008, Gilbert et al., 2008, Ward et al., 2008, Minh et al., 2009, Loth et al., 2010, Paul et al., 2010, Martin et al., 2011) and a similar combination of variables - duck abundance, human population density and rice-cropping intensity – was identified as the main drivers of H5N1 occurrence in the 2004-05 epidemics waves in Thailand and Vietnam (Gilbert et al., 2008), it has previously proved difficult to quantify the contribution of each variable to H5N1 occurrence leading to speculation as to which of the three variables was the main driver of disease distribution in Asia (Gilbert et al., 2008). The results of this study however appear to confirm the central role played by domestic waterfowl in the broad-scale distribution of H5N1 in Asia, together with the supporting roles of rice-growing and human or chicken densities. However, it is important to bear in mind that although much of H5N1 occurrence in Asia may conform to this pattern, there may well be areas where local effects override these broad patterns. For instance, domestic backyard ducks were not found to be significantly associated with the presence of H5N1 in Indonesia, where disease spread and persistence has instead been shown to be driven largely by a combination of chickens and humans rather than the typical duck-rice synergy (Gilbert et al., 2008, Loth et al., 2011).

Probability of H5N1 occurrence increased sharply with increasing domestic waterfowl density up to approximately 1200 heads/km^2 and plateaued thereafter suggesting that producers with medium and large sized flocks pose the greatest risk. However, possibly more important are the very high levels of risk associated with even low densities of domestic waterfowl possibly highlighting the fundamental role these birds play as reservoirs for the virus.

Knowledge- versus data-driven models

Despite the fact that it is not restricted by the need for data, MCDA has been used infrequently in the animal health field (Clements et al., 2006, Clements et al., 2007, Rakotomanana et al., 2007). Two reasons for this may be (i) the subjectivity associated with the approach and (ii) the common assumption that knowledge-driven models are inferior to data-driven approaches.

Although we tried to eliminate subjectivity by selecting and weighting risk factors based on the number of times each has been reported in the scientific literature, together with the level of statistical significance achieved (an approach used initially by Clements et al. (2006)), a comparison of the risk factor weights and the fuzzy membership functions used as inputs for our MCDA model with the percentage contributions and individual response curves generated by the BRT and Maxent models revealed a number of important discrepancies. Firstly, although fuzzy membership functions and response curves generally followed the same shape, the point-of-inflexion values frequently differed. Secondly, relative weighting of the six risk factors was very different to the percentage contributions generated by the BRT and Maxent models; although density of domestic waterfowl was the most important risk factor in all models, proximity to rice-growing areas and chicken density received the lowest weights which was at variance to the BRT and Maxent models where those risk factors were amongst the main drivers of H5N1 occurrence. Thus, the approach used here does not appear to eliminate all subjectivity and has the added disadvantage of being heavily dependent on the results of previous studies for the identification and weighting of risk factors and thus, as our knowledge of the disease grows, the risk factors, relationships and weightings included in the model will inevitably be subject to change. The alternative is to take advantage of the strong participatory element of the method and involve a range of stakeholders in the modelling process thus bringing together different points of view.

However, despite the seeming inaccuracies in the MCDA model inputs, model validation using disease presence and pseudoabsence data produced a ROC AUC of 0.743 (95 % CI 0.740 – 0.745) which challenges, to some extent, the assumption of inferiority of this method. In other words, a continental-level distribution map with fair predictive accuracy was produced without using data to fine-tune the model parameters which suggests it could be a useful modelling approach for decision-makers in situations where disease event details are unavailable (e.g. if a country has not yet detected a disease incursion).

Boosted regression trees versus maximum entropy

To a large extent the BRT and Maxent risk maps mirrored each other with both showing comparable localised areas of high risk although in all instances the BRT model assessed the level of risk in these areas to be higher than the Maxent model. In addition the BRT model had a higher predictive accuracy than the Maxent model (AUC 0.95 and 0.803 respectively). The lower AUC of the Maxent model could be the result of calibrating the model with background rather than pseudoabsence data. By using background data - sampled from the whole study area (i.e. all cells are included in the sampling frame including those where the species is known to be present) - as opposed to sampling only from areas where the disease agent has not yet been detected (i.e. presence cells are excluded from the sampling frame) (Peterson et al., 2011), the Maxent model lends itself to reduced sensitivity. These results contrast with those of Elith et al's (2006) comparative study of modelling methods where both the BRT and Maxent models had similarly high AUC values (~0.72 and 0.725). However, that study used background data to calibrate both models, rather than calibrating the BRT model with pseudoabsence data and the Maxent model with background data.

However, by using background and psueodoabsence data, the two approaches are essentially modelling different regions of the potential-occupied ecological niche gradient (Jimenez-Valverde et al., 2008; Sillero, 2011) with the BRT approach modelling a niche that more closely approximates the occupied than the Maxent model. Therefore, although the BRT model has a higher AUC and thus appears to be the 'better' model, the choice of model will ultimately depend on what part of the ecological niche we are attempting to model which hinges on the research question.

CONCLUSION

All three spatial modelling approaches have the potential to provide the decision-maker with valuable information upon which to base disease control and surveillance measures, particularly with respect to areas of both high and low risk for disease occurrence. The BRT and Maxent models identified important risk factors of H5N1 occurrence to be medium-to-high domestic waterfowl density and proximity to areas suitable for rice-growing. Such information could be used to design a surveillance strategy targeting regions with these characteristics. In addition, this study has also shown that it is possible to model the continental-level risk of H5N1 occurrence in domestic poultry with a fair degree of predictive accuracy using only knowledge of the relationship between key risk factors and H5N1 occurrence and has highlighted the value of MCDA as a practical tool for synthesizing knowledge of a disease.

REFERENCES

Busby, J. (1986). A biogeographical analysis of Nothofagus cunninghamii (Hook.) Oerst. in southeastern Australia. Aust. J. Ecol. 11, 1-7

Center for International Earth Science Information Network (CIESIN), C.U.a.C.I.d.A.T.C., (2005). Gridded Population of the World Version 3 (GPWv3): Population Density Grids. Palisades, NY: Socioeconomic Data and Applications Center (SEDAC), Columbia University. Available at http://sedac.ciesin.columbia.edu/gpw., NY

Clements, A.C.A., Pfeiffer, D.U. and Martin, V. (2006). Application of knowledge-driven spatial modelling approaches and uncertainty management to a study of Rift Valley fever in Africa. Int. J. Health Geog. 5, 57-69

Clements, A.C.A., Pfeiffer, D.U., Martin, V., Pittliglio, C., Best, N. and Thiongane, Y. (2007). Spatial risk assessment of Rift Valley fever in Senegal. Vector Borne Zoonotic Dis. 7, 203-216

Eastman, J.R. (1997). GIS and uncertainty management: new directions in software development. Lurralde 20, 53-66

Elith, J., Graham, C., Anderson, R., Dudik, M., Ferrier, S., Guisan, A., Hijmans, R., Huettmann, F., Leathwick, J., Lehmann, A., Li, J., Lohmann, L., Loiselle, B., Manion, G., Moritz, C., Nakamura, M., Nakazawa, Y., Overton, J., Peterson, A., Phillips, S., Richardson, K., Scachetti-Pereira, R., Schapire, R., Soberon, J., Williams, S., Wisz, M. and Zimmermann, N. (2006). Novel methods improve prediction of species distributions from occurrence data. Ecography 29, 129-151

Elith, J. and Graham, C.H. (2009). Do they? How do they? WHY do they differ? On finding reasons for differing performances of species distribution models. Ecography 32, 66-77

Elith, J., Leathwick, J.R. and Hastie, T. (2008). A working guide to boosted regression trees. J. Anim. Ecol. 77, 802-813

Fang, L.-Q., de Vlas, S.J., Liang, S., Looman, C.W.N., Gong, P., Xu, B., Yan, L., Yang, H., Richardus, J.H. and Cao, W-C. (2008). Environmental factors contributing to the spread of H5N1 avian influenza in mainland China. PLoS ONE 3, e2268

Franklin, J. (2009). Species distribution modelling. Mapping Species Distributions: Spatial Inference and Prediction. Oxford University Press, New York, 3-20

Gilbert, M., Chaitaweesub, P., Parakamawongsa, T., Premashthira, S., Tiensin, T., Kalpravidh, W., Wagner, H. and Slingenbergh, J. (2006). Free-grazing ducks and highly pathogenic avian influenza, Thailand. Emerg. Infect. Dis. 12, 227-234

Gilbert, M. and Pfeiffer, D. (2012). Risk factor modelling of the spatio-temporal patterns of highly pathogenic avian influenza (HPAIV) H5N1: a review. Spat. Spatio-temporal Epidemiol. 3, 178-183

Gilbert, M., Xiao, X., Pfeiffer, D., Epprecht, M., Boles, S., Czarnecki, C., Chaitaweesub, P., Kalpravidh, W., Minh, P. and Otte, M. (2008). Mapping H5N1 highly pathogenic avian influenza risk in Southeast Asia. Proceedings of the National Academy of Sciences, USA 105, 4769-4774

Hernandez, P., Franke, I., Herzog, S., Pacheco, V., Paniagua, L., Quintana, H., Soto, A., Swenson, J., Tovar, C., Valqui, T., Vargas, J. and Young, B. (2008). Predicting species distributions in poorly-studied landscapes. Biodivers. Conserv. 17, 1353-1366

Hogerwerf, L., Wallace, R., Ottaviani, D., Slingenbergh, J., Prosser, D., Bergmann, L. and Gilbert, M. (2010). Persistence of highly pathogenic avian influenza H5N1 virus defined by agro-ecological niche. Ecohealth, 7, 213-225

Huberty, C.J. (1994). Applied Discriminant Analysis. Wiley Interscience New York, USA

Jiménez-Valverde, A., Lobo, J.M. and Hortal, J. (2008). Not as good as they seem: the importance of concepts in species distribution modelling. Divers. Distrib. 14, 885-890

Lobo, J.M., Jiménez-Valverde, A. and Real, R. (2008). AUC: a misleading measure of the performance of predictive distribution models. Glob. Ecol. Biogeog. 17, 145-151

Loth, L., Gilbert, M., Osmani, M.G., Kalam, A.M. and Xiao, X. (2010). Risk factors and clusters of Highly Pathogenic Avian Influenza H5N1 outbreaks in Bangladesh. Prev. Vet. Med. 96, 104-113

Loth, L., Gilbert, M., Wu, J., Czarnecki, C., Hidayat, M. and Xiao, X. (2011). Identifying risk factors of highly pathogenic avian influenza (H5N1 subtype) in Indonesia. Prev. Vet. Med. 102, 50-58

Malczewski, J. (1999). GIS and Multicriteria Decision Analysis. John Wiley & Sons, Inc New York

Malczewski, J. (2000). On the use of weighted linear combination method in GIS: common and best practice approaches. Trans. GIS 4, 5-22

Martin, V., Pfeiffer, D.U., Zhou, X., Xiao, X., Prosser, D.J., Guo, F. and Gilbert, M. (2011). Spatial distribution and risk factors of highly pathogenic avian influenza (HPAI) H5N1 in China. PLoS Pathog. 7, e1001308

Minh, P.Q., Morris, R.S., Schauer, B., Stevenson, M., Benschop, J., Nam, H.V. and Jackson, R. (2009). Spatio-temporal epidemiology of highly pathogenic avian influenza outbreaks in the two deltas of Vietnam during 2003-2007. Prev. Vet. Med. 89, 16-24

Paul, M., Tavornpanich, S., Abrial, D., Gasqui, P., Charras-Garrido, M., Thanapongtharm, W., Xiao, X., Gilbert, M., Roger, F. and Ducrot, C. (2010). Anthropogenic factors and the risk of highly pathogenic avian influenza H5N1: prospects from a spatial-based model. Vet. Res. 41, 28

Peterson, A.T., Soberón, J., Pearson, R.G., Anderson, R.P., Martínez-Meyer, E., Nakamura, M. and Araújo, M.B. (2011). Chapter 7: Modeling Ecological Niches. In: Levin, S.A., Horn, H.S. (Eds.), Ecological Niches and Geographic Distributions. Princeton University Press Princeton and Oxford, 97-137

Pfeiffer, D., Robinson, T., Stevenson, M., Stevens, K., Rogers, D. and Clements A.C. (2008a). Spatial risk assessment and management of disease. Spatial Analysis in Epidemiology. Oxford University Press, Oxford, 110-119

Pfeiffer, D.U., Robinson, T.P., Stevenson, M., Stevens, K.B., Rogers, D.J. and Clements, A.C.A. (2008b). Identifying factors associated with the spatial distribution of disease. Spatial Analysis in Epidemiology. Oxford University Press, Oxford, 81-109

Pfeiffer, D.U., Minh, P.Q., Martin, V., Epprecht, M. and Otte, M.J. (2007). An analysis of the spatial and temporal patterns of highly pathogenic avian influenza occurrence in Vietnam using national surveillance data. Vet. J. 174, 302-309

Phillips, S. (2012). A brief tutorial on Maxent. Lessons in Conservation 3, 107-135

Phillips, S., Anderson, R. and Schapier, R. (2006). Maximum entropy modeling of species geographic distributions. Ecol. Modell. 190, 231-259

Phillips, S.J. and Dudík, M. (2008). Modeling of species distributions with Maxent: new extensions and a comprehensive evaluation. Ecography 31, 161-175

Prasad, A., Iverson, L. and Liaw, A. (2006). Newer classification and regression tree techniques: bagging and random forests for ecological prediction. Ecosystems 9, 181-199

Prosser, D., Wu, J., Ellis, E.C., Gale, F., Van Boeckel, T.P., Wint, W., Robinson, T., Xiao, X. and Gilbert, M. (2011). Modelling the distribution of chickens, ducks, and geese in China. Agriculture, Ecosystems and Environment 141, 381-389

Rakotomanana, F., Randremanana, R., Rabarijaona, L., Duchemin, J., Ratovonjato, J., Ariey, F., Rudant, J. and Jeanne, I. (2007). Determining areas that require indoor insecticide spraying using multi criteria evaluation, a decision-support tool for malaria vector control programmes in the Central Highlands of Madagascar. Int. J. Health Geog. 6, 2

Saaty, T.L. (1990). Multicriteria Decision Making: The Analytic Hierarchy Process. RWS Publications Pittsburgh, PA

Segurado, P. and Araujo, M. (2004). An evaluation of methods for modelling species distributions. J. Biogeog. 31, 1555-1568

Sillero, N. (2011). What does ecological modelling model? A proposed classification of ecological niche models based on their underlying methods. Ecol. Modell. 222, 1343-1346

Stärk, K., Regula, G., Hernandez, J., Knopf, L., Fuchs, K., Morris, R. and Davies, P. (2006). Concepts for risk-based surveillance in the field of veterinary medicine and veterinary public health: Review of current approaches. BMC Health Serv. Res. 6, 20

Stevens, K.B., Gilbert, M. and Pfeiffer, D.U. (2013). Modeling habitat suitability for occurrence of highly pathogenic avian influenza virus H5N1 in domestic poultry in Asia: A spatial multicriteria decision analysis approach. Spatial and Spatio-temporal Epidemiology 4, 1-14

Stockwell, D. and Peters, D. (1999). The GARP modelling system: problems and solutions to automated spatial prediction. Int. J. Geog. Inf. Sci. 13, 143-158

Tsoar, A., Allouche, O., Steinitz, O., Rotem, D. and Kadmon, R. (2007). A comparative evaluation of presence-only methods for modelling species distribution. Divers. Distrib. 13, 397-405

Van Boeckel, M., Prosser, D., Wint, W., Robinson, T. and Gilbert, M. (2011). Modelling the distribution of domestic duck in Monsoon Asia. Agriculture, Ecosystems and Environment 141, 373-380

Walker, P.A. and Cocks, K.D. (1991). HABITAT: a procedure for modelling a disjoint environmental envelope for a plant or animal species. Global Ecology and Biogeography Letters 1, 108-118

Ward, M., Maftei, D., Apostu, C. and Suru, A. (2008). Environmental and anthropogenic risk factors for highly pathogenic avian influenza subtype H5N1 outbreaks in Romania, 2005−2006. Vet. Res. Comm. 32, 627-634

Warren, D.L., Glor, R.E. and Turelli, M. (2010). ENMTools: a toolbox for comparative studies of environmental niche models. Ecography 33, 607-611

A TREND ANALYSIS OF ANTIMICROBIAL RESISTANCE IN INDICATOR COMMENSAL BACTERIA FROM LIVESTOCK IN BELGIUM (2011-2013)

J.B. HANON, S. JASPERS, P. BUTAYE, P. WATTIAU, M. AERTS, H. IMBERECHTS,
K. VERMEERSCH AND Y.VAN DER STEDE[*]

SUMMARY

A trend analysis was performed based on antimicrobial resistance data observed over three years in commensal *E.coli* and *Enterococcus* spp. isolated from faecal samples collected from several livestock species (veal calves, young beef cattle, broiler chickens and slaughter pigs) in Belgium. Using logistic regression and Generalized Estimating Equation, significant trends (increasing or decreasing) were observed and varied according to bacteria and animal species. Moreover, high prevalence values of resistant *E. coli* strains (>50%) were observed during this period in several animal species and for several antimicrobials. Levels of antimicrobial resistance and of multi-resistance were especially high in broiler chickens. The results of this study emphasizes on the necessity to follow the evolution of antimicrobial resistance in livestock and to take measures to reduce this phenomenon. When analysing Belgian data in the coming years it will be possible to confirm or adjust the trends obtained after this 3 year period.

INTRODUCTION

Antimicrobial resistance in humans and animals has become a major public health concern leading to the set-up of national and European surveillance programmes to monitor its evolution. It is believed that resistant bacteria found in animals could spread to humans not only through direct contact but also by contaminating the environment or through the food chain (Geenen et al., 2010).

Intestinal commensal bacteria present in animals and in humans are considered as good indicators to monitor antimicrobial resistance as they are subjected to the continuous selection pressure of the antimicrobials and they are abundant and relatively easy to isolate and identify. The bacterial species which are monitored can be considered as representative of both Gram positive and Gram negative bacteria.

The objective of this study was to perform a trend analysis of the prevalence of antimicrobial resistance of three bacterial species of the commensal flora from livestock: *Escherichia coli*, a Gram negative bacteria and two *Enterococcus spp*. (*E. faecium and E. faecalis*) which are Gram positive. The bacterial strains isolated were obtained from faecal samples of several economically important livestock categories, collected during three consecutive years (2011-2012-2013) in Belgium. A secondary objective was to evaluate the level of multi-resistance (resistance against at least three antibiotics by the same strain) in the commensal flora and its trend over the same period. The trends described in this report are

---

[*] Yves Van der Stede, CODA-CERVA (Veterinary and Agrochemical Research Center), Groeselenberg 99, 1180 Brussels, Belgium. Email: Yves.VanderStede@coda-cerva.be

based upon data obtained from a national annual monitoring programme for antimicrobial resistance which started in Belgium in 2011. Hence, observations from three years only were available when the study was performed, which is a strict minimum for a trend analysis. When analysing the Belgian data of the coming years it will be possible to confirm or adjust these trends. On the other hand, we may observe some trends in the future that could not be detected after only three years of surveillance.

MATERIALS AND METHODS

Sampling

Faecal samples were collected each year by veterinarians of the Federal Agency for Safety of the Food Chain (AFSCA-FAVV) according to standardised technical sampling instructions as part of a nationwide surveillance programme. The same faecal samples were used to isolate strains of *E. coli* and *Enterococcus spp*. They were taken from the following categories of livestock species:

- Veal calves: young cattle kept in specialised units for fattening and slaughtered at an average age of 8 months. In 2011 faecal samples were taken at the farm level (one sample consisted of a pool of faeces collected from different spots on the floor and representing 10 animals < 7 months old) while in 2012 and 2013 the samples were taken directly from the rectum of the animals at the slaughterhouse (1 animal sampled/farm).

- Beef cattle (meat production): young animals (< 7 months old) from farms raising beef cattle for meat production. Faecal samples were taken from the floor at the farm (one sample consisted of a pool of faeces collected from different spots on the floor and representing 10 animals).

- Broiler chickens: samples were taken at the slaughter house (pools of pairs of caeca from 10 chickens/batch).

- Slaughter pigs: faecal samples of fattened pigs > 3 months old were taken from the rectum at the slaughter house (1 animal sampled/farm).

EFSA has recommended to have a sample size designed to reach a target of 170 isolates/year for each livestock category and each bacterial species, in order to be able to detect significant changes of prevalence of resistance (in function of the observed prevalence) and with an acceptable precision (+/- 8% in the worst case scenario). Such a sample size is also able to detect annual trends such as a 5% decrease per year if starting from an initial 50% prevalence of resistance or an increase of 2% per year if starting from an initial 0.1% prevalence (EFSA, 2008). This target figure was not always reached for isolates of *Enterococcus* spp. thus decreasing the precision in the estimation of the prevalence of resistant strains in some cases. To improve representativeness, the sampling was stratified according to the different Belgian provinces and the number of samples taken in each province was proportional to the number of registered cattle herds for beef cattle samples and to the number of slaughtered veal calves, broiler chickens and slaughter pigs for samples from other livestock categories.

Table 1. Panel of antimicrobials tested for *E. coli* isolates with cut-off values for susceptibility

Antimicrobial	Symbol	Cut-off value (mg/ml)
Ampicillin	AMP	8
Chloramphenicol	CHL	16
Ciprofloxacin	CIP	0.03
Colistin	COL	2
Florphenicol	FFN	16
Cefotaxime	FOT	0.25
Gentamicin	GEN	2
Kanamycin	KAN	8
Nalidixic acid	NAL	16
Sulphonamide	SMX	64
Streptomycin	STR	16
Ceftazidime	TAZ	0.5
Tetracycline	TET	8
Trimethoprim	TMP	2

Table 2. Panel of antimicrobials tested for *Enterococcus* spp. isolates with cut-off values for susceptibility

Antimicrobial	Symbol	Cut-off value (mg/ml) for *E. faecalis*	Cut-off value (mg/ml) for *E. faecium*
Ampicillin	AMP	4	4
Chloramphenicol	CHL	32	32
Ciprofloxacin	CIP	4	4
Erythromycin	ERY	4	4
Florfenicol	FFN	8	8
Gentamicin	GEN	32	32
Linezolid	LZD	4	4
Salinomycin	SAL	4	4
Streptomycin	STR	512	128
Synercid (quinupristin/dalfopristin)	SYN	32	1
Tetracycline	TET	2	2
Vancomycin	VAN	4	4

Laboratory testing

Isolates of *E. coli* (n=2504) and enterococcal strains (n=1380) were obtained from these faecal samples at the two regional laboratories ARSIA and DGZ-Vlaanderen following their specific standard operating procedures (SOP) as described by Butaye (2014). The isolated strains were sent to the National Reference Laboratory (CODA-CERVA) for confirmation of identification and for susceptibility testing using a micro-dilution technique (Sensititer®). A panel of 14 antimicrobials specified by the European Commission was used for *E.coli* and a custom panel including 12 antibiotics was used for *Enterococcus* spp. isolates. For each isolated strain and each antimicrobial substance tested, the Minimal Inhibitory Concentration (MIC) was read through a semi-automated procedure and stored in a database. MIC is defined as the lowest concentration by which no visible growth could be detected. To differentiate between susceptible and resistant strains, quantitative MIC values were converted into binary qualitative values (Resistant/Susceptible) based on the susceptibility breakpoints defined by EUCAST (European Committee on Antimicrobial Susceptibility Testing) (EUCAST, 2014). A bacterial strain is considered as resistant to a specific antimicrobial if the MIC value is greater than the corresponding cut-off value (Table 1 and 2).

Statistical analysis

Descriptive statistics: For each bacterial species and each antimicrobial separately, the percentage (with 95% confidence intervals) of observed resistant strains was calculated, per year and per animal category. The percentages of resistant strains per year for each antimicrobial were then plotted on graphs.

The percentages of multi-resistant strains (i.e. strains resistant to at least three drugs) and their 95% confidence intervals were also calculated per year for each bacterial species and each animal category and were plotted on graphs. In addition, diversity indices (entropy and weighted entropy) were calculated using the R software to describe the degree of diversity of multi-resistance: these indices take a value between 0 and 1; a higher weighted entropy index reflecting a shift to multi-resistance against a larger number of antibiotics. These indices were calculated per year for each bacterial species and each animal category.

Trend analysis: Using SAS 9.2 software, several statistical methods were tested to model the observed trends. Univariate models, based upon categorical data (logistic regression, generalised logit models) or upon continuous data (models for interval-censored data, mixture models) were used to analyse the time trend of resistance for each antimicrobial agent separately. Multivariate models (Generalised Estimating Equation models (GEE)) were used to take into account a possible correlation between antimicrobial agents in the time trend of resistance. After evaluating these various models for their capacity to accurately reflect the data and after comparing the results and their possible interpretation, it was decided to restrict the trend analysis to the logistic regression (univariate analysis) and to the GEE (multivariate analysis). These two approaches offered the best convergence and gave outputs that were convenient to interpret and to compare and that could be easily plotted on graphs for presentation to authorities and decision makers.

If, in the logistic regression model, π_i represents the probability for an isolate to be resistant to a certain antimicrobial in year of reporting t_i and $f(t_i)$ represents a function of time, then we can consider a linear time trend and use the logit link function, which is the logarithm of the odds of the probability as expressed in Eq.(1).

$$\mathrm{LOG}\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 t_i \tag{1}$$

where β_0 is an intercept .The results were described in the form of Odds Ratio (OR) as in the logistic regression β_1 = ln OR . In this model, an OR > 1 means that the probability to be resistant increases with time.

GEE was used to perform multivariate analysis and take into account possible correlations between antimicrobials through the specification of one of a variety of possible working correlation matrix structures. We used an unstructured working correlation matrix, as correlations between any two responses are unknown and need to be estimated.

For multi-resistance a logistic model was used to check whether there was a significant trend (increase or decrease) over the years regarding the prevalence of multi-resistant strains, for each animal category. In this model an OR >1 means that the probability for a strain to be multi-resistant increases with time.

A note on multiple comparisons: in this study, the effects of the different antimicrobials were assessed on an individual level. Hence, the 5% significance levels were specified for each antimicrobial separately. If the interest is in making a statement on the entire pool of antimicrobials jointly, a family wise significance level should be specified. Different correction methods exist, including the very conservative Bonferroni. Another way to correct for multiple comparisons is by controlling the false discovery rate. In this respect, a less conservative method is the linear step-up method of Benjamini and Hochberg (1995). These methods were not applied to the results presented here.

RESULTS

In the results presented and summarised hereunder, the trends described are based on the univariate analysis (logistic regression). More detailed descriptive statistics are described in Butaye (2014) and Hanon et al. (2014) and results of the multivariate analysis are presented in Hanon et al. (2014).

E. coli

High levels of resistance (prevalence > 50%) against several antimicrobials were observed for the three consecutive years in all animal categories except in beef cattle. Decreasing trends were observed in veal calves and slaughter pigs for antimicrobials for which there was a low to moderate resistance prevalence (Table 3).

In broiler chickens, high resistance prevalence (> 50%) for half of the tested antimicrobials (7/14) was observed. Moreover, in this animal category, an increasing trend of resistance was observed for 4 different antimicrobials, including three substances for which there was high resistance prevalence (ciprofloxacin, nalidixic acid, streptomycin) (Fig. 1).

Enterococcus spp.

For these bacterial species, the number of tested isolates was sometimes insufficient to obtain significant trends. This was especially the case for the year 2011.

For *E. faecalis* the resistance prevalence was high (> 45%) during the three consecutive years for 3 antimicrobials (erythromycin, streptomycin and tetracyclin) in all animal categories except in slaughter pigs for which only the resistance against tetracycline was high. Increasing resistance was observed mostly in strains from veal calves, including resistance against 2 antimicrobials for which there was a high prevalence of resistance (erythromycin and tetracycline) (Table 4).

Table 3. Summary of observed trends of antimicrobial resistance for *E. coli* isolates per livestock category

Antimicrobial	Veal calves	Beef cattle	Broiler chickens	Slaughter pigs
Ampicillin	++		++	+
Chloramphenicol	↓		↑	
Ciprofloxacin	↓		↑ ++	↓
Colistin				
Florphenicol				
Cefotaxime				↓
Gentamicin				
Kanamycin				
Nalidixic acid	↓		↑ ++	↓
Sulphonamide	++		++	++
Streptomycin	++		↑ ++	++
Ceftazidime				
Tetracycline	++		++	++
Trimethoprim	↓		++	+

++ : High prevalence of antimicrobial resistance (>50%) during three consecutive years
+ : Prevalence of antimicrobial resistance > 40% during three consecutive years
↑ : significant increasing trend of antimicrobial resistance prevalence
↓ : significant decreasing trend of antimicrobial resistance prevalence
No symbol: no significant trend and no persisting high prevalence of antimicrobial resistance

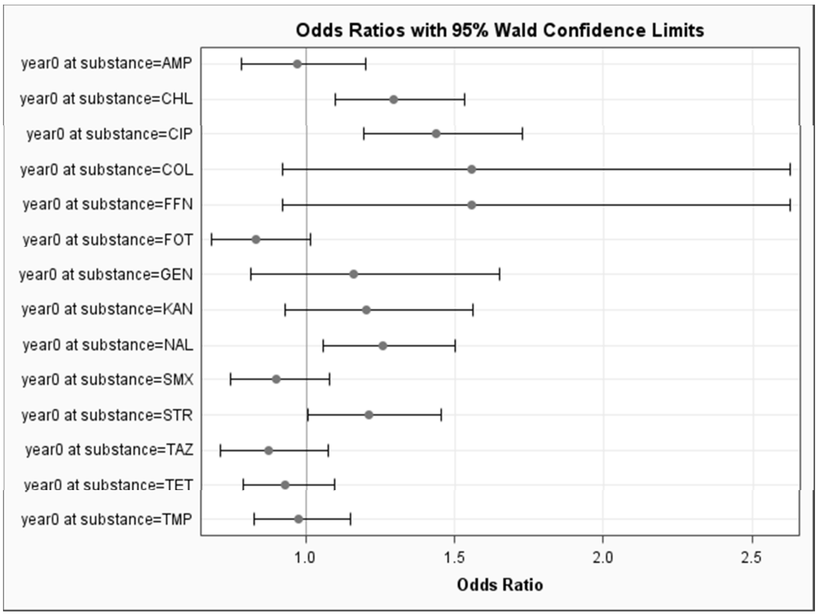


Fig. 1 Odds Ratios and their 95 % CI (univariate analysis) for the trends in *E.coli* isolates from broiler chickens to be resistant. An OR > 1 indicates an increasing trend (see legend for antimicrobials symbols in Table 1)

Table 4. Summary of observed trends of antimicrobial resistance for *E. faecalis* isolates per livestock category

Antimicrobial	Veal calves	Beef cattle	Broiler chickens	Slaughter pigs
Ampicillin				
Chloramphenicol	↑	↑		
Ciprofloxacin				
Erythromycin	+ ↑	++	++	
Florfenicol				
Gentamicin				
Linezolid			↓	
Salinomycin				
Streptomycin	++	++	++	
Synercid (quinupristin/ dalfopristin)				
Tetracycline	++ ↑	++	++	++
Vancomycin				

++: High prevalence of antimicrobial resistance (>50%) during three consecutive years
+ : Prevalence of antimicrobial resistance > 40% during three consecutive years
↑ : significant increasing trend of antimicrobial resistance prevalence
↓ : significant decreasing trend of antimicrobial resistance prevalence
No symbol: no significant trend and no persisting high prevalence of antimicrobial resistance

Table 5. Summary of observed trends of antimicrobial resistance for *E. faecium* isolates per livestock category

Antimicrobial	Veal calves	Beef cattle	Broiler chickens	Slaughter pigs
Ampicillin				
Chloramphenicol		↓	↓	↓
Ciprofloxacin				
Erythromycin	↑	↓		
Florfenicol				
Gentamicin				
Linezolid			↓	
Salinomycin				
Streptomycin		↓		
Synercid (quinupristin/ dalfopristin)	++	++	++	++
Tetracycline	↑	↓	↓	
Vancomycin			↓	

++ : High prevalence of antimicrobial resistance (> 50%) during three consecutive years
↑ : significant increasing trend of antimicrobial resistance prevalence
↓ : significant decreasing trend of antimicrobial resistance prevalence
No symbol: no significant trend and no persisting high prevalence of antimicrobial resistance

For *E. faecium* the resistance prevalence was generally low to moderate except for Synercid (quinupristin and dalfopristin) for which there was a very high prevalence of resistance (> 80%) in all animal categories for the three consecutive years. Decreasing trends were observed for several antimicrobials in all animal categories except in veal calves for which there was an increasing resistance to 2 substances (erythromycin and tetracycline) (Table 5).

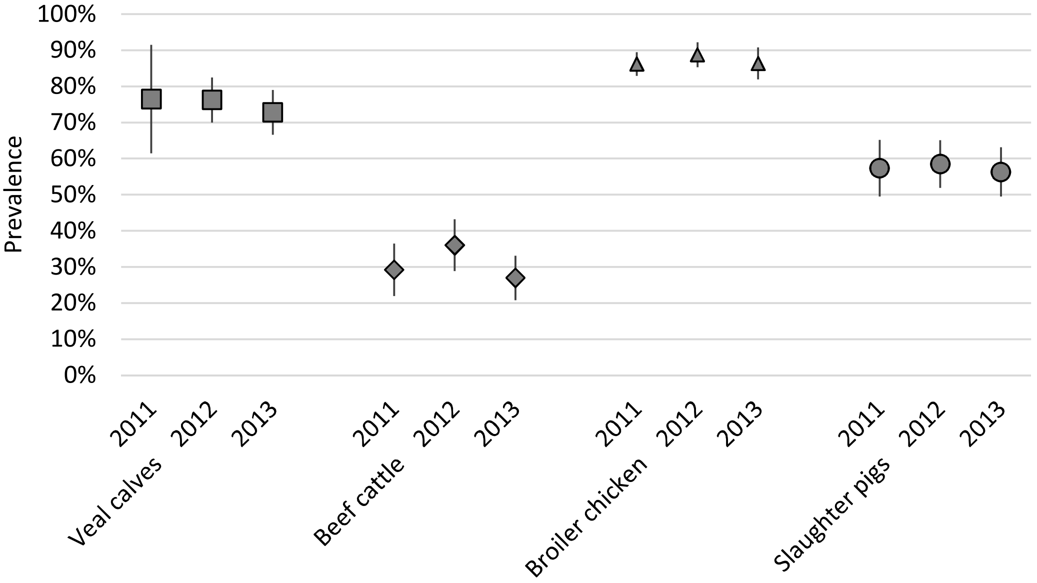


Fig. 2 Prevalence (with 95% C.I.) of multi-resistant E. coli isolates per animal category and per year

Table 6. Summary of observed trends of antimicrobial multi-resistance for *E. coli* and *Enterococcus spp.* isolates per livestock category

Bacterial species	Veal calves	Beef cattle	Broiler chickens	Slaughter pigs
E. coli	++		+++	++
E. faecalis	↑		++	
E. faecium	↑	↓	+++	↓

++ : High prevalence of antimicrobial resistance (> 50%) during three consecutive years
+++ : Very high prevalence of antimicrobial resistance (> 70%) during three consecutive years
↑ : significant increasing trend of antimicrobial resistance prevalence
↓ : significant decreasing trend of antimicrobial resistance prevalence
No symbol: no significant trend and no persisting high prevalence of antimicrobial resistance

Multi-resistance

In broiler chickens, the percentage of multi-resistant strains remained high (> 50%) to very high (> 70%) during the three consecutive years both for *E. coli* and for *Enterococcus* spp. In veal calves it was very high (>70%) during the three years for *E. coli*; it was increasing for *Enterococcus* spp. although the lack of data in 2011 due to low number of samples makes such trend questionable. In slaughter pigs it was high for *E. coli* and decreasing for *E. faecium*. In beef cattle the level of multi-resistance was moderate for E. coli and decreasing for *E. faecium* (Table 6). Although the prevalence of multi-resistant *E. coli* strains did not increase during the 3-years period, it remained high for all livestock categories except for beef cattle (Fig. 2).

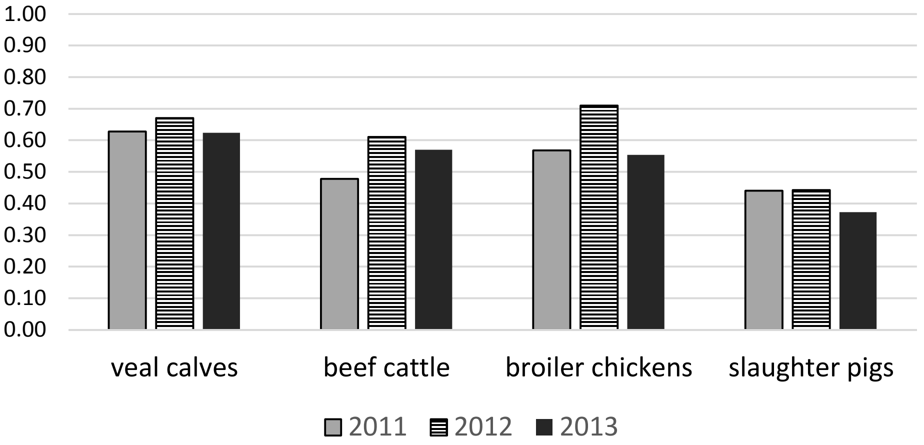


Fig. 3 Indices of diversity: weighted entropy per animal category and per year for E. coli isolates

The comparison of diversity indices (weighted entropy) shows that for *E.coli* strains, multi-resistance against a large number of antibiotics was the highest in isolates from veal calves and the lowest in isolates from pigs (Fig. 3). The indices were higher for *E. coli* isolates than for *Enterococcus* spp. isolates, in all animal categories meaning that resistance to high number of antimicrobials was more frequent with *E. coli* (data not shown).

DISCUSSION

This study was based upon data collected over a three years period. As already mentioned one must remain cautious when drawing conclusions about increasing or decreasing trends from observations of such a limited time period. In addition, the number of bacterial isolates per year was sometimes quite low when stratified by the various livestock categories, occasionally leading to large confidence intervals in the estimation of the prevalence of resistant strains. This lack of data was more pronounced for *Enterococcus* spp. in 2011 as the isolation success from the faeces samples was low but it improved in the following years by adapting the isolation method at the laboratory level.

On the other hand, even when no trends were demonstrated, persisting high levels of resistance for some specific antimicrobials were observed during the three consecutive years. This was the case for some of the tested antibiotics such as ampicillin, sulphonamide, streptomycin and tetracycline, for which the prevalence of resistant *E. coli* strains remained high (> 50%) during the three consecutive years in veal calves, chickens and pigs. High levels of resistance have already been observed previously, both in pathogenic and non-pathogenic bacteria isolated from livestock, through other surveillance programmes implemented in several European countries (Butaye et al., 2001, Hendriksen et al, 2008a, Hendriksen et al, 2008b, AFSSA, 2009, EFSA/ECDC, 2014, CVI, 2014). The use of such antimicrobials should therefore be carefully monitored especially in livestock species with intensive treatment practices (veal calves, broiler chickens, slaughter pigs), for which the highest resistance prevalence values were observed in this study.

The levels of antimicrobial resistance revealed by this study are particularly worrying for *E. coli* strains isolated from broiler chickens: a high prevalence of resistance against half of the tested antimicrobials was observed during the three years and, moreover, increasing trends of resistance were detected against three of these antibiotics (ciprofloxacin, nalidixic acid, streptomycin). In addition it was shown that the level of multi-resistance was the highest in broiler chickens compared to other livestock categories, both in *E. coli* and *Enterococcus* spp. isolates. The prevalence of multi-resistance was also high for slaughter pigs and veal calves in *E. coli* isolates but no significant increasing/decreasing trend was detected in these animal species.

The models show that trends of resistance prevalence were sometimes diverging between livestock categories for the same antibiotic and the same bacterial species, increasing in one livestock category and decreasing for others (e.g. resistance of *E. coli* to ciprofloxacin was increasing in broiler chickens and decreasing in veal calves and slaughter pigs; resistance of *E. faecium* to tetracycline was increasing in veal calves and decreasing in beef cattle and broiler chickens). These contradictory results may be linked to the uncertainty of trends which were estimated over a short period and sometimes with a limited number of samples (*Enterococcus* spp.) and it is possible that such differences will not appear anymore when more data will be available. However, another possible explanation of such differences is that trends of antimicrobial resistance differ between livestock categories due to different management and animal husbandry practices, and to different habits and needs in the prescription and use of antibiotics according to the livestock species. If some trends are confirmed in the future for a specific livestock category, any measure taken at national level to control antibiotic resistance should be targeted and adapted to the epidemiological situation.

Another observation is that resistance to chloramphenicol is still present, although this antimicrobial has been prohibited for years for veterinary use. For this antimicrobial the observed trends were conflicting between bacteria species and between livestock categories, without obvious explanation: for *E. coli* there was a decreasing resistance in veal calves and an increasing resistance in broiler chickens, for *E. faecalis* an increasing resistance in veal calves and beef cattle and for *E. faecium* a decreasing resistance in all livestock categories except in veal calves.

To conclude, the methodology and statistical tools applied in this study led to the observation, after three years of monitoring, of some significant trends and in some cases of persisting high prevalence values of antimicrobial resistance; however these results need to be confirmed by data covering a longer period. It is therefore recommended to continue the surveillance programme (i) to advise the public health and animal health authorities, based on objective and scientific information, on the measures and actions to be taken to control and regulate the use of antimicrobials in livestock species with the objective to reduce antimicrobial resistance, (ii) to evaluate the efficiency of such measures and actions.

ACKNOWLEDGEMENTS

This study was commissioned by the Belgian Federal Agency for the Safety of the Food chain (FAVV-AFSCA) and carried out by the epidemiology unit and the bacteriology department of CODA-CERVA (Veterinary and Agrochemical Research Center, Brussels) in close collaboration with the Center for Statistics (CenStat, Hasselt University, Belgium) which developed the statistical models adapted to the available data and the expected outputs.

REFERENCES

AFSSA (2009). Farm 2005-2006: French antimicrobial resistance monitoring program in bacteria of animal origin. Available at http://www.anses.fr/Documents/SANT-Ra-FARM2006.pdf

Benjamini Y. and Hochberg Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Statist Soc Ser B (Methodological). 57, 289-300

Butaye, P., Devriese, L.A. and Haesebrouck, F. (2001). Differences in antibiotic resistance patterns of *Enterococcus faecalis* and *Enterococcus faecium* strains isolated from pet and farm animals. Antimicrob. Agents Chemother., 45, 1347-1378

Butaye, P., (2014). Annual Reports on antimicrobial resistance in commensal E. coli from poultry, pigs, cows and veal calves. (2011, 2012, 2013). Available at http://www.coda-cerva.be

Butaye, P., (2014). Annual Reports on antimicrobial resistance in commensal Enterococcus spp. from poultry, pigs, cows and veal calves, (2011, 2012, 2013). Available at http://www.coda-cerva.be

CVI (Central Veterinary Institute of Wageningen), (2014). MARAN 2014: Monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands in 2013. Central Veterinary Institute, Wageningen. Available at www.cvi.wur.nl

EFSA, (2008). Report from the Task Force on Zoonoses Data Collection including guidance for harmonized monitoring and reporting of antimicrobial resistance in commensal Escherichia coli and Enterococcus spp. from food animals. The EFSA Journal (2008) 141, 1-44

EFSA/ECDC, (2014). The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria for humans, animals and food in the EU in 2012. EFSA Journal 2014; 12(3): 3590, 336pp., doi:10.2903/j.efsa.2014.3590

EUCAST (European Committee on Antimicrobial Susceptibility Testing), (2014). Data from the EUCAST MIC distribution website. Available at http://www.eucast.org/mic_distributions/

Geenen, P.L., Koene, M.G.J., Blaak, H., Havelaar, A.H. and van de Giessen, A.W. (2010). Risk profile on antimicrobial resistance transmissible from food animals to humans. RIVM-rapport 330334001, 2010. Available at http://www.rivm.nl

Hanon, J.B., Méroc E., Van der Stede, Y. (2014). Antimicrobial Resistance in indicator commensal bacteria from livestock in Belgium: Trend Analysis 2011-2013. Available at http://www.coda-cerva.be

Hendriksen, R.S., Mevius, D.J., Schroeter, A., Teale, C., Jouy, E., Butaye, P., Franco, A., Utinane, A., Amado, A., Moreno, M., Greko, C., Stark, K.D., Berghold, C., Myllyniemi, A.L., Hoszowski, A., Sunde, M. and Aarestrup, F.M. (2008a). Occurrence of antimicrobial resistance among bacterial pathogens and indicator bacteria in pigs in different European countries from year 2002 - 2004; the ARBAO-II study. Acta Vet. Scand. 50, 19

Hendriksen, R.S., Mevius, D.J., Schroeter, A., Teale, C., Jouy, E., Butaye, P., Franco, A., Utinane, A., Amado, A., Moreno, M., Greko, C., Stark, K.D., Berghold, C., Myllyniemi, A.L., Wasyl, D., Sunde, M. and Aarestrup, F.M. (2008b). Prevalence of antimicrobial resistance among bacterial pathogens isolated from cattle in different European countries: 2002-2004. Acta Vet. Scand. 50, 28

SOCIETY FOR VETERINARY EPIDEMIOLOGY AND PREVENTIVE MEDICINE

PAST VENUES AND ORGANISERS OF ANNUAL MEETINGS

Year	**Venue**	**Organiser(s)**
1983	Southampton	Davies & Thrusfield
1984	Edinburgh	Thrusfield
1985	Reading	Thrusfield
1986	Edinburgh	Thrusfield
1987	Solihull	Thrusfield
1988	Edinburgh	Thrusfield
1989	Exeter	Howe
1990	Belfast	McIlroy
1991	London	Jones
1992	Edinburgh	Thrusfield
1993	Exeter	Howe
1994	Belfast	Menzies
1995	Reading	Paterson
1996	Glasgow	Reid
1997	Chester	Clarkson
1998	Ennis, Ireland	Collins
1999	Bristol	Green
2000	Edinburgh	Thrusfield & Mellor
2001	Noordwijkerhout, Netherlands	van Klink
2002	Cambridge	Wood & Newton
2003	Warwick	Green
2004	Martigny, Switzerland	Stärk
2005	Nairn	Gunn
2006	Exeter	Peeler
2007	Dipoli, Finland	Virtala & Alban
2008	Liverpool	Pinchbeck & Robinson
2009	London	Verheyen & Pfeiffer
2010	Nantes, France	Fourichon & Hoch
2011	Leipzig, Germany	Thulke & Lange
2012	Glasgow	Parkin & Others
2013	Madrid, Spain	Martínez-López & Vargas Alvarez
2014	Dublin, Ireland	More & Collins

PAST PRESIDENTS

1982-’83	G. Davies
1983-’84	P.R. Ellis
1984-’85	G. Gettinby
1985-’86	R.W.J. Plenderleith
1986-’87	M.V. Thrusfield
1987-’88	K.S. Howe
1988-’89	A.M. Russell
1989-’90	S.G. McIlroy
1990-’91	J.E.T. Jones
1991-’92	J.M. Booth
1992-’93	E.A. Goodall
1993-’94	R.G. Eddy
1994-’95	J.T. Done
1995-’96	G.J. Gunn
1996-’97	M.S. Richards
1997-’98	J.D. Collins
1998-’99	F.D. Menzies
1999-’00	K.L. Morgan
2000-’01	S.W.J. Reid
2001-’02	A.D. Paterson
2002-’03	L.E. Green
2003-’04	J.L.N. Wood
2004-’05	E.G.M. van Klink
2005-’06	D.J. Mellor
2006-’07	E. J. Peeler
2007-’08	J. R Newton
2008-’09	L. Alban
2009-’10	D.U. Pfeiffer
2010-’11	L.A. Kelly
2011-’12	C. Fourichon
2012-’13	T.D.H. Parkin
2013-’14	K.L.P. Verheyen

EXECUTIVE COMMITTEE 2014-2015

K. Mintiens (President), K. Verheyen (Senior Vice-President), H-H. Thulke (Junior Vice-President), A. Lindberg (Honorary Secretary), M. Brennan (Honorary Treasurer), D. Brodbelt, R. Christley, M. McIntyre, L. Rosenbaum Nielsen, B. van den Borne, J. Dewulf (co-opted)

Honorary Auditors: Dominic Mellor & Fraser Menzies

LIFE MEMBERS

J.M. Booth, M.J. Clarkson, J.D. Collins (deceased), P. Cripps, G. Davies, J.T. Done (deceased), R.G. Eddy, P.R. Ellis, E.A. Goodall, G. Gettinby, K.S. Howe, M.E. Hugh-Jones, W. Martin, F. Menzies, A.M. Russell, M.V. Thrusfield, J. Wilesmith, K. Morgan

PLENARY TALKS

Year	**Gareth Davies Lecture**	**Conference Opening Plenary**
2015	Piet Vanthemsche Preventive Veterinary Medicine as an essential part of sustainable animal production	Crawford Revie Hype and Hysteria: Should veterinary epidemiologists really care about Big Data?
2014	Ian Gardner, Bridging the gap in infectious disease epidemiology between aquatic and terrestrial food animals: challenges and future opportunities	Nils Toft Confessions of a wannabe Bayesian
2013	Andreas Hensel Dioxins, EHEC and strawberries: Risk assessment and risk communication in practice	José Manuel Sánchez-Vizcaíno The Spanish experience on the control and eradication of infectious diseases: from the old to the current system
2012	Stuart Reid Evidence-based prevention: well done or rare	Didier Boichard Genomic selection: an opportunity for improving health of farm animals
2011	Karin Schwabenbauer From science to policy - the case of classical swine fever (CSF) control	Dominic Mellor The trouble with epidemiology: the tyranny of numbers
2010	David Waltner-Toews Beyond one world, one health and ecohealth…what's out there?	James Wood From pathogen adaption to host ecology: epidemiological and experimental contributions to the understanding of emerging infectious diseases
2009	Jørgen Westergaard The interaction between veterinary science, legislation and management in animal disease control in the European Union	Katharina Stärk Food safety challenges in a global market – are we ready?

2008	Paul Fine Infectious disease eradication – meanings and implications	Kenton Morgan For the benefit of Mr Kite
2007	Yrjö Gröhn Food supply veterinary medicine: Modelling of production, health and food safety	Laura Green Improving Animal Health
2006	David Galligan From partial budgets to real options - concepts in animal health economics	Nigel French Understanding human exposure to zoonoses from food and the environment: The application of molecular tools and modeling
2005	Bill Reilly From TB to VTEC: The changing epidemiology of foodborne zoonoses	Simon More Towards eradication of bovine tuberculosis in Ireland: A critical review of progress
2004	Ulrich Kihm BSE and the stable to table concept	Gary Smith Spatial models of infectious disease in the USA: a crisis of conference and confidentiality
2003	Sir David Cox The current state of statistical science	Ynte Schukken Molecular and mathematical epidemiology of bovine mastitis
2002	George Gettinby Informatics and epidemiology – the first 400 years	Bryan Grenfell Deterministic and stochastic influences on the dynamics and control of infectious diseases
2001	Will Houston Science politics and animal health policy: epidemiology in action	Mart de Jong Design and analysis of transmission experiments
2000	Jim Scudamore Surveillance – past, present and future	Dirk Pfeiffer Spatial analysis – a new challenge for veterinary epidemiologists
1999	Aalt Dijkhuizen The 1997/98 outbreak of classical swine fever in the Netherlands: lessons learned from an economic perspective	Mark Woolhouse Understanding the epidemiology of scrapie
1998	Wayne Martin Art, science and mathematics revisited: the role of epidemiology in promoting animal health	

SOCIETY FOR VETERINARY EPIDEMIOLOGY AND PREVENTIVE MEDICINE

APPLICATION FOR MEMBERSHIP

Name ....

Address ....

....

....

....

Telephone: ....

Fax: ....

E-mail: ....

Signed .... Date ....

Please enclose the membership fee (£40 sterling to cover two years' membership) along with this application form. Overseas members without British bank accounts are requested to pay 2 - 3 years in advance. Cheques should be in £ sterling and drawn from a British bank. British members should pay future dues by standing order (forms are available from the Secretary or Treasurer). Payment can also be made by credit card; the appropriate form is available from the Society's website, http://www.svepm.org.uk/, or from the Secretary or Treasurer.

Please send this form to the Society's Treasurer:

Dr Marnie Brennan
School of Veterinary Medicine and Science
Sutton Bonington Campus
College Road
Sutton Bonington
Leicestershire LE12 5RD
UK

TEL +44 (0) 115 951 6577
FAX +44 (0) 115 951 6415
Email: marnie.brennan@nottingham.ac.uk

Please turn over

INTEREST GROUPS

Please tick appropriate boxes to indicate your interests:

- ☐ Analytical Epidemiology (Observational Studies)
- ☐ Quantitative Epidemiology & Statistical Techniques (Incl. Statistical/Mathematical Modelling)
- ☐ Herd/Flock Level Disease Control Strategies
- ☐ National/International Disease Control Policy
- ☐ Sero-Epidemiology
- ☐ Herd Health and Productivity Systems
- ☐ Disease Nomenclature and Epidemiological Terminology
- ☐ Economic Effects of Disease on Animal Production
- ☐ Veterinary Public Health and Food Hygiene
- ☐ Computing, including data logging
- ☐ Computer Programming *per se*
- ☐ Population and Animal Disease Databases
- ☐ Information System Design
- ☐ Geographical Information Systems (GIS)
- ☐ Risk Analysis

CONSTITUTION AND RULES

NAME

1. The society will be named the Society for Veterinary Epidemiology and Preventive Medicine.

OBJECTS

2. The objects of the Society will be to promote veterinary epidemiology and preventive medicine.

MEMBERSHIP

3. Membership will be open to persons either actively engaged or interested in veterinary epidemiology and preventive medicine.
4. Membership is conditional on the return to the Honorary Treasurer of a completed application form and subscription equivalent to the rate for two calendar years at first application or subsequent application following an elapsed subscription. Subsequent annual subscriptions fall due on the first day of May each year.
5. Non-payment of subscription for six months will be interpreted as resignation from the Society.

OFFICERS OF THE SOCIETY

6. The Officers of the Society will be President, Senior Vice-President, Junior Vice-President, Honorary Secretary and Honorary Treasurer. Officers will be elected annually at the Annual General Meeting, with the exception of the President and Senior Vice-President who will assume office. No officer can continue in the same office for longer than six years.

COMMITTEE

7. The Executive Committee of the Society normally will comprise the officers of the Society and not more than five ordinary elected members. However, the Committee will have powers of co-option. Elected officers and ordinary members of the committee have normal voting rights at committee meetings but co-opted and ex-officio members (e.g. the proceedings editors) do not

ELECTION

8. The election of office bearers and ordinary committee members will take place at the Annual General Meeting. Ordinary members of the Executive Committee will be elected for a period of three years. Retiring members of the Executive Committee will be eligible for re-election. Members will receive nomination forms with notification of the Annual General Meeting. Completed nomination forms, including the signatures of a proposer, seconder, and the nominee, will be returned to the Secretary at least 21 days before the date of the Annual General Meeting. Unless a nomination is unopposed, election will be by secret ballot at the Annual General Meeting. Only in the event of there being no nomination for any vacant post will the Chairman take nominations at the Annual General Meeting. Tellers will be appointed by unanimous agreement of the Annual General Meeting.

FINANCE

9. An annual subscription will be paid by each member in advance on the first day of May each year. The amount will be decided at the annual general meeting and will be decided by a simple majority vote of members present at the Annual General Meeting.

10. The Honorary Treasurer will receive, for the use of the Society, all monies payable to it and from such monies will pay all sums payable by the Society. The Treasurer will keep account of all such receipts and payments in a manner directed by the Executive Committee. All monies received by the Society will be paid into such a bank as may be decided by the Executive Committee of the Society and in the name of the Society. All cheques will be signed by either the Honorary Treasurer or an elected Committee member.

11. Two auditors will be appointed annually by members at the Annual General Meeting. The audited accounts and balance sheet will be circulated to members with the notice concerning the Annual General Meeting and will be presented to the meeting.

MEETINGS

12. Ordinary general meetings of the Society will be held at such a time as the Executive Committee may decide on the recommendations of members. The Annual General Meeting will be held in conjunction with an ordinary general meeting.

GUESTS

13. Members may invite non-members to ordinary general meetings.

PUBLICATION

14. The proceedings of the meetings of the Society will not be reported either in part or in whole without the written permission of the Executive Committee.

15. The Society may produce publications at the discretion of the Executive Committee.

GENERAL

16. All meetings will be convened by notice at least 21 days before the meeting.

17. The President will preside at all general and executive meetings or, in his absence, the Senior Vice-President or, in his absence, the Junior Vice-President or, in his absence, the Honorary Secretary or, in his absence, the Honorary Treasurer. Failing any of these, the members present will elect one of their number to preside as Chairman.

18. The conduct of all business transacted will be under the control of the Chairman, to whom all remarks must be addressed and whose ruling on a point of order, or on the admissibility of an explanation, will be final and will not be open to discussion at the meeting at which it is delivered. However, this rule will not preclude any member from raising any question upon the ruling of the chair by notice of motion.

19. In case of an equal division of votes, the Chairman of the meeting will have a second and casting vote.

20. All members on election will be supplied with a copy of this constitution.

21. No alteration will be made to these rules except by a two-thirds majority of those members voting at an annual general meeting of the Society, and then only if notice of

intention to alter the constitution concerned will have appeared in the notice convening the meeting. A quorum will constitute twenty per cent of members.

22. Any matter not provided for in this constitution will be dealt with at the discretion of the Executive Committee.

Laid down April, 1982
Revised March, 1985; April, 1988; November 1994, March 2014
Corrected January 1997; April 2002