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Society for Veterinary Epidemiology and Preventive Medicine

NEW APPLICATIONS

APPLICATION OF A BAYESIAN HIDDEN MARKOV MODEL TO DETERMINE DAIRY CATTLE HERD STATUS AND TEST CHARACTERISTICS FROM *SALMONELLA* DUBLIN NATIONAL SURVEILLANCE DATA

E. MELETIS*, L.R. NIELSEN, A. MADOUASSE AND B. CONRADY

SUMMARY

The aims were two-fold. First, to develop a statistical model predicting the probabilities of freedom from *Salmonella enterica* subspecies *enterica* serovar Dublin (*S.* Dublin) antibodies in Danish dairy herds using longitudinal herd-level surveillance data. These data were obtained via antibody-detecting ELISA testing on bulk tank milk (BTM), four times a year. Second, to estimate the sensitivity (Se) and specificity (Sp) of the testing procedure. A total of 8,310 BTM test results from 500 Danish dairy herds were used for this study between 2017 and 2022. These data were combined with prior distributions in a Bayesian Hidden Markov Model ('the STOC free model') to predict herd-level probabilities of antibody presence (and freedom from antibodies). The model fitted the *S.* Dublin data and gave meaningful results when compared to previous studies and other types of models, i.e., Se = 0.945 (95% credible interval (CI): 0.921-0.962) and Sp = 0.995 (95% CI: 0.992-0.997).

INTRODUCTION

Salmonella enterica subspecies *enterica* serovar Dublin (*S.* Dublin) is a host-adapted bacterium known to have an impact on human and animal health. Zoonotic infections may be acquired by direct contact with cattle or faecal matter, or through ingesting unpasteurised milk products and/or consumption of contaminated beef products (Henderson et al., 2017). Infected cattle may shed the bacterium constantly, intermittently or may become latent carriers (i.e., those that temporarily shed bacteria in faeces, becoming infectious to susceptible animals). To safeguard animal and public health by reducing welfare losses, economic losses in infected cattle herds and the number of human cases, there is a national surveillance and control programme in place in Denmark. All cattle herds are regularly tested and classified according to signs of *S.* Dublin infection. Cattle herds have been assigned into three infection levels since 2002: Level 1 herds are test-negative according to given test-criteria codified in law; Level 2 herds are test-positive or, for other reasons not classifiable as Level 1 (e.g., due to contact with infected herds) and Level 3 herds are Salmonellosis herds based on clinical signs and culture positive samples (Level 3 was dropped from 2021 onwards). To determine whether animals in dairy herds have been exposed to *S.* Dublin in the national surveillance programme, some of the bulk tank milk (BTM) samples already routinely collected from dairy herds for milk quality

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purposes have been tested four times per year since 2000 onwards using an indirect O-antigen-based ELISA, targeting antibodies directed against serogroup-D salmonellae (in Denmark mainly *S.* Dublin) (Nielsen, 2013). Dairy farmers do not know when or which BTM samples will be used for the *S.* Dublin ELISA analyses. Classification of herds into Level 1 is based on the average of the ELISA optical density coefficient (ODC%) value of four consecutive BTM samples collected at least 3 weeks apart and a comparison of the ODC% of the most recent of these samples to the average of the previous three samples (Nielsen, 2013; Foddai, 2021). There are two criteria to remain in Level 1: First, the average ODC%, of the last four BTM-samples must be below 25 and second, the ODC%-value of the most recent BTM-sample must not be more than 20 units higher than the average of the previous three samples ('the jump criteria'). For the analyses in this study, each BTM sample was dichotomized using an ODC% cut-off of 25 and the binary test result (Test_Res_bin) was the model input (This was done because it allows for later analyses of the effect of changing cut-off values in the BTM-testing programme).

If a herd becomes test-positive (indicative of *S.* Dublin infection according to specified criteria) in the surveillance programme, special requirements to prevent the spread of infection within and between farms have to be introduced. For instance, herds will be put under official veterinary supervision by the veterinary authorities and strict animal movement restrictions are put in place. In case where clinical salmonellosis is present on the farm, animals can only be sent to slaughter under special hygienic conditions. Despite all mitigation efforts, an increase in the number of infected farms has been observed between 2015 and 2022. At the beginning of 2022, 11.2% of dairy herds were not found test-negative for *S.* Dublin (i.e., not in Level 1), whereas in 2015 this prevalence was just below 6%. Most of the test-positive dairy herds are located in specific regions of North and South Denmark (Nielsen et al., 2021).

The aims of this study were to: (1) predict the probabilities of freedom from antibodies directed against *S.* Dublin in Danish dairy herds using longitudinal BTM surveillance data, and to (2) estimate the sensitivity (Se) and specificity (Sp) of the BTM testing procedure. For this purpose, a Bayesian Hidden Markov model called the STOC free model (Madouasse et al., 2022) was applied.

MATERIALS AND METHODS

The assumptions of Hidden Markov Models (HMMs) are that the observed data are imperfect measures of a latent state that undergoes Markovian dynamics. In the STOC free model (Madouasse et al., 2022), the latent state is the true disease state which may be infection or, as is this case, antibodies against the given disease being present in the herd. The model focuses on the monthly latent status (*S*) of each herd. This latent status determines test results through Se and Sp. Each *S.* Dublin BTM test result (*T*) follows a Bernoulli distribution with parameter (p) that represents the probability of being seropositive, Eq.(1):

$$T_t \sim Bernoulli(p_t),\ t = 1, 2, 3\ \ldots\ months \tag{1}$$

Where p_t is the apparent seroprevalence at time *t* and is defined as a function of test Se and Sp and the true herd latent state (S_t) of the herd at time *t*, Eq.(2):

$$p_t = \begin{cases} Se\ if\ S_t = 1 \\ 1 - Sp\ if\ S_t = 0 \end{cases} \tag{2}$$

If S_t is equal to one (i.e., the lactating herd contains ≥1 seropositive cow), then p_t represents the probability of the BTM ELISA being positive (≥ 25 ODC%), while if S_t is equal to zero (i.e., no seropositive cow in the herd), then p_t represents the probability of being false positive. Another aspect of the modelling approach is the latent status dynamics. The unobserved latent variable (true herd antibody status) satisfies the Markov property i.e., the latent status in a given month only depends on the latent status in the previous month (Gurvits and Ledoux, 2005). The latent status is a binary variable (0 or 1) and the associated transition probabilities are summarised in Table 1.

Table 1. Transition probabilities for a herd's latent status (S) between two consecutive months ("t" and "t+1")

		Latent status at Month t +1 (S_{t+1})	
		0	**1**
Latent Status at Month t (S_t)	**0**	$1 - \tau_1$	τ_1[a]
	1	$1 - \tau_2$	τ_2[b]

[a] $\tau_1 = Pr(S_{t+1} = 1 \mid S_t = 0)$

[b] $\tau_2 = Pr(S_{t+1} = 1 \mid S_t = 1)$

Probabilities $1-\tau_1$, $1-\tau_2$ can be estimated given that the row vectors of the transition probability matrix must sum to 1. Further, the initial distribution of the Markov chain has to be defined, i.e., the unconditional probability of the Markov chain being in a given state at the first-time step (π_1). Again, this latent variable represents the herd antibody status and follows a Bernoulli distribution with parameter π_1, that describes the probability of having a herd with antibodies present at time point 1, Eq.(3):

$$S_1 \sim Bernoulli(\pi_1) \tag{3}$$

Prior distributions

The model parameters are the test characteristics (Se, Sp) and the latent status dynamics (τ_1, τ_2, π_1). For each one of these five parameters of interest, prior distributions need to be specified. For the test characteristics, we specified priors using Beta distributions. For the latent status dynamics, we specified priors using the normal distribution on the logit scale. The prior distributions for the test characteristics and the model parameters are in Figs. 1(a) and 1(b) and 2 (a) to 2 (c), respectively. We used Beta (1,1) and Beta (90,10) for Se and Sp respectively, and slightly informative, normally distributed (on the logit scale) priors for τ_1 τ_2 and π_1 were used. Specifically, the means (standard deviation) for τ_1 τ_2 and π_1 were 0.27 (0.73), 0.82 (0.73) and 0.05 (0.73), respectively.

Model software

The model was implemented in the R programming language (R Core Team, 2021), and using the STOC free R-package (https://github.com/AurMad/STOCfree). It was run for 1000 iterations, with a warm-up of 2000 iterations and two chains. Model convergence was assessed by checking the parameters trace plots.

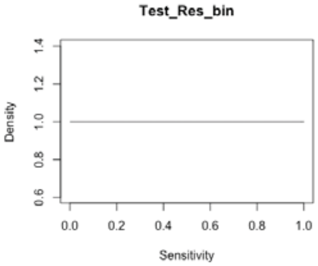

Figure 1a. Prior Beta distributions for the Sensitivity of the testing procedure (declared variable Test Res bin)

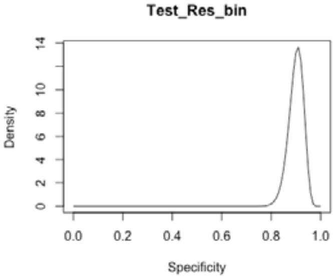

Figure 1b. Prior Beta distributions for the Specificity of the testing procedure (declared variable Test_Res_bin)

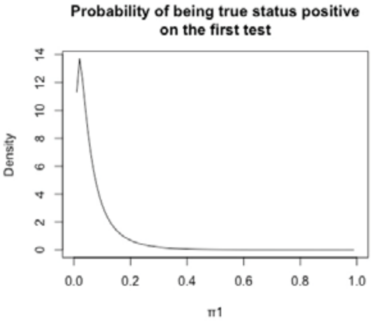

Figure 2a. Prior distribution for the probability of being true-status positive (i.e., the lactating herd contains ≥ 1 seropositive cow) on the first test (π1)

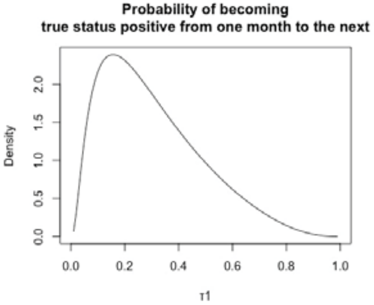

Figure 2b. Prior distribution for the probability of becoming true-status positive (i.e., the lactating herd contains ≥ 1 seropositive cow) from one month to the next ($\tau 1$)

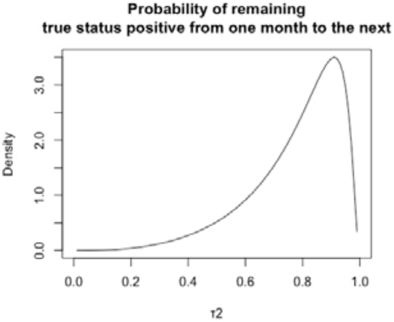

Figure 2c. Prior distribution for the probability of remaining true-status positive (i.e., the lactating herd contains ≥ 1 seropositive cow) from one month to the next ($\tau 2$)

RESULTS

A total of 8,310 BTM test results from 500 Danish dairy herds between 2017 and 2022 were used for this study. This data was used with the prior distributions for the five model parameters to predict antibody-presence (and freedom from antibodies) at the herd-level. The posterior medians and 95% credible intervals (CIs) of the five model parameters are summarized in Table 2. The posterior distribution for the BTM Se was 0.945 (95% CI: 0.92 - 0.96) indicating a high probability that dairy herds with antibodies directed against *S.* Dublin will test positive (≥ 25 ODC%) in a randomly collected single BTM-sample. The posterior distribution for the BTM Sp was estimated to be 0.995 (95% CI: 0.992 - 0.997) indicating a high probability that dairy herds without antibodies directed against *S.* Dublin will test negative (< 25 ODC%). Furthermore, the parameters for the true-latent status (i.e., the lactating herd contains ≥1 seropositive cow) dynamics infer that a herd is very likely to keep having antibodies in BTM from one month to the next (τ_2) (posterior median and 95% CI - 0.96; 0.95-0.97), while it was unlikely that a herd would become status positive from one month to the next (τ_1) (0.004; 0.003 - 0.005).

Table 2. Posterior medians and 95% credible intervals (CIs) for the Sensitivity (Se) and Specificity (Sp) of the testing procedure and the latent status dynamics (τ_1, τ_2, π_1)

Model Parameters	Median	95% CI
Se[a]	0.945	0.921 – 0.962
Sp[b]	0.995	0.992 – 0.997
τ_1[c]	0.004	0.003 – 0.005
τ_2[d]	0.963	0.952 – 0.974
π_1[e]	0.042	0.021 – 0.063

[a] probability of testing positive to BTM (≥ 25 ODC%) given that the herd contains ≥ 1 seropositive cow
[b] probability of testing negative to BTM given that the herd contains no seropositive cows
[c] probability of a herd's latent status becoming positive (i.e., the lactating herd contains ≥ 1 seropositive cow) one month later, given a negative herd latent status in the current month
[d] probability of a herd's latent status remaining positive one month later, given a positive herd latent status in the current month
[e] probability of a herd's latent status being positive (i.e., the lactating herd contains ≥1 seropositive cow) at the beginning

DISCUSSION

This study illustrates an application of the STOC free model (Madouasse et al., 2022) to antibody ELISA tests performed on BTM samples for *S.* Dublin, between 2017 and 2022, in 500 dairy herds from Denmark. It was of interest to explore the model's ability to be fitted to *S.* Dublin data and give meaningful results that are close to estimates from other types of models. The model output provides very high estimates of BTM ELISA Se and Sp, which is due to the pattern of the binary test result; a repetition of only positive/negative results. This also results in high posterior estimates of τ_2, because a repetition of positive test results decreases the uncertainty of it being a false positive and this herd is treated as an infected herd. Again, a repetition of negative test results increases the probability of staying negative between two months, yielding a low posterior estimate of τ_1, i.e., probability of becoming status positive between two consecutive months. In this study the latent variable was the true herd antibody status (determined by the BTM testing procedure that measures antibody presence) and not whether the herd actually had infectious animals. The reported sensitivities for the BTM test are lower in other studies where other diagnostic tests (e.g., bacteriologic culture) were also performed (Veling et al., 2002; Um et al., 2022). Furthermore, Warnick et al., (2006) through a simulation model to estimate the accuracy of herd classification in Danish dairy herds suggested that Se and Sp are not independent of the underlying true herd level prevalence. It is expected that at a higher prevalence there will be more spread, (i.e., disease dynamics) and more false positives and false negatives at any given point in time.

In conclusion, the model can be fitted to *S.* Dublin BTM surveillance data and provide estimates on the probability of antibody-presence (and freedom from antibodies) that are meaningful when compared to estimates from previous studies based on other types of models and comparisons to other true herd status definitions. To this end further work is required to examine how the model and the output behaves under (i) different % ODC cut-off selection (ii) different prior distribution and (iii) different combinations of BTM number of samples.

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CAUSAL INFERENCE IN VETERINARY EPIDEMIOLOGY; TARGET TRIAL EMULATION USING OBSERVATIONAL DATA AS AN ALTERNATIVE TO RANDOMISED CONTROLLED TRIALS

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SUMMARY

This study emulated a randomised controlled trial by applying the causal inference target trial framework to a large observational database. Cranial cruciate ligament rupture in dogs was used as the condition of interest to determine the causal effect of surgical versus non-surgical management on short- and long-term lameness. Inverse probability of treatment and censoring weighting was used to control for confounding and missing data. The risk difference for short-term lameness in surgically managed cases (compared with non-surgically managed cases) was -23.7% (95% CI -35.5% to -11.8%) and the risk difference for long-term lameness -29.4% (95% CI -40.8% to -18.0%). Therefore, the causal effect of surgical management is a risk reduction in short- and long-term lameness compared with non-surgical management in dogs. The study demonstrated that the target trial framework can be successfully adopted to veterinary observational data as an alternative when randomised controlled trials are not available or feasible.

INTRODUCTION

Randomised controlled trials (RCTs), along with their synthesis in the forms of systematic reviews and meta-analyses, are considered the gold standard method for assessing the effectiveness of treatment interventions and are a valuable source of information on which to base clinical decisions (Balshem et al., 2011; Wareham et al., 2017). The primary advantage of RCTs is that random allocation of the treatment provides a means to control confounding (Pfeiffer, 2010). However, RCTs often require large groups, can be costly and ethically challenging and the eligibility criteria may result in trial participants being poorly representative of the wider population of interest (Pfeiffer, 2010). Therefore, observational data are increasingly recognised to represent a valuable alternative resource for information to estimate real-world causal effects, especially in the absence of available randomised experiments (or in complement), and might even more accurately reflect the "usual conditions" under which a treatment would be taken (Maringe et al., 2020).

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Causal inference from large observational databases (Big Data) can be viewed as an attempt to emulate the randomised experiment - the target experiment or target trial - that would answer the question of interest (Hernán and Robins, 2016). Hernán and Robins (2016) have described a framework for research into comparative effectiveness using Big Data that aims to make the target trial explicit (Hernán and Robins, 2016). In broad terms, the framework explicitly defines the "target trial" as the trial we would like to conduct if it were feasible and then describes how to emulate this target trial using observational data. Observational data are subject to various confounding, selection and information biases that can result in underestimation or overestimation of the effect of interest (Dohoo et al., 2009; Hammerton and Munafò, 2021). The target trial emulation, in conjunction with other statistical techniques, such as inverse probability of treatment weighting (IPTW), aims to address and reduce potential confounding bias.

The VetCompass database holds large volumes of anonymised veterinary clinical data with the potential for use to answer causal questions of interest. Cranial cruciate ligament (CCL) rupture is the most frequent specific cause of lameness in dogs (Johnson et al., 1994) and is clinically managed either surgically or non-surgically (Kirkness, 2020). Surgical management is considered the gold standard treatment of choice for a CCL rupture, with multiple surgical techniques available that aim to stabilise the affected stifle and return the dog to full function where possible (Kirkness, 2020). It is reported, based on limited evidence, that the clinical outcomes for dogs managed surgically are superior to dogs managed non-surgically (Comerford et al., 2013; Wucherer et al., 2013), although reasonably good outcomes for small breed dogs managed non-surgically have been reported (Pond and Campbell, 1972; Vasseur, 1984). However, outcomes in dogs across the range of sizes managed surgically versus non-surgically have not previously been directly compared.

Using anonymised veterinary clinical data from the VetCompass Programme (VetCompass, 2019), this study aimed to implement the target trial framework to answer causal questions for veterinary first opinion observational data. More specifically, this study aimed to compare the effects of surgical management relative to non-surgical management on short- and long-term lameness for CCL rupture in dogs. Duration of analgesia prescription was also assessed as a secondary outcome. Since the study uses observational data, target trial emulation and causal inference analyses were adopted to attenuate confounding bias. To the authors' knowledge, this is the first study to adopt the target trial framework for veterinary observational data, whilst also the first to focus on estimating the treatment effect of surgical versus non-surgical management of CCL rupture in dogs.

MATERIALS AND METHODS

Data source and power calculation

VetCompass collates de-identified electronic health record (EHR) data from primary-care veterinary practices in the UK for epidemiological research (VetCompass, 2019). The study population included all available dogs under primary veterinary care at clinics participating in the VetCompass Programme during 2019. Available data fields included a unique animal identifier along with species, breed, date of birth, sex, neuter status, insurance status and bodyweight, and also clinical information from free-form text clinical notes, summary diagnosis terms (The VeNom Coding Group, 2019) and treatment with relevant dates.

Sample size calculations estimated that approximately 224 surgical cases and 56 non-surgical cases were required, assuming 30% of surgical cases and 50% non-surgical cases had long term lameness, 80% power, 95% confidence and a ratio of surgical to non-surgical cases of 4:1 (Vasseur, 1984; Christopher et al., 2013; Taylor-Brown et al., 2015), using ClinCalc Sample Size Calculator (www.clincalc.com). Ethics approval was obtained from the RVC Social Science Ethical Review Board (reference number SR2018-1652).

Case definition, finding and covariates

Incident cases only were included in the study, with these cases defined as dogs aged ≥ 1.5 years and < 12 years first diagnosed with unilateral cruciate ligament rupture in either stifle between January 1 and December 31, 2019; and with no prior history of contralateral ligament rupture or stifle surgery. Candidate cases were identified by applying search terms relevant to the diagnosis and management of CCL rupture in the clinical notes (Taylor-Brown et al., 2015). The search findings were merged, and a random subset of these candidate cases had their clinical notes examined manually in detail to identify dogs that met the case definition. For dogs that met the case definition, demographic data were extracted automatically from the VetCompass database, with further data relating to clinical management extracted manually from the EHR.

Based on existing evidence and expert opinion, a directed acyclic graph (DAG) was constructed that encapsulates beliefs about the causal relationships relevant to the question of interest. The DAG was used to identify which variables should be controlled for (Greenland et al., 1999), with data on the following variables consequently extracted: age, breed, bodyweight, overweight status, neuter status, insurance status, non-orthopaedic comorbidities, orthopaedic comorbidities and veterinary group. Long-term lameness was evaluated as a primary outcome, with short-term lameness and analgesia prescription secondary outcomes (with the same covariate set for analgesia prescription as for lameness). Lameness was categorised as "lameness", "no lameness" or "lameness not recorded". Short-term lameness was defined as evidence of lameness in the limb diagnosed with CCL rupture reported in the EHR at 6 weeks – 4.5 months after diagnosis of CCL rupture. Long-term lameness was defined as evidence of lameness in the limb diagnosed with CCL rupture reported in the EHR at 7.5 months – 16.5 months after diagnosis. Lameness recorded between 4.5 and 7.5 months was not included in this analysis as few dogs fell into this category. Analgesia prescription was defined as "prescription", "no prescription" or "prescription information not available". Final prescription date for analgesia dispensed specifically for CCL rupture was extracted and prescription at 3-, 6- and 12-months after diagnosis recorded.

Age at diagnosis (years) was included as a continuous variable. Breed included all specific breeds with at least 15 dogs managed surgically or 5 dogs managed non-surgically, with remaining dogs grouped as either "Purebred – Other" or "Crossbred". Adult bodyweight was categorised as "< 15kg", "≥ 15kg" or "not recorded". Overweight status within 12 months prior to CCL rupture diagnosis was categorised as "overweight/obese", "ideal bodyweight", "underweight" or "not recorded". Neuter status was defined as "neutered" or "entire" and insurance status as "insured" or "non-insured". Orthopaedic comorbidities at (or within one month prior to) diagnosis were included as a distinct disorder if at least 10 dogs managed either surgically or non-surgically were affected with the condition. Otherwise, they were recorded as "other comorbid disorders". Presence of non-orthopaedic comorbidities at (or within one month prior to) diagnosis were categorised as "yes" or "no".

Target trial specification and emulation

A target trial of interest was specified and emulated using EHR data (Danaei et al., 2013; Hernán and Robins, 2016; Hernán and Robins, 2020). The surgical management intervention was defined as dogs receiving surgery within 4 weeks of CCL rupture diagnosis, to ensure the strategy was reflective of clinical practice. Non-surgical management was defined as dogs not receiving surgery in the 4 weeks after diagnosis (with or without any additional strategy such as rest, analgesia and physiotherapy). Dogs were censored at loss to follow up, death, or administrative censoring (i.e., at the end of the study period). Dogs that switched from non-surgical to surgical management were censored at the date of surgery. Dogs with a subsequent contralateral CCL rupture were censored at the date of the subsequent rupture. The intention to treat was not known from the data, therefore the per protocol effect was estimated. The risk differences in presence of lameness and analgesia prescription at follow-up in dogs managed surgically compared to dogs managed non-surgically were computed. Age at first diagnosis of CCL, breed, bodyweight, insurance status, orthopaedic comorbidities, presence of non-orthopaedic comorbidities, overweight status and vet group were included as adjustment variables for inverse probability of treatment weighting.

Statistical analysis of the emulated trial

Lameness and prescription of analgesia at follow-up were compared between dogs managed surgically and dogs managed non-surgically for CCL rupture. To emulate randomisation at the baseline point of diagnosis with CCL rupture, the following variables were considered sufficient to control for confounding: age, breed, bodyweight, insurance status, neuter status, orthopaedic comorbidities at diagnosis, non-orthopaedic comorbidities at diagnosis, overweight status and veterinary group attended (as categorised above and based on the DAG).

Inverse probability of treatment weighting (IPTW) was used to adjust for confounding. For IPTW, a pseudo-population is created by weighting each individual in the population by the inverse of the conditional probability of receiving the treatment level they did receive (Hernán and Robins, 2020). The goal was to balance covariates between the two treatment groups (Barter, 2017). To derive the weights using IPTW, a binary logistic regression model was first fitted, with treatment (surgical versus non-surgical) as the outcome regressed on the main term confounding variables described (i.e., including no interaction or non-linear terms). The model generated predicted probabilities for each dog of receiving either treatment, which were then used to calculate stabilised inverse probability (IP) weights (Xu et al., 2010).

Censored dogs were accounted for in the IPTW analysis using inverse probability of censoring weighting (IPCW). IPCW compensates for censored subjects by giving more weight to subjects with similar characteristics who are not censored (Dong et al., 2020). To perform IPCW, a binary logistic regression model at each outcome time point (short- and long-term lameness and analgesia prescription at 3-, 6- and 12-months) was fitted, with censor as the outcome regressed on treatment and the confounding variables described. The model generated predicted probabilities of being censored, which were then used to calculate IP of censoring weights. These weights were then combined (by multiplication) with the stabilised IP weights generated from IPTW and used to weight each individual's contribution to the binary logistic regression outcome models (Robins and Finkelstein, 2000; Hernán and Robins, 2020). Separate models were created for each outcome (short-term lameness, long-term lameness and analgesia prescription at 3-, 6- and 12-months), based on the weighted data and regressed on treatment i.e., surgical or non-surgical management for CCL rupture. The robust (or sandwich) variance estimator was used to obtain valid standard errors (Zou, 2004).

The standardised mean difference (SMD) examines the balance of covariate distribution between treatment groups (Zhang et al., 2019). For each covariate SMDs for pre- and post-IPTW were calculated, with SMD < 0.1 indicating good covariate balance between the two treatment arms (Austin, 2009). Missing data were handled using the missing-indicator method, which uses a dummy variable in the statistical model to indicate whether the value for that variable is missing (Burton and Altman, 2004). Data were checked for internal validity and cleaned in Excel (Microsoft Office Excel 2013, Microsoft Corp.), with analyses conducted using R version 4.0.2 (R Core Team, Vienna, Austria). The "IPW" package was used to generate IP weights (and validated manually) (van der Wal and Geskus, 2011), with code for IPCW derived from Hernán and Robins (2020). The "survey" package was used for binary logistic regression outcome modelling (Oberski, 2014).

RESULTS

The database contained EHRs for 2,250,741 dogs under primary veterinary care in the VetCompass database during 2019. CCL search terms yielded 32,372 candidate cases, of which 4,122 (12.7%) were manually reviewed. Of these, 815 (19.8%) were confirmed CCL cases eligible for the emulated trial. Specifically, the emulated trial included 615 (75.5%) surgical cases and 200 (24.5%) non-surgical cases. There were 21 (10.5%) originally non-surgical cases that went on to have surgery and were censored at date of surgery. The number of surgically and non-surgically managed cases of dogs diagnosed with CCL rupture by selected categorical variables are summarised in Table 1.

Descriptive analysis of clinical outcomes

The following descriptive analysis of clinical outcomes reports confounded estimates i.e., prior to methods used to adjust for confounding and excludes dogs with missing outcome data. A smaller proportion of dogs managed surgically (compared to non-surgically) had short-term lameness (32.2% versus 55.3%, risk difference (RD) -23.1%) and long-term lameness (16.7% versus 43.3%, RD -26.6%). Likewise, a smaller proportion of dogs managed surgically had an analgesic prescription at ≥ 3 months (27.4% versus 60.1%, RD -32.7%), ≥ 6 months (21.4% versus 48.5%, RD -27.1%) and at ≥ 12 months (17.4% versus 39.7%, -22.3%) than dogs managed non-surgically.

Emulated trial results

The standardised mean differences between groups for each of the covariates pre and post IPTW are shown in Table 2. Other than breed, the standardised mean differences in the weighted sample were all below 0.1 for each covariate, indicating well-balanced groups post weighting. Therefore, breed was also added to weighted outcome models, to further control for any residual confounding. The final models included the following main effect covariates to generate propensity scores: age, breed, bodyweight, overweight status, neuter status, insurance status, non-orthopaedic comorbidities, orthopaedic comorbidities and veterinary group. Whilst management and breed were included as separate terms in the outcome models.

Table 1. Numbers (%) of surgically (n = 615) and non-surgically (n = 200) managed cases of dogs diagnosed with cranial cruciate ligament rupture attending primary-care veterinary practices in the VetCompass Programme in the UK by selected categorical variables

Variable	Category	Surgical no. (%)	Non-surgical no. (%)
Breed	Crossbred	175 (28.5)	58 (29.0)
	Labrador Retriever	42 (6.8)	5 (2.5)
	Jack Russell Terrier	39 (6.3)	17 (8.5)
	West Highland White Terrier	24 (3.9)	7 (3.5)
	Staffordshire Bull Terrier	24 (3.9)	7 (3.5)
	Golden Retriever	22 (3.6)	3 (1.5)
	English Springer Spaniel	22 (3.6)	9 (4.5)
	Cocker Spaniel	21 (3.4)	11 (5.5)
	Yorkshire Terrier	20 (3.3)	8 (4.0)
	Bichon Frise	20 (3.3)	6 (3.0)
	Rottweiler	15 (2.4)	4 (2.0)
	Purebred - other	191 (31.1)	65 (32.5)
Bodyweight (kg)	< 15	242 (39.3)	103 (51.5)
	≥ 15	307 (49.9)	70 (35.0)
	Not recorded	66 (10.7)	27 (13.5)
Neuter status	Entire	167 (27.2)	73 (36.5)
	Neutered	448 (72.8)	127 (63.5)
Insurance status	Non-insured	171 (27.8)	110 (55.0)
	Insured	444 (72.2)	90 (45.0)
Overweight status	Overweight/obese	179 (29.1)	81 (40.5)
	Ideal bodyweight	46 (7.5)	19 (9.5)
	Not recorded	390 (63.4)	100 (50.0)
Orthopaedic comorbidity at diagnosis	No recorded comorbidity	413 (67.2)	149 (74.5)
	Osteoarthritis	146 (23.7)	37 (18.5)
	Patellar luxation	26 (4.2)	10 (5.0)
	Other	30 (4.9)	4 (2.0)
Non-orthopaedic comorbidities at diagnosis	No	592 (96.3)	180 (90.0)
	Yes	23 (3.7)	20 (10.0)
Veterinary Group	1	171 (27.8)	53 (26.5)
	2	204 (33.2)	60 (30.0)
	3	16 (2.6)	7 (3.5)
	4	115 (18.7)	29 (14.5)
	5	109 (17.7)	51 (25.5)

Table 2. Standardised mean differences (SMD) for each of the prespecified covariates before and after applying inverse probability of treatment weighting

Variable	SMD before weighting	SMD after weighting
Breed	0.285	0.254
Age (years)	0.416	0.022
Bodyweight (kg)	0.306	0.036
Neuter status	0.202	0.040
Insurance	0.574	0.014
Overweight status	0.274	0.044
Orthopaedic comorbidities at diagnosis	0.216	0.030
Non-orthopaedic comorbidities at diagnosis	0.249	0.019
Vet group	0.213	0.048

After balancing covariates between the surgical and non-surgically managed dogs using IPTW, and accounting for censoring using IPCW, surgical management reduced risk of short- and long-term lameness compared with non-surgical management. Additionally, surgical management reduced the proportion of dogs being prescribed analgesia at 3, 6 and 12 months after diagnosis compared to non-surgical management. Specifically, the risk difference for short-term lameness in dogs treated surgically versus non-surgically was -23.7% (95% CI -35.5 to -11.8), whilst the risk difference for long-term lameness was -29.4% (-40.8 to -18.0). The risk difference for analgesia prescription in dogs treated surgically versus non-surgically was -36.2% (-45.0 to -27.3) at 3 months, -30.2% (-39.7 to -20.7) at 6 months and -26.7% (-38.0 to -15.3) at 12 months following diagnosis.

DISCUSSION

Using IPTW to control for confounding in conjunction with IPCW, it was identified that surgical management of CCL rupture resulted in reduced risk of short- and long-term lameness compared with non-surgical management. Additionally, surgical management caused reduced risk of analgesic prescription at 3-, 6- and 12-months compared with non-surgical management.

After balancing covariates between surgically and non-surgically treated dogs using IPTW, accounting for censoring using IPCW and adjusting further for breed, the marginal risk difference for short-term lameness in dogs treated surgically versus non-surgically was -23.7%, whilst the risk difference for long-term lameness was -29.4%. Clinically, these results highlight that surgical management of CCL rupture results in improved short- and long-term lameness outcomes compared to non-surgical management, and to a similar extent at both the short- and long-term time points. This is consistent with a previous study in which subjective lameness outcomes at 3 and 12 months respectively were improved by 20.6% and 11.4% in dogs managed surgically compared with those managed non-surgically (Wucherer et al., 2013). The long-term lameness improvement was less marked at 12 months in the previous study, compared to the current study, however this previous study used descriptive analysis methods only and was restricted to just 40 overweight dogs weighing > 20kg.

The findings for analgesia prescription in the current study are consistent with those of lameness, with the risk difference for analgesia prescription in dogs treated surgically versus non-surgically -36.2% at 3 months, -30.2% at 6 months and -26.7% at 12 months following diagnosis. This finding suggests analgesia prescription could be used as proxy measure for lameness. Whilst the risk difference for lameness slightly increased from short- to long-term follow-up, the risk difference for analgesia prescription reduced, i.e. was greatest at 3 months following diagnosis. It is generally recommended that dogs are prescribed analgesia for a period of two weeks following surgery for CCL rupture, to account for post-operative pain, provided there are no post-operative complications affecting this decision (Gruen et al., 2014). Therefore, this might explain the slightly increased risk difference in analgesia prescription at 3 months relative to 6 and 12 months, as uncomplicated surgical cases are likely to cease analgesic treatment by two weeks after surgery, with residual usage more likely to relate to CCL-related pain rather than post-operative.

The limitations of this study are similar to previous VetCompass studies, and are largely based on the nature of retrospective analysis of EHR data, including missing data, loss to follow-up and application of an appropriate case definition to the primary-care data available, that is neither too specific nor too broad (O'Neill et al., 2014). However, we used appropriate statistical methods to account for missing data and loss to follow-up. Expert opinion was sought in construction of the DAG, however it is possible unmeasured confounders could influence the risk differences calculated. Longer-term outcomes were not assessed, which further prospective studies might help to address.

Overall, this study demonstrated the application of the target trial framework to veterinary observational data. CCL rupture was used as the diagnosis of interest, with lameness and analgesia prescription as outcomes. The findings show that surgical management causes a reduction in short- and long-term lameness compared with non-surgical management in dogs of all sizes. These findings can inform discussions between veterinarians and owners when deciding on treatment for CCL rupture.

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TRANSMISSION MODELLING

MODELLING PATHOGEN-SPECIFIC INFECTION DYNAMICS OF BOVINE RESPIRATORY DISEASE IN A MULTI-BATCH FATTENING FARM

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SUMMARY

Bovine Respiratory Disease (BRD) affects young bulls, causing animal welfare concerns as well as economical costs. BRD is caused by an array of pathogens as well as environmental factors. How farming practices influence the spread of these causal pathogens remains unclear. Our goal was to assess the impact of zootechnical practices on the spread of three causal agents of BRD, namely bovine respiratory syncytial virus (BRSV), *Mannheimia haemolytica* and *Mycoplasma bovis*. To that extent, we used a stochastic mechanistic model monitoring risk factors, infectious processes, detection and treatment in a farm possibly featuring several batches. The model was calibrated using data extracted from literature. Small batches were found to be more effective for reducing the spread of pathogens. Moreover, it was found that individual risk level heterogeneity in batches contributed to reducing epidemic peaks and antimicrobial usage. These findings provide supporting evidence for optimal farming practices for limiting BRD occurrence.

INTRODUCTION

Bovine Respiratory Disease (thereafter named BRD) is a disease of the lower respiratory tract of cattle that is multifactorial in origin and considered a worldwide economic and sanitary burden in the cattle farming industry (Babcock et al., 2009; Delabouglise et al., 2017). Its management also raises concerns in terms of extensive antimicrobial use (AMU) (Ollivett, 2020). In France, it has been estimated that the cost of BRD could represent up to 20% of farmers' income (Bareille et al., 2009). Although many efforts have been made in prevention and treatment of BRD, both morbidity and mortality have increased over the past 20 years (Hilton, 2014).

BRD is caused by several pathogens such as commensal bacteria and viruses (Biswas et al. 2013), enhanced by compromised host immune system, and environmental factors (Grissett et al., 2015). In Europe, the most common bacteria associated with BRD complex are *M. bovis, M. haemolytica* and *P. multocida.* As for viruses, bovine respiratory syncytial virus (BRSV), and parainfluenza virus type 3 (PI3) are the most reported (Grissett et al., 2015). Each of the BRD pathogens has unique features that contribute to the ability of the pathogen to cause the disease and to resist host defenses (Gershwin et al., 2015). Unfortunately, the symptoms caused by the different agents are not specific of a given pathogen; BRD symptoms include depression,

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cough, nasal discharge, whatever the causative pathogen (Griffin et al., 2010). Consequently, the causative pathogen is generally not precisely identified in the event of an outbreak on farm (Griffin, 2014).

The individual risk of contracting BRD, and subsequently spreading it, is heterogeneous among animals upon arrival at feedlots (Poizat et al., 2019). Environmental factors increasing the probability of BRD onset include stress, weaning, poor sanitary situation of the breeding farms (Grissett et al., 2015). In Europe, this risk is not taken into account at pen constitution (Poizat et al., 2019).

The organisation of the European cattle production system is based on practices that can affect the welfare, health and growth performance of young bulls (Herve et al., 2020). In this system, most young bulls from beef breeds are produced by cow/calf breeders and fattened by specialised fatteners (Poizat et al., 2019). After weaning, young bulls are transported to sorting facilities and sorted in batches by bodyweight, then shipped to the fatteners. These operations were shown to cause stress affecting cattle performance (Cernicchiaro et al., 2012). Moreover, including individual BRD risk factors into consideration when composing batches could play a role in young bull health on feedlots (Herve et al., 2020). However, whether the batches should be homogeneous or not in terms of individual risk level has not been addressed yet.

Modelling could be a way to explore the influence of farming practices on the spread of pathogens involved in BRD. Modelling is used in order to understand complex infection dynamics and rank intervention scenarios (Ferguson et al., 2005; Keeling, 2005). In the case of BRD, models describing mathematical equilibria in a BRSV epidemic have been published (Greenhalgh and Griffiths, 2009), as well as models ranking interventions and zootechnical practices, such as metaphylaxis and pen size (Picault et al., 2019; Picault et al., 2022). Risk factors were also used in predictive tools showing limited success (Babcock et al., 2013; Amrine et al., 2019). However, no model combining pathogen specific dynamics with scenario ranking on medical and zootechnical interventions has been published yet.

Our objective in this paper is to get a better understanding of the impact of farming practices on the spread of different pathogens involved in BRD. To that extent, we will be using an original multi-batch mechanistic stochastic model.

MATERIALS AND METHODS

We chose to model the spread of BRSV, *M. haemolytica*, and *M. bovis* as they are representatives of the three different groups of pathogens frequently involved in BRD: respiratory viruses, pasteurellaceae, and mycoplasms, respectively. They are also widely reported as causing primary cellular damage and may have a role in coinfection (Rice et al., 2007; Brodersen, 2010).

Global model structure

We implemented an original stochastic mechanistic individual-based model calibrated with three sets of parameters relative to each pathogen. This model was developed in the framework EMULSION (Picault et al., 2019). This framework fosters a decomposition of the modelled events and processes. Processes are described as finite state machines, a formalism broadly used in computer science to represent states and transitions, and able to encompass flow diagrams more classically used in epidemiological modelling.

Processes and assumptions: The model is an individual-based stochastic model in discrete time (time step of 1/2 day). It monitors six processes: risk status, hyperthermia, health status, clinical signs, detection, and treatment. Each of these processes has several states, listed in Table 1.

Risk status defines the individual risk of shedding pathogens and of becoming infected. It provides qualitative information on the level of stressors known by the individual prior to its arrival at feedlot. The higher the risk, the higher the infection rate and the more likely the animal is to shed pathogens if infected.

Hyperthermia state machine is composed of two states: hyperthermic (H) and non-hyperthermic (NH) animals. NH becomes H with probability pH due to non-infectious causes, and then stays in H for a duration dH drawn in a Beta distribution calibrated from observed data, before returning to NH. The transitions from NH to H and then back to NH can also be totally driven by the infection process.

We considered four health statuses: susceptible (S), asymptomatic carrier (AC), infectious (I), and recovered (R) animals. Asymptomatic carriers can spontaneously turn infectious with probability p_AC but can also be infected by surrounding infectious individuals. When entering I state, two actions are triggered: (1) a delay before exhibiting observable clinical signs dC is drawn from a Beta distribution calibrated from observed data, (2) the animal changes from NH to H state. Recovery without partial immunity (transition from I to S) occurs after duration dI drawn from a gamma distribution according to the given bacterial pathogen. For BRSV, the individual will transition to recovered (R) state at the end of the infection. Recovered individuals can still be subsequently infected, but with a lesser rate, which represents partial immunity. This state only exists for viral infections. When returning to S or R state, animals changes from H to NH.

Transitions from not treated (NT) to treated (T) state are driven by diseased animal detection. Two detection methods were included. A visual on-farm appraisal of clinical signs is modelled, assuming depression is the most significant sign to calibrate the delay (dC) between infection and sign occurrence. In the model, this detection mode can be used at any time for any animal. The detection of the first case by visual appraisal is followed by identifying all hyperthermic animals via rectal temperature measured at next feeding time 12h later.

Each animal detected as diseased or hyperthermic receives one antibiotic dose, assumed to be effective after duration dT. Animals still hyperthermic after this duration are treated again (same duration), the number of treatments per episode being limited (maxT). Transitions from T to NT occurred in three cases: (1) recovery after dT due to treatment with probability pr, (2) end of infection while under treatment, (3) still hyperthermic but already treated maxT times (treatment failure). In spite of the absence of curative treatment for viral infections, the treatment process is kept in order to monitor the antimicrobial use caused by virus (i.e., when no pathogen identification is performed). The treatment success probability is however null in this case.

Table 1. Detailed states of each model process

Risk status	Hyperthermia	Health state	Clinical signs	Detection	Treatment
Low risk (LR)	Hyperthermic (H)	Susceptible (S)	Asymptomatic (A)	Detected (D)	Treated (T)
Medium risk (MR)	Non hyperthermic (NH)	Asymptomatic carrier (AC)	Mild clinical signs (MC)	Undetected (U)	Non treated (NT)
High risk (HR)		Infectious (I) Recovered (R)	Severe clinical signs (C)		

Force of infection: The computation of the force of infection (FOI) allows taking into account the multi-batch nature of our model. Let B be the set of batches of n individuals each raised simultaneously in a farm. In each batch i, the intra batch force of infection is the sum of the individual contribution β_d of each infectious individual of risk level d ($I_{d,i}$). The contribution increases with the individual risk level d. Mathematically, this translates to Eq.(1).

In a given batch i, the susceptible individuals experience an intra batch force of infection with the addition of the contributions of the other batches of set B deprived of i ($B\backslash\{i\}$) multiplied by a scaling factor c accounting for a smaller contact rate between animals of different batches. A susceptibility factor σd increasing with the individual risk level d multiplies this total. Mathematically, this translates to Eq.(2).

$$\forall i \in B, \lambda_i = \sum_{d \in D} \beta_d I_{d,i} \tag{1}$$

$$FOI_i = \sigma_d \left(\frac{\lambda_i + c \sum_{b \in B \backslash \{i\}} \lambda_b}{N_i + c(N - N_i)} \right) \tag{2}$$

with D the set of individual risk levels, b_d the shedding level of individual with risk level d, $I_{d,i}$ the number of infectious individuals with risk level d in batch i, N_i the total number of individuals in batch i, $N > 0$ the total population size.

Review of individual pathogen characteristics

In order to find the relevant information to implement pathogen-specific models, a literature review was performed. The database used for this investigation was the Web of Science with queries built as pathogen name + (BRD OR respiratory disease OR cattle) + parameter name. Inclusion criteria for this investigation were the country of origin (Europe) as well as the size of the studied sample. The models were meant to fit a European context, with relatively small pen sizes (<50).

Key information for building our model were relative to pathogen transmission (rate, probability of spontaneous shedding), duration of clinical signs, infectious period and probability of displaying severe forms. Information on the probability of treatment success was also taken into account. In total, we used data from 16 articles to calibrate our model on BRSV, *M. haemolytica* and *M. bovis*. The parameters are summarised in Table 2.

Tested scenarios

We investigated the influence of pen size and composition on the spread of the three pathogens. To do so, we built four scenarios and assessed the importance of batch size and composition in the appraisal of cases:

Sc1: 10 batches of 20 individuals each with equal distribution of animals among the three possible individual risk levels (30, 40 and 30 % of low, medium and high risk animals, respectively).

Sc2: 10 batches of 20 individuals each with animals sorted by risk level. The risk level proportions at farm level remain equal to Sc1.

Sc3: 1 batch of 200 individuals with the same distribution of risk levels as in Sc1.

Sc4: same as Sc1, but with proportions of individual risk levels of 60, 30 and 10 % for low, medium and high risk respectively.

Each of these four scenarios was tested on each pathogen with identical initial conditions of 200 individuals fattened for 40 days. The initial proportions of carriers were set by pathogen according to epidemiological data reported in Table 2. The inter batch contact rate was set at 0.01. Each scenario had 100 stochastic replicates.

We observed the peak appraisal of clinical signs and its persistence, with and without treatment of detected cases. We also observed the number of treatment doses used. The distributions along the repetitions are not statistically different from a normal distribution (Shapiro test, p-value<0.05). We thus used the Student's t-test for comparing scenarios, arbitrarily taking Sc1 as the reference scenario. The significance threshold was set at 5%. In the figures, we used standard graphic formalism for significance levels: * symbolises a p-value ≤ 0.05, ** a p-value inferior to 0.01, *** a p-value inferior to 0.001 and **** a p-value inferior to 0.0001. The mention ns stands for non significant.

Table 2. Parameter values used for bovine respiratory syncytial virus (BRSV) as a model of respiratory virus, Mannheimia haemolytica (M. haemolytica) as a model of Pasteurellaceae and Mycoplasma bovis (M. bovis)

	BRSV		*M. haemolytica*		*M. bovis*	
Parameter	Value	Source	Value	Source	Value	Source
Transmission rate to susceptible *(β)*	3/day	[26]	0.005/h	Expert opinion	0.005/h	Expert opinion
Transmission rate to recovered *(β2)*	0.095/day	[26]	NA		NA	
Spontaneous shedding probability	0.91	[24]	0.14	[27]	0.65	[28]
Initial prevalence	0.63	[29], [30]	0.48	[31]	0.094; 0.4 and 0.6 for low, medium and high risk level respectively	[23], [32], [33]
Clinical sign duration	2-10 (med=5) days	[7]	2-8 days	[7]	5-13 (med=8) days	[7]
Infectious period duration	7-17 (med=12) days	[7]	14.8 (CI 95: 10.6-20.9)	[34]	14-28 (med=21) days	[7]
Asymptomatic period duration	2-5 (med=3) days	[7]	1 day	[7]	1-5 (med=2) days	[7]
Probability of successful treatment	0		0.71	[35]	0.6	[23]
Probability of severe forms	0.6	[36]	0.65	[31]	0.23	[28]

RESULTS

Sorting animals in batches according to their risk level led to stratified circulation of every pathogen, especially for bacteria (Fig.1, middle column). Batches composed mainly of high risk individuals tend to have a higher epidemic peak, as well as a persistent pathogen circulation at steady state. As risk levels modulate pathogen prevalence as well as transmission rate and susceptibility, this was an expected finding. Conversely, we observe that all batches behave similarly in Sc1 and Sc4.

At farm scale, Fig.2 shows that only the scenario with increased low risk proportion (Sc4) showed an average epidemic peak significantly lower than Sc1 for every pathogen (p-value < 0.05). For *M. haemolytica*, the scenario with batches sorted by risk levels (Sc2) significantly reduced the height of the average epidemic peak in comparison to Sc1. This scenario did not perform as good with *M. bovis*; conversely, the scenario with one unique batch (Sc3) yielded significantly lower average peak when compared to Sc1.

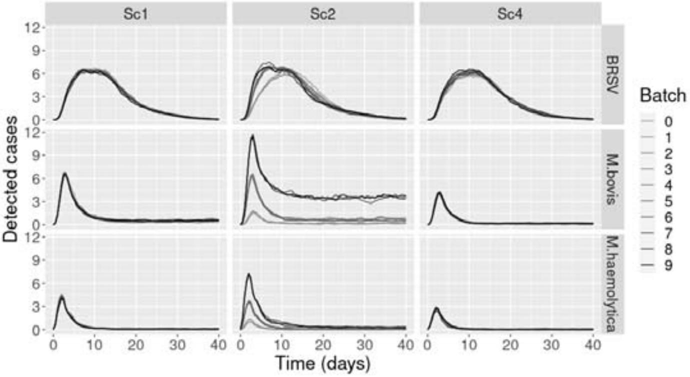

Figure 1. Average number of detected cases (by displaying either clinical signs or hyperthermia) in each batch over time. In lines: pathogens. Left column: 10 batches with equal risk level proportions of 30, 40 and 30 % of low, medium and high risk individuals respectively (Sc1). Middle column: batches 0 to 2 are entirely composed of low risk individuals, 3 to 6 are entirely composed of medium risk level and 7 to 9 are entirely composed of high risk individuals (Sc2). Right column: 10 batches with equal proportions of 60, 30 and 10 % of low, medium and high risk individuals respectively (Sc4)

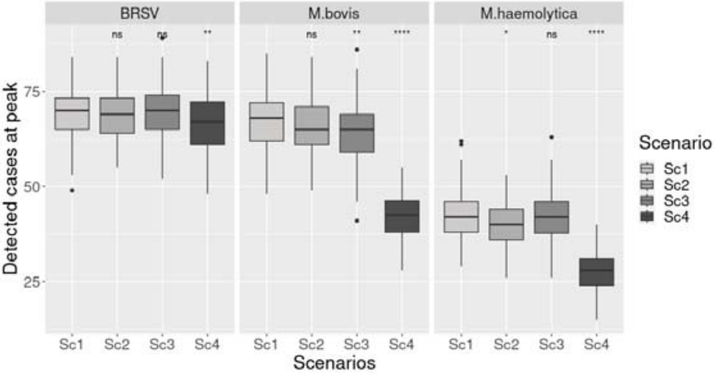

Figure 2. Impact of the scenarios on the height of the peak of detected cases (by either clinical signs or hyperthermia) for each pathogen. Sc1: 10 batches with equal risk level proportions of 30, 40 and 30% of low, medium and high risk individuals respectively. Sc2: 10 batches of 20 individuals sorted by individual risk levels. Sc3: one unique batch of 200 individuals, with the same risk level proportions as Sc1 and Sc2. Sc4: 10 batches with equal proportions of 60, 30 and 10 % of low, medium and high risk individuals respectively. Sc1 is the reference scenario for the Student's t-tests

In spite of close epidemic peaks, the measure of the visible persistence of the three pathogens was more contrasted (Fig.3, Fig.4). Consistently with field study, Fig.4 shows that *M. bovis* had the highest case persistence among the three pathogens. Surprisingly, sorting animals into batches according to their individual risk level increased persistence. This observation could also be made for BRSV and *M. haemolytica*. A unique large batch (Sc3) also yielded significantly higher persistence for BRSV and *M. bovis*. As expected, the lowest persistence distributions for both bacterial agents were found when the initial proportion of low risk individuals in the farm was larger.

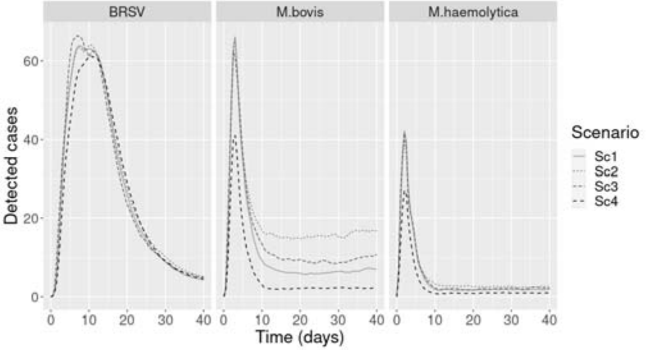

Figure 3. Impact of the scenario on average case detection (by either clinical signs or hyperthermia) over time at farm scale sorted by pathogen. Sc1: 10 batches with equal risk level proportions of 30, 40 and 30% of low, medium and high risk individuals respectively. Sc2: 10 batches of 20 individuals sorted by individual risk levels. Sc3: one unique batch of 200 individuals, with the same risk level proportions as Sc1 and Sc2. Sc4: 10 batches with equal proportions of 60, 30 and 10% of low, medium and high risk individuals respectively

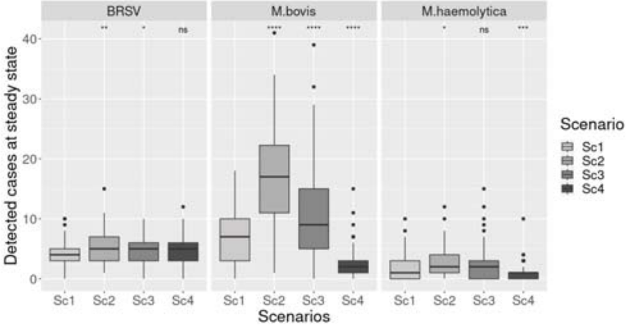

Figure 4. Pathogen persistence in each scenario. Sc1: 10 batches with equal risk level proportions of 30, 40 and 30% of low, medium and high risk individuals respectively. Sc2: 10 batches of 20 individuals sorted by individual risk levels. Sc3: one unique batch of 200 individuals, with the same risk level proportions as Sc1 and Sc2. Sc4: 10 batches with equal proportions of 60, 30 and 10% of low, medium and high risk individuals respectively. Sc1 is taken as the reference scenario for the Student’s t-tests

Monitoring antimicrobial usage also proves to be impacted by batch size and composition. Indeed, Fig.5 shows that AMU was significantly higher when batches were sorted or when the farm was composed of a unique batch. These results however did not hold for BRSV, as the distributions were not significantly different from one another, except for Sc4.

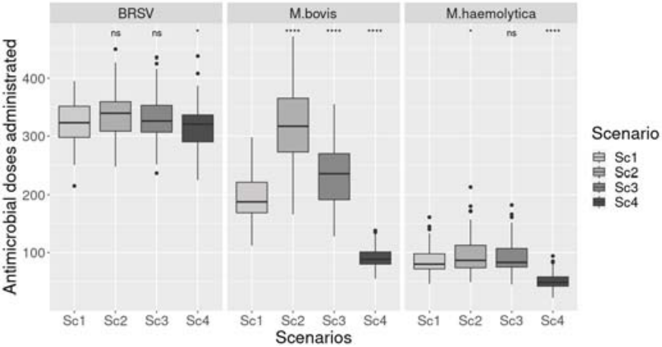

Figure 5. Impact of batch size and composition on total antimicrobial usage. Sc1: 10 batches with equal risk level proportions of 30, 40 and 30 % of low, medium and high respectively. Sc2: 10 batches of 20 individuals sorted by individual risk levels. Sc3: one unique batch of 200 individuals, with the same risk level proportions as Sc1 and Sc2. Sc4: 10 batches with equal proportions of 60, 30 and 10 % of low, medium and high risk individuals respectively

DISCUSSION

We showed that batch size has an impact on the spread of two of the main pathogens involved in bovine respiratory diseases (BRD), namely BRSV and M. bovis. As underlined in Picault et al. (2022), bigger batches tend to increase the risk of BRD. In other published research, higher prevalence of respiratory diseases can be found in larger groups in veal calves or in other species such as chickens (Studer et al., 2021; Tablante et al., 1999). We could thus expect several smaller pens to be a better option than a single large pen. However, the impact could be mitigated by inter-batch transmission, and further investigation should be conducted on this matter.

Our model also allowed us to assess the importance of batch composition on pathogen circulation at farm scale. Our results showed that reducing the proportion of high-risk individuals in the fattening farm successfully reduces the size of the epidemic peak as well as the persistence of the pathogen in the population. This finding is in agreement with results obtained in Hervé et al. (2020). This author highlighted that minimising transportation and increasing vaccination yielded better cattle performances. We tested this assumption through individual risk level, which indirectly summarised these factors. Similar conclusions were drawn out in Hay et al. (2014), where group composition and the distance travelled were proven to be risk factors for developing BRD. We built the model under the assumption that individual risk level influences the susceptibility of the individuals, as well as their transmission rate in the event of their infection. In other words, a population with more high-risk individuals is more susceptible to infection and infectious animals are more likely to contaminate susceptible ones.

However, it appeared that composing batches according to such individual risk levels tended to translate to a higher pathogen persistence. This can be explained by the fact that pathogen circulation is mostly maintained by the high-risk batches. As we do consider inter-batch transmission, these high-risk groups constitute a reservoir for the rest of the farm. This result is surprising as we expected a protective effect of sorted batches. Indeed, animals coming from similar breeder farms should be of similar risk level. Minimising the number of source farms for batch composition has been shown to reduce the risk of BRD outbreak (Morel-Journel et al., 2021). However, it has also been shown that body weight (BW) heterogeneity participates in reducing the risk of outbreak (Herve et al., 2020). Such heterogeneity cannot be obtained by animals coming from the same breeder as one breeder tends to produce animals of homogeneous BW. Therefore, there is a trade-off to consider at batch composition. Further data are needed to quantify this trade-off.

Moreover, our simulations showed that the antimicrobial usage (AMU) was the highest in the scenario with sorted batches. Conversely, in Santinello et al. (2022), sorting high risk individuals apart from the herd (*i.e.:* a quarantine) proved to be an efficient way to reduce the AMU. This counter-intuitive result can in part be explained by the high persistence of the bacterial agents in the second scenario. Further investigation should be conducted by changing the inter-batch contact rate, in order to assess the protective effect of sorting individuals according to their risk level. Metaphylaxis and batch-scale preventive treatments were not included in this study but could possibly outline benefits of sorting batches to limit AMU.

Antimicrobial usage for the first scenario in the case of BRSV did not differ from the second scenario. Antimicrobials have no effect on BRD due to BRSV but treatment was kept anyway in the model, assuming that the involved pathogen was not identified before treatment and that AMU was the standard procedure in the event of clinical signs appraisal. AMU is therefore a mere reflection of BRSV spread.

Interesting operational perspectives could arise from a pathogen-specific BRD model. In the event of a BRD outbreak, such a modelling tool could help formulating specific recommendations, provided that the pathogen is identified on farm. This work still faces some pending questions, such as the optimal batch size and number to mitigate pathogen circulation. The influence of the inter-batch contact rate should also be investigated, even if it remains very difficult to relate quantitatively such a contact rate to the on-farm biosecurity level. Metaphylaxis and batch-scale preventive treatments were not included in this study but could possibly outline benefits of sorted batches in limiting AMU.

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SUPPORTING POLICY BY ESTIMATING THE TRANSMISSION DYNAMICS OF HIGHLY PATHOGENIC AVIAN INFLUENZA H5 INFECTIONS IN POULTRY FLOCKS FROM FRANCE AND THE NETHERLANDS

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A.R.W. ELBERS AND T. VERGNE

SUMMARY

Since 2014, Europe has been affected by several devastating epidemics of highly pathogenic avian influenza viruses (HPAI). During such epidemics, characterising disease transmission dynamics is crucial for efficient contact-tracing and the timely identification of new outbreaks. By fitting a mechanistic model of within-flock transmission dynamics to daily mortality data recorded in 57 HPAI-infected flocks from France and the Netherlands, we estimated various transmission parameters, including the transmission rate and the average durations of the latent and infectious periods. Times of first infection ranged between 5.1 days (95% credible interval: 2.3, 9.7) and 22.5 days (95%CrI: 17.9, 28.8) prior to culling. Our results suggest that efficient modelling pipelines fed with daily mortality data in outbreak farms could provide real-time support to policy by estimating realistic ranges of dates of first infections to inform contact tracing.

INTRODUCTION

Since its emergence in 2014, a new genetic lineage of H5Nx highly pathogenic avian influenza viruses (HPAI) clade 2.3.4.4 has spread globally, causing major epidemics in poultry farms worldwide with viruses of subtype H5N8 and H5N6 between 2014 and 2021 (Shi and Gao, 2021) and of subtype H5N1 since autumn 2021 (Wille and Barr, 2022). In addition to the damages caused to domestic poultry with thousands of outbreaks and millions of birds culled to prevent further spread, these HPAI epidemics can also cause high mortality in some wild bird populations, representing a major threat to wildlife conservation (Kuiken and Cromie, 2022; Miller, 2022). The global spread of avian influenza viruses (AIV) is also of concern for public health because of their zoonotic and pandemic potential (Shi and Gao, 2021; Wille and Barr, 2022).

Europe has been affected particularly hard by these epidemics of HPAI H5N8, H5N6 and H5N1 viruses, with ever-growing numbers of reported outbreaks in poultry farms and millions of birds killed (EFSA et al., 2022). During the last 2021-2022 epidemic, there were a total of 2,398 outbreaks on commercial poultry farms, the highest number ever-reported so far (EFSA et al., 2022). Considering the high negative impact of these HPAI epidemics, preparedness and prevention strategies should be designed and implemented, especially in high-risk areas and

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production systems (EFSA et al., 2021). Among preparedness strategies, control measures designed to improve early detection and rapid response should be applied to reduce the duration of an epidemic and to prevent farm-to-farm spread (EFSA et al., 2021).

Contact-tracing may be used for early detection of outbreaks and implementation of control measures aimed at preventing further spread, such as isolation or culling (Klinkenberg et al., 2006). In the case of HPAI, when an infected flock is detected, veterinary services perform contact-tracing to identify the potential origin of the outbreak (backward tracing) as well as potential secondary cases (forward tracing). Currently, veterinary services trace the contacts of infected farms during a fixed three week-long interval prior to their detection (European Commission, 2020; EFSA Panel on Animal Health and Welfare et al., 2021), assuming that the infectious contact happened during this interval. Although contact tracing may play an important role in controlling an epidemic, it is very resource-demanding and focusing efforts on the most relevant period could help increase efficiency and allocate more time to other control strategies. The relevant time window for contact-tracing of HPAI-infected flocks depends on the delay between first infection and reporting, which in turn depends on (i) the within-flock infection dynamics that may vary between flocks (Hobbelen et al., 2020; Hayama et al., 2022), and (ii) the delay in detecting and reporting the infection. Accurate estimation of the dates of first infection for each infected flock is therefore paramount to focus tracing efforts on the most relevant time window.

In addition, characterising the infectivity, transmissibility and pathogenicity of emerging HPAI viruses is critical for decision-makers to implement appropriate disease control strategies. Usually, these characteristics are determined using experimental infections studies (Leyson et al., 2019; Beerens et al., 2021), but such experiments are expensive, time consuming, and challenging to carry out.

Alternatively, mathematical modelling approaches can be used to both estimate the date of first infection and characterize HPAI transmission dynamics, using field observations of mortality data within infected flocks (Hobbelen et al., 2020; Vergne et al., 2021). In the context of HPAI viruses, this type of approach was used in various settings, either to estimate the within-flock transmission dynamics alone (Tiensin et al., 2007; Bos et al., 2009, 2010; Ssematimba et al., 2019) or to estimate both transmission dynamics and the dates of first infection (Hobbelen et al., 2020; Vergne et al., 2021; Hayama et al., 2022).

The aim of this study was to estimate flock-specific most likely dates of first infections, along with flock-specific transmission parameters, using a previously developed modelling approach (Vergne et al., 2021). To achieve this, daily mortality data recorded by farmers in infected flocks were collected between 2014 and 2022 in France and the Netherlands. Data from 57 infected flocks were included in our analysis, representing the most comprehensive dataset of within-flock mortality analysed so far.

MATERIALS AND METHODS

Data

We analysed mortality data from 57 poultry flocks in France ($n = 23$) and the Netherlands ($n = 34$) with outbreaks of clade 2.3.4.4 HPAI viruses during the years 2014-15 (H5N8, $n = 5$), 2016-17 (H5N8, $n = 25$), 2020-21 (H5N8, $n = 10$) and 2021-22 (H5N1, $n = 17$).

Table 1. Descriptive characteristics of the farms included in the study

Production type	No. of flocks	Mean age in days (min.; max.)	Mean initial flock size (min.; max.)
Chicken broiler	*n* = 20 (35%)	58 (28; 93)	20,980 (4,200; 63,540)
Chicken layer	*n* = 13 (23%)	356 (159; 503)	22,561 (5,000; 51,592)
Chicken breeder	*n* = 5 (9%)	237 (82; 465)	10,476 (6,145; 16,080)
Broiler ducks	*n* = 8 (14%)	30 (19; 48)	10,889 (7,800; 15,000)
Breeding ducks	*n* = 10 (17%)	49 (28; 63)	5,204 (2,000; 10,506)
Force-feeding ducks	*n* = 1 (2%)	92	945

Farmers recorded the daily mortality observed in the poultry house where each flock was raised, until detection of the disease and subsequent culling (Hobbelen et al., 2020; Vergne et al., 2021). Records of the daily mortality were gathered by the Netherlands Food and Consumer Product Safety Authority (NVWA) for the Dutch data (Hobbelen et al., 2020) and by the local veterinary services of the French Ministry of Agriculture for the French data. Depending on the flocks, the number of data points ranged from 3 up to 240. We used the day of culling as the point of reference (day 0) for each flock. For each flock, the initial flock size, the age of birds at depopulation and the production type were available (Table 1).

In broiler flocks, we systematically removed the first week of life, when the mortality (due to other causes than HPAI infection) is the highest (Elbers and Gonzales, 2021). For all flocks, we kept at most 30 days before the day of culling, and we focused on the initial exponential increase in mortality. In some flocks, a second phase was observed where mortality decreased, but it was not possible to distinguish whether this decrease was due to the outbreak dynamics or due to an underreporting by the farmer (e.g. when the number of dead birds became too high to count or after the HPAI infection was confirmed).

Mechanistic model

To estimate parameters from daily mortality data, we adapted a previously developed modelling framework that was first applied to African swine fever (Guinat et al., 2018) and then to HPAI (Vergne et al., 2021). To represent within-flock transmission of HPAI, we used a stochastic SEIRD epidemic model. Briefly, domestic birds were divided into five compartments: susceptible (S), exposed (infected but not yet infectious, E), infectious (I), recovered (R) and deceased (D). The output of interest was the number of dead birds (either from natural mortality or as a result of HPAI infection) each day. We considered a single homogenously mixing population within a poultry house, and a frequency-dependent contact rate (Vergne et al., 2021). Therefore, the force of infection in the model was given by Eq.(1):

$$\lambda(t) = \beta \frac{I(t)}{N(t)} \tag{1}$$

where β is the transmission rate (the number of individuals effectively contacted by each individual per unit time), $I(t)$ is the number of infectious birds at time t and $N(t)$ is the total number of live birds at time t: $N(t) = S(t) + E(t) + I(t) + R(t)$. At the initial time step, $N(t) = S(t) = N_0$, the initial number of (susceptible) birds in the flock. Introduction of the virus was assumed to happen at $t = t_0$ (time of first infection), by moving one susceptible individual into the exposed (E) compartment (Vergne et al., 2021).The durations of the latent and infectious periods were assumed to follow exponential distributions with means μ_E and μ_I, respectively. At the end of the infectious period, birds could either die (D) or survive the infection and recover (R), according to the case fatality parameter $case_f$ (Vergne et al., 2021). Birds from all compartments could also die from other causes, according to the *per capita* natural mortality rate r_M (Vergne et al., 2021).

Transitions between compartments were stochastic processes (Vergne et al., 2021). The number of transitions of each type during a small interval δt was drawn from a binomial distribution with population size n and transition probability Eq.(2):

$$p = 1 - \exp[-\kappa(t) \times \delta t] \tag{2}$$

where $\kappa(t)$ was the appropriate per capita rate. When multiple transitions could apply to a given compartment (e.g. dying of natural mortality or getting infected for susceptible birds), multinomial distributions were used to simultaneously draw the numbers involved in each transition during a small interval δt, rather than using binomial distributions sequentially. In that case, the probability associated with each transition j for a compartment i was Eq.(3):

$$p_{ij} = \left[1 - \exp\left(-\sum_{j \neq i} \kappa_{ij} \times \delta t\right)\right] \times \frac{\kappa_{ij}}{\sum_{j \neq i} \kappa_{ij}} \tag{3}$$

where $\kappa_{ij}(t)$ was the appropriate *per capita* rate for transition j in compartment i, and $p_{ii} = 1 - \sum_{j \neq i} p_{ij}$ was the probability of staying in compartment i. The small interval δt was set to 0.01 day, i.e. less than fifteen minutes.

Estimating flock-specific parameters

To fit the model to the observed daily mortality data of each flock separately, we used an approximate Bayesian computation sequential Monte Carlo (ABC-SMC) algorithm (Toni et al., 2009), more specifically the adaptive algorithm of Lenormand et al. (2013) implemented in the R package EasyABC (Jabot et al., 2013, 2015). Put briefly, the idea behind ABC is to run the model a large number of times using parameter sets sampled from a multivariate prior distribution, and to approximate the posterior distribution by keeping the parameter sets that produced simulated outputs close enough to the observed data (Hartig et al., 2011). In ABC-SMC, the initial step consists in sampling initial model parameters in the prior distribution, in order to obtain a first rough posterior distribution of parameter values. In each subsequent step, parameters are then sampled from the rough posterior distribution from the previous step with a perturbation kernel. A parameter set is accepted if the distance between the simulated outputs and observed data is less than a threshold defined at the previous step. The accepted parameter sets from the final SMC step approximates the posterior distribution.

We used uniform prior distributions for all six parameters (the transmission rate, the average durations of the latent and infectious periods, the natural mortality rate, the case fatality parameter, and the time of first infection), with ranges based on literature values (Table 2). For the time of first infection t_0, we considered that it could happen at most 30 days prior to culling. For the within-flock transmission rate β, most estimates in previous studies were below 10 (Kirkeby and Ward, 2022), which we used as the upper limit for this parameter. For the average durations of the latent and infectious periods, we considered upper values of 5 days (Grund et al., 2018; Hobbelen et al., 2020) and 10 days (Hobbelen et al., 2020), respectively. Finally, for the natural mortality rate, we considered an upper value of 0.005 per day, corresponding to a maximum daily mortality of 0.5% (Gonzales and Elbers, 2018; Elbers and Gonzales, 2021).

Table 2. Prior distributions used for parameters in the model for the within-flock transmission of highly pathogenic avian influenza H5 viruses in France and the Netherlands

Parameter (dimension)	Range (min. – max.)	References
t_0: time of first infection (day)	-30 – t_2	-
β: transmission rate (day^{-1})	0 – 10	(Kirkeby and Ward, 2022)
μ_E: average duration of the latent period (day)	0 – 5	(Grund et al., 2018; Hobbelen et al., 2020)
μ_I: average duration of the infectious period (day)	0 – 10	(Hobbelen et al., 2020)
r_M: natural mortality rate (day^{-1})	0 – 0.005	(Elbers and Gonzales, 2021; Gonzales and Elbers, 2018)
$case_F$: probability of dying of disease	0 – 1	-

The distance between simulated outputs and observed data was calculated as Eq.(4) (Guinat et al., 2018; Vergne et al., 2021):

$$\rho = \sum_{t=t_1}^{t_2} [D_{sim}(t) - D_{obs}(t)]^2 \tag{4}$$

where $D_{sim}(t)$ and $D_{obs}(t)$ denote the simulated and observed number of dead birds in the flock on day t, respectively, with the observation period for the flock running from day t_1 to day t_2.

For our analyses, we kept 5,000 parameter sets to approximate the posterior distributions. Convergence of the posterior distributions was monitored by visual inspection of the posterior distributions from all consecutive SMC steps between the initial prior distribution and the final posterior distribution. We also checked by visual inspection whether the posterior distributions differed from the prior distributions. Finally, we performed posterior predictive checks by checking the model fit to observed data by running 1,000 iterations of the model, sampling from the joint posterior distributions of the parameters (Vergne et al., 2021). With these simulations, we graphically compared the simulated number of dead birds each day with the observed data, and we also predicted the within-flock dynamics of the number of susceptible, exposed and infectious birds. The predicted dynamics were summarized with the 2.5th, 25th, 50th, 75th and 97.5th percentiles of the 1,000 simulated number of birds in each compartment each day. Similarly, the posterior distributions were summarized with the 2.5th, 25th, 50th, 75th and 97.5th percentiles of the 5,000 parameter values kept at the final step of the ABC-SMC.

RESULTS

We estimated the posterior distributions of all parameters for each flock independently. The posterior distributions converged well and the model fit to observed data was good in all flocks. As an illustration, we showed the predicted within-flock dynamics for a chicken flock from the Netherlands infected by HPAI H5N8 virus in 2014-15 (Fig.1). The model adequately captured the trend in mortality, with the observed daily mortality lying close to the centre of the prediction intervals. For this specific flock, the time of first infection was estimated to happen between 15.1 and 4.8 days prior to culling, as illustrated in Fig.1D.

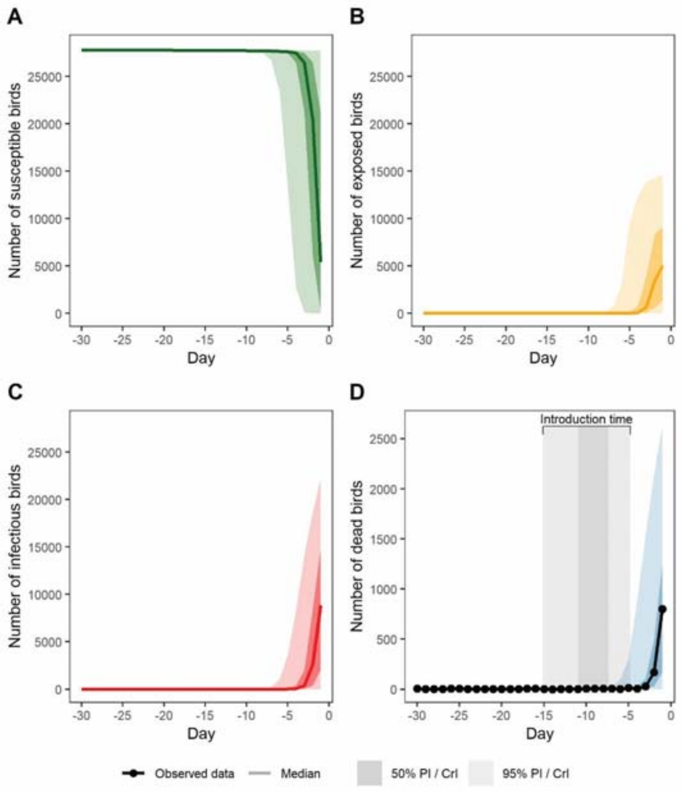

Figure 1. Reconstructed within-flock dynamics of highly pathogenic avian influenza H5N8 for a specific flock to illustrate the results of the model. Panels A-D represent the dynamics of the number of susceptible (A), exposed (B), infectious (C) and dead (D) birds over time with day 0 being the day the flock was culled. Predicted dynamics are shown as the median (solid lines) and the 50 and 95% projection intervals (PI – colour shaded areas). Results are based on 1,000 iterations of the model sampling from the joint posterior distribution. In panel D, the black dots and solid line represent the observed daily mortality. The grey shaded areas indicate the 50% and 95% credible intervals (CrI) for the time of the first infection

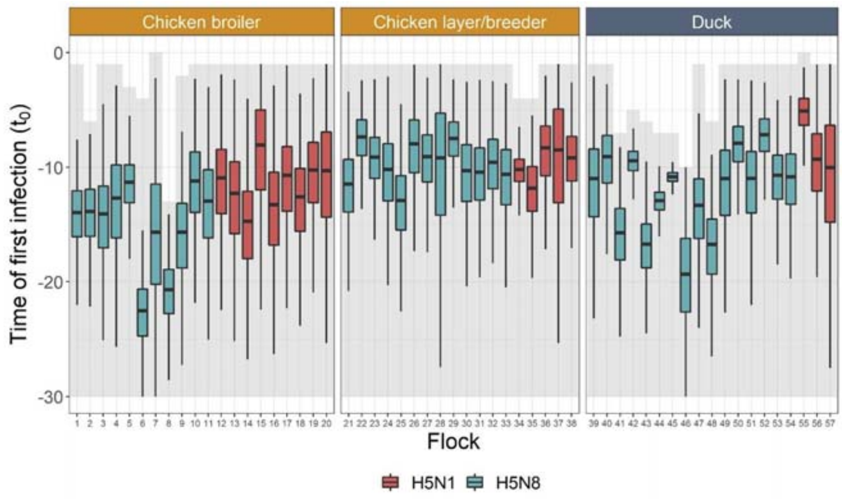

Figure 2. Flock-specific posterior distributions of the time of first infection for highly pathogenic avian influenza H5 viruses in France and the Netherlands. Flocks were distinguished according to host species and virus subtype. Chicken flocks were further distinguished between short (broiler) and long (layer and breeder) production cycles. Uniform prior distributions of the time of first infection are represented in light grey rectangles behind the boxplots for each flock

The estimates of the time of first infection for each flock, which differed from the initial uniform prior distribution in most cases, are represented in Fig.2. These estimates ranged between a minimum of 5.1 (95% equal-tailed credible interval – CrI: 2.3, 9.7) and a maximum of 22.5 (95% CrI: 17.9, 28.8) days prior to culling (Table 3). The flock-specific estimates of the other five parameters are not shown, but their lower and upper estimates are provided in Table 3. Although the model fit to observed data was good in each flock, in some cases the prior and posterior distributions of some of these five parameters were similar, meaning that the data was not always informative for these parameters.

Table 3. Posterior distributions of parameters for highly pathogenic avian influenza H5 viruses estimated using mortality data from infected flocks in France and the Netherlands

Parameter (dimension)	Lower estimate	Upper estimate
t_0: time of first infection (day)	-22.5 (-28.8, -17.9)	-5.1 (-9.7, -2.3)
β: transmission rate (day^{-1})	3.0 (0.7, 8.9)	7.9 (4.7, 9.9)
μ_E: average duration of the latent period (day)	0.13 (0.01, 0.47)	3.24 (0.64, 4.90)
μ_I: average duration of the infectious period (day)	2.1 (0.6, 4.2)	6.1 (1.2, 9.8)
r_M: natural mortality rate (day^{-1})	0.45 (0.04, 1.07)$\times 10^{-4}$	29.2 (2.77, 48.6)$\times 10^{-4}$
$case_F$: probability of dying of disease	0.35 (0.01, 0.94)	0.95 (0.82, 0.997)

DISCUSSION

We estimated flock-specific parameters, including the time of first infection and the transmission rate, for 57 HPAI-infected poultry flocks from France and the Netherlands. To estimate those parameters, we used a mechanistic SEIRD model that was fitted to daily mortality data. We found high variability in the estimates of the time of first infection, which ranged between 5.1 (95% CrI: 2.3, 9.7) and 22.5 (95% CrI: 17.9, 28.8) days prior to culling (Fig.2, Table 3).

Our results suggest that the time window used for contact-tracing, currently fixed to 21 days, could be shortened or extended depending on the flock. For instance, for flock 55 (Fig.2) whose estimated time of first infection was 5.1 days (95% CrI: 2.3, 9.7) prior to culling, using a 21 day-window for contact-tracing would mean that a lot of effort and resources are used to trace contacts that happened before virus introduction and are therefore not really relevant. In this case, focusing on e.g. a 10-day window could have been sufficient, meaning that resources could have been saved for other control or surveillance purposes. On the other hand, for flock 10 with an estimate of 22.5 days (95% CrI: 17.9, 28.8), using a 21 day-window means that epidemiological links, including the potential source of infection, could have been missed. In that case, a longer time window, .e.g. 29 days, would maximise the chances to capture all relevant contacts with the infected farm.

Therefore, our approach could be used to tailor the optimal time window to each flock, potentially in near real-time, as our modelling approach can provide results in a few hours and is based on easy-to-collect mortality data. Our approach also has the advantage of being able to quickly characterise virus properties, such as the transmission rate or the probability of dying of disease. When a new HPAI virus strain emerges, our approach could therefore be used to obtain this information quickly using field data from the index case, without the need to wait for infection experiments. Such results could inform decision makers in a timely manner, and also feed mathematical models of between-flock transmission of HPAI virus used to evaluate the efficacy of control strategies.

However, our approach is limited to infected poultry flocks displaying abnormal mortality, and cannot be applied to infected flocks that are detected before any significant increase in mortality. Another limitation of our approach was the use of non-informative priors (Table 2). In Bayesian estimation methods, such as the ABC-SMC algorithm that we used here, it is possible to take advantage of previous knowledge by using informative priors, which can then be updated when fitted the model to the data. Previous studies have shown that the parameter estimates can be sensitive to the choice of the prior distribution (Guinat et al., 2018; Vergne et al., 2021). Therefore, it would be interesting in the future to compare the results obtained when using non-informative and informative priors.

Finally, a next step in our study will be to analyse the characteristics (e.g. poultry species, production system, virus subtype) that could explain the observed variability between estimates of the time of first infection or of other transmission parameters.

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ESTIMATING THE RISK OF WITHIN-COMPANY SPREAD OF HIGHLY PATHOGENIC AVIAN INFLUENZA VIRUS IN THE UK, AND HOW THIS TRANSMISSION ROUTE INFLUENCES THE EFFECTIVENESS OF PROTECTION AND SURVEILLANCE ZONES.

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SUMMARY

Analysis of Highly Pathogenic Avian Influenza (HPAI) UK outbreak data (October 2021 – July 2022) suggests multiple farms with shared keepers have become infected. Our analysis suggests that the likelihood of this occurring by chance, or potentially 100% wild bird mediated, is very low and the average probability that a company with one infected premises will have at least one more infected premises is 13.3% (2.5 percentile = 5.1%, 97.5 percentile = 24.5%). Furthermore, we estimate 61% of all premises that have shared keepers are >10km from any randomly selected farm from the same keeper, so would not have measures imposed resulting from being within a 10km zone. More high-resolution data around poultry farming contact structures are required to confirm whether shared keepers are a risk factor for HPAI transmission between farms, but the consideration of alternative mitigation measures for vertically integrated poultry systems is advisable to help prevent spread of HPAI.

INTRODUCTION

Highly Pathogenic Avian Influenza (HPAI) virus causes peracute systemic disease with a mortality rate of up to 100% in poultry (Munster and Fouchier, 2009). Some Influenza A viruses of avian origin can also cross the species barrier into swine and humans. Globally, from January 2003 to 11 November 2022, there have been 868 cases of human infection with avian influenza A(H5N1) virus reported from 21 countries. Of these 868 cases, 457 were fatal (Case Fatality Rate (CFR) of 53% (WHO, 2022).

Highly Pathogenic Avian Influenza has been detected in over 60 countries across Africa, Asia, Australia, Europe and North and South America (Putri et al., 2020). The first report of HPAI H5N1 in poultry was detected in China in 1996 (Ali et al., 2015), though it is likely to have circulated well before this. HPAI has become enzootic in wild avian populations across many continents (Ali et al., 2015), resulting in large scale mortality. The impacts of annual HPAI outbreaks include economic losses to poultry producers as well as trade partners on an individual and country-wide level. Global attempts at eradication have not been successful

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(Putri et al., 2020), though in non-enzootic countries eradication is the focus of control measures.

In 2021/22 the UK saw the main reservoir hosts of HPAI H5N1 shift from wild anatidaes to seabirds, with high die-off rates continuing into the summer (APHA, 2022a). Interactions of colony breeding seabirds with other resident birds such as gulls and birds of prey may have led to the spread of HPAI further into the UK from the coastlines.

Historically, HPAI cases in poultry holdings occur sporadically across the UK, associated with the seasonal incursion of migratory waterfowl. Wild bird interactions are considered the most likely source of the disease to a UK poultry holding. In the UK, approximately 40% of poultry layer flocks are free range, meaning there is access to an outdoor range. However, during periods of higher risk for Avian Influenza (AI), increased biosecurity measures are required, which may include housing or netting poultry when appropriate. In farms with what may be considered high biosecurity standards, the chances of wild bird interactions should markedly decrease, yet HPAI still occurs in these premises. This poses the question as to how HPAI is introduced to a high biosecurity flock, or what the true level of biosecurity is on these farms. Additionally, the introduction of housing orders should reduce the risk of HPAI exposure in poultry from wild birds, but does not eliminate it. This raises the need for consideration of other pathways for disease transmission between poultry farms (APHA, 2022b).

There have been instances in the UK where groups of premises owned by the same keeper have become infected with HPAI during the same outbreak; such groups of premises are likely to share resources, or be part of a vertically integrated poultry system. These systems see the amalgamation of multiple poultry production sites under singular management, and is an approach that is growing in popularity due to economic viability in the poultry sector. There has been consistent evidence from past epidemics to suggest that human-mediated interactions between poultry flocks can also be a cause of HPAI spread between farms (Alexander, 1995; Ssematimba et al., 2013). Risk factors associated with seroprevalence on commercial broiler and layer chicken farms in Bangladesh highlighted an association between H5 seropositivity and vehicles entering the farms (Odds Ratio (OR) = 5.8, 95% Confidence Interval (CI): 1.5–22.4), and H9 seroprevalence was associated with traders supplying feed (OR = 5.9, 95% CI: 1.0–33.9) and visits conducted of other commercial poultry farms (OR = 4.7, 95% CI: 1.1–20.6) (Gupta et al., 2022). The effect of human-caused disease spread is not constrained to commercial farms; studies show that backyard flocks in which family and friends frequently visited increased the risk of a HPAI H5N1 outbreak (OR = 8.2; 95% CI: 1.0 - +infinity) in Viet Nam (Henning et al., 2011). Vehicles are also acknowledged to be a considerable risk factor for Avian Influenza Virus (Hazard Ratio (HR)=2.50, 95% CI=1.52 - 4.10) in France (Duvauchelle et al., 2013).

In GB, the Animal and Plant Health Agency (APHA) are responsible for the implementation of outbreak response measures. In the case of HPAI one of the measures is a 3km Protection Zone (PZ) and a 10km Surveillance Zone (SZ) surrounding the Infected Premises (IP). Various movement and trade restrictions are then put in place for any poultry-holding premises that are present in these zones, with greater restrictions in the PZ than the SZ. Restrictions are placed on: movements of live animals, hatching eggs and day old chicks, waste and animal by-product movement, movement of birds to slaughter or table eggs, processing of poultry meat or eggs; and other activities in the zones include active and increased passive surveillance during the high risk spread period (Defra, 2017). These geographical zones are designed to be effective against local spread of the disease, e.g., via fomite transmission, but may not be as effective against wild bird transmission.

The European Food Safety Authority (EFSA) Scientific Opinion panel assessed that the probability of HPAI transmission beyond the 3km PZ was over 50%, although this reduced to 5% beyond the SZ (EFSA Panel on Animal Health and Welfare, 2021).

The Great British Poultry Register (GBPR) recorded 46,025 poultry premises present within the UK in 2021. The UK poultry farming sector is moving towards more vertically integrated poultry systems to take advantage of economies of scale; that is, more poultry holdings under singular management/ownership, resulting in shared personnel, resources, and services moving between poultry sites. As such, biosecurity between farms is more important than ever to prevent large scale HPAI outbreaks and consequent culling.

The aim of this study was to analyse recent UK data on the 2021/22 HPAI outbreak with regards to the efficacy of protection and surveillance zones and whether there is a link between groups of companies being owned by the same keeper and HPAI disease occurrence.

MATERIALS AND METHODS

Data collection

All records were acquired through APHA. All data were anonymised for confidentiality.

The GBPR was used to provide location information of poultry holdings across Great Britain as of 2021, as well as those poultry holdings with shared Keepers. The GBPR is frequently updated by APHA staff.

Case data from the 2021/22 AI season (October 2021 – July 2022) was collated by the National Emergency Epidemiology Group (NEEG). Due to the Notifiable status of HPAI, poultry keepers and/or veterinarians are required to report any suspicion of the disease to APHA for investigation and verification. This was used in conjunction with the GBPR to identify those premises that became IPs during the timeframe, and if there were multiple IPs under mutual ownership.

UK wild bird abundance data collated from a previous project was utilised here (Hill et al., 2019) to produce a gridded map of GB. Each grid square covers a 10km x 10km area and is ranked from 1 to 6 identifying the relative wild bird abundance in the cell (1 being the least abundant and 6 being the most). The ranks are split such that there are an equal number of grid squares in each rank.

Data Management and Descriptive Analysis

For the purpose of this report, a ‘company’ is referring to a group (or cluster) of premises that are related by a single keeper, as identified in the GBPR. Keepers that were identified on the GBPR more than once were highlighted as potential company-clusters and extracted from the GBPR. The premises associated with each keeper were collated and each ‘cluster’ given a unique Company ID number that related the premises to each other through a shared keeper. The number of premises within a company-cluster were counted (before including disease status).

Identified keepers with more than one premise were searched for in the 2021/22 season case data, and the number of cases per keeper counted. This was then added to the company-cluster data. The proportion of IPs belonging to a company-cluster was calculated using the number of IPs and the number of premises per cluster.

Strength and direction of association between variables (proportion of cluster infected and number of premises in a cluster; area of convex hull polygons of each cluster, and number of premises in a cluster) were tested for using Spearman's correlation coefficient. Continuous variables were chosen and plotted on a scatter graph to check for monotonicity before carrying out Spearman's correlation.

Risk Outputs

Multiple risks expressed as probabilities were generated using the "probability of at least one success" formula, shown in Table 1.

Table 1. Definitions of the conditional risk probabilities calculated using @RISK

Notation[a]	Definition
P1	Company cluster has at least one infected premise
P2	Company cluster has >1 infected premise given that P1 has already occurred

[a] Each probability (P1 and P2) was generated using a Beta distribution to account for uncertainty in a small dataset

Equations 1 and 2 show how each risk output was calculated whilst fitting to the data, using the program @RISK.

$$P1 = RiskBeta(x + 1, \quad y - x + 1) \tag{1}$$

$$P2 = RiskBeta(z + 1, \quad x - z + 1) \tag{2}$$

x = Total number of companies with 1 or more IPs. y = Total number of companies. z = Total number of companies with more than 1 IPs.

Other outputs such as the number of IPs per infected cluster, number of premises in a cluster, and the proportion of the cluster infected were estimated after fitting estimates to the data. The distributions were fit to the data using @Risk, but biological plausibility was also considered when selecting the distributions.

Calculating the distance between premises within a company

For each premises that was identified as being part of a cluster, the Euclidean distance of the premises from any other premises in the same cluster was calculated.

Arc-GIS software was then used to generate convex hull polygons of the distance between premises within the same company cluster based on a point-data layer plotting all poultry premises. The polygon area per company was plotted against the number of premises per company and the Spearman's correlation coefficient was computed.

Probability observed IPs within a company occur at random

We test the hypothesis that the distribution of IPs in a given area, in terms of belonging to the same company or not, could have occurred at random (i.e., not affected by any possible factor). For each company cluster, j, we identified the first IP and then defined an area of radius, k, around that IP. Then for each company/radius combination, we identified the number of farms in the area, $F_A(j,k)$, the number of farms that belong to the company in the area, $F_C(j,k)$, the number of IPs in the area, $I_A(j,k)$, and the number of IPs in the area that are part of the company, $I_C(j,k)$. The probability, $p_{ran}(j,k)$, that we observe the data due to chance, i.e., that for the given total number of IPs in the area we observe the number of IPs that are part of the company cluster, can be calculated deterministically as we assume that each farm has the same probability of being infected. This is calculated by considering the number of combinations of farms equal to the total number of IPs, $I_A(j,k)$, that can be chosen from all the farms in the area, $F_A(j,k)$, and determining the proportion of those that contain a number of company farms equal to the exact number of company IPs, $I_C(j,k)$. Mathematically, for each company cluster, j, and radius, k, this can be expressed using binomial coefficients as Eq.(3).

$$p_{ran} = \frac{\binom{F_C}{I_C}\binom{F_A - F_C}{I_A - I_C}}{\binom{F_A}{I_A}} \tag{3}$$

We consider 3 different areas around the first IP – the PZ (3km radius); the SZ (10km radius); and a circle with a 30km radius.

Probability IPs within a company occur as a result of Wild Birds

We also test the hypothesis that wild bird abundance is the only factor which affects the likelihood of a farm being infected. For each company cluster and area combination, we run 10 simulations of 500,000 iterations each. In each iteration we selected $I_A(j,k)$ farms from the total number of farms in the area, $F_A(j,k)$, with the probability of a farm being selected weighted by the wild bird abundance rank in the 10km x 10km cell it is located in. We assume that the probability increases linearly with wild bird abundance rank, so a farm in a rank 6 cell is 6 times more likely to be infected than a farm in a rank 1 cell. The proportion of iterations in each simulation where the number of company IPs matched the observed number of company IPs gave an estimate for the probability, $p_{wb}(j,k)$, that the observed number of company IPs could have occurred by chance, with the only factor making it more likely that they were an IP being the wild bird abundance rank.

HPAI presence in wild bird population

Wild bird submissions to APHA were used to estimate the prevalence of HPAI in those birds submitted. Information regarding the submissions were extracted from the laboratory information management system (LIMS) and categorised between disease status, location, and date of submission.

It must be noted that this is not an estimate of true disease prevalence; the submissions are based on APHA being notified of reports of infection in certain target species and so are not a true representation of the whole wild bird population across the UK. Additionally, when there are large numbers of cases in one area, once disease has been confirmed in the area, they are not necessarily all collected, or sent to be sampled.

RESULTS

Descriptive Analysis

There was a total of 608 companies with more than one premises identified. Of these companies 458 had two premises, 65 had three premises, 26 had four premises, and 59 had five or more premises. Of the 608 companies, 43 (7.07%) had at least one infected premises: 38 with a single IP, three with two IPs and two with five IPs. There were no companies with three or four IPs.

The average proportion of premises that became infected within an infected cluster is 35% with a highest of 100% and lowest of 14%, but Fig. 1 shows a downward trend of the proportion of premises within a cluster infected as the number of premises within a cluster increases. There was a strong negative correlation between the proportion of premises that became infected within an infected cluster and the number of premises within a cluster, which was statistically significant, r_s= -0.933, p < 0.0001.

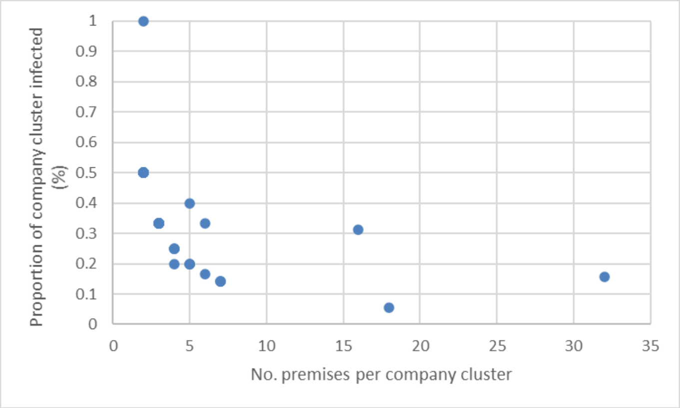

Figure 1. Graphical illustration of the trend between the proportion of premises within a cluster that is infected, and the number of premises in a cluster

Risk Probabilities

The average probability a company cluster will have at least one infected premises during the outbreak season, P1, was estimated at 7.2% (2.5 percentile = 5.3%, 97.5 percentile = 9.4%). The average probability that a company with at least one infected premise will have at least one more infected premise during the outbreak season, P2, was estimated as 13.3% (2.5 percentile = 5.1%, 97.5 percentile = 24.5%).

Other outputs fitted to the data estimated that there are an average of two IPs per infected cluster (95th percentile = 3) and an average of three premises in a cluster (95th percentile = 6). The proportion of infected premises in a cluster is estimated at 33.3% (95th percentile = 59.5%). Table 2 shows the outputs and distributions.

Table 2. Other outputs estimated using the 2021/22 data, and the distribution of best fit for each output

Output	Distribution of best fit
Number of IPs per cluster	Poisson (1.2558)
Number of premises in a cluster	Binomial (34, 0.082172)
Proportion of the cluster infected	Laplace (0.33333, 0.16106)

Distribution of premises in companies

Figure 2 graphically displays the relationship between the area covered by the company clusters and the number of premises included within the cluster. There was a general positive correlation between the variables, but a few companies with low numbers of premises had very large areas. There was a strong positive correlation between the area of the convex hull polygons per cluster and the number of premises within a cluster, which was statistically significant, $r_s = 0.6527$, $p < 0.0001$.

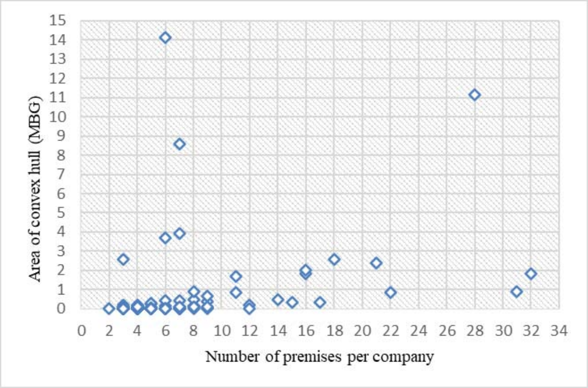

Figure 2. Relationship between area of convex hull polygons and the number of premises per cluster. MBG = Minimum bounding geometry

Analysis of the data showed that 61% (6384/10543) of premises were more than 10km away from any other premise in their company-cluster, i.e., would be outside the SZ if any of the other farms in the cluster were to become an IP. Only 29% (3045/10543) were within 3km of another farm in the same company, i.e., would be within the PZ if any of the other farms in the cluster were to become an IP.

Probability observed IPs within a company occur at random

Table 3 below shows the probabilities of observing the data given that each farm is equally likely to become an infected premise. The probabilities, which were calculated deterministically, for each area around each cluster are very small (in almost all cases $p_{ran} < 0.01$) and when combined across clusters for the likelihood of all events occurring as in reality, the probability is even smaller.

Table 3. Probabilities, $p_{ran}(j, k)$, for observing the data for each company cluster (j)/area (k) combination assuming that each farm is equally likely to be infected

Cluster	3km	10km	30km
1	[a]NA	[a]NA	0.00000052
2	0.0083	0.00019	0.0000038
3	0.0024	0.0020	0.00033
4	0.0033	0.00013	0.0000095
5	0.016	0.0016	0.00016

[a] Note that in these areas for cluster 1 there was only one IP and so the results for these areas would have no relevance

Probability IPs within a company occur as a result of Wild Birds

Table 4 below shows the probabilities of observing the data given that the likelihood of a farm being infected is proportional to the wild bird abundance rank of the cell in which the farm is located. For each area around each cluster, the table details the minimum, maximum, and mean values from the 10 simulations. The mean value is also equivalent to the point value from 5 million samples, as each sample and each run is independent. Like the deterministic approach in which each farm had the same likelihood of being infected, the probabilities of observing the data are very small ($p_{wb} < 0.01$ in all cases).

Table 4. Mean (Min, Max) probability, $p_{wb}(j, k)$, of observing the data from biased random sampling by wild bird abundance rank for PZ (3km), SZ (10km), and 30km radius (k) around the first IP for each cluster (j)

Cluster	3km	10km	30km
1	[a]NA	[a]NA	[b]0.00000060 (0, 0.0000020)
2	0.0083 (0.0080, 0.0084)	0.00022 (0.00021, 0.00024)	[b]0.0000030 (0, 0.000010)
3	0.0022 (0.0021, 0.0023)	0.0021 (0.0020, 0.0022)	0.00029 (0.00026, 0.00032)
4	0.0034 (0.0033, 0.0035)	0.00018 (0.00015, 0.00022)	0.000013 (0.0000060, 0.000020)
5	0.0090 (0.0088, 0.0091)	0.00089 (0.00084, 0.00094)	0.000058 (0.000038, 0.000080)

[a] Note that in these areas for cluster 1 there was only one IP and so the results for these areas would have no relevance

[b] Many simulations for the 30km radius for cluster 1 and 2 produced a zero probability, i.e. none of the 500,000 iterations matched the observed data, which suggests the probability may be around or less than 1/500,000

HPAI presence in wild bird population

Of wild birds submitted to APHA for sampling on suspicion of HPAI during the study period, 46.1% tested positive, meaning that the birds submitted for suspicion of HPAI were more likely to test negative than positive. The West Midlands saw the largest proportion of positive wild bird submissions during the 2021/22 AI season (59.9%), as well as the highest odds of infection (1.5) indicating that wild bird submissions in the West Midlands were one and a half times more likely to test positive than negative. London had the largest proportion of negative wild bird submissions (77.4%), and was one of the groups to have the least submissions. Scotland saw the most submissions during the time period (1024).

DISCUSSION

The results from our study suggest that the risk of a premises under shared keepership becoming infected is 7.2%, with the risk of a second IP occurring within a company cluster being almost double that of prior infection (13.3%). This increase between the two probabilities, along with the likelihood of the distribution of IPs occurring due to chance or only from wild bird abundance being very low (<0.01), indicates that contact structures unique to company clustering may influence the risk of disease. We also considered the likelihood that distributions where more than the observed number of company IPs within each cluster/area combination could occur due to random chance or only wild bird abundance. This likelihood was much smaller than matching exactly the observed distribution, which suggests that it is unlikely that companies had a beneficial effect on reducing the spread of infection. The correlation between the number of premises within a company and the proportion of the company that became IPs (r_s= -0.933, $p < 0.0001$) is also indicative of a unique characteristic to company clustering having an effect on HPAI incidence. These results are in line with observations in France during the 2016-17 HPAI H5N8 outbreak in duck farms, where two contact networks were established: the animal introduction network (exchange of live ducks) and the transit network (transit of transport vehicles). Investigations showed how farms were more connected through the transit network, and that this network provided more opportunities for virus transmission (Bauzile et al., 2022). The level of poultry farming for foie gras production is likely to have influenced this outcome based on the frequency of bird movements to and from the gavage establishments. Foie gras is not produced in the UK. Disease transmission risk in premises under shared keepership may be due to interaction via transit networks within company clusters, or common management resulting in similar biosecurity practices. However, without more data surrounding how premises interact within a company cluster, this cannot be ascertained. Thus, better capturing the contact structures within and between farms is key to better understand how HPAI is spread within the poultry sector.

Analysis suggests that the wild birds submitted to APHA for suspicion of HPAI were more likely to test negative than positive. These results cannot be described as prevalence, and the number of submissions could have been due to factors such as the surveillance techniques e.g., general public based reporting vs risk-based patrolling. The very low likelihood of the 2021/22 case data being as a result of wild bird abundance only (<0.01), along with the knowledge that housing orders do not eliminate the risk of HPAI in poultry, suggests that wild bird interaction may not be the only factor influencing HPAI incidence on premises that are part of a company cluster.

The way in which information is used to identify between-farm connectivity is a key factor in this area of research. In this study we used shared keepership as the connectivity link, with assumptions that this directly resulted in shared personnel/services between those farms under the same keepership. However, this does not account for the variability in production-scales of poultry premises and what that means on a shared keepership level. For example, large commercial poultry premises are likely to run independently (i.e., choosing delivery companies, catcher companies etc. themselves) despite shared keepership with other premises. Similarly, those premises under shared keepership that are not within reasonable geographic means of each other, are less likely to share personnel between sites. According to Rossi et al., (2017), indirect contacts between farms are best represented in modelling methods describing links using personnel itineraries as opposed to the distribution of between-farm contacts and inter-farm distances.

Often in the study of contact structures for disease spread within a heterogenous population it is important to identify the high-risk nodes (or superspreaders). The identification of these high-risk nodes is helpful for surveillance or treatment programmes, as treating these nodes in the contact structure affects other nodes that are both directly and indirectly linked to the high-risk node, due to the spread of interaction from the high-risk nodes. A similar level of interaction may be seen in commercial poultry farming; where a small number of high-risk nodes interact with multiple other premises becoming a key source of disease spread. High-risk nodes in this example could be: catcher-companies, feed providers, egg collection companies, site managers of multiple premises, or others, such as gavage sites in the EU. However, without high resolution contact network data it is not possible to accurately identify these high-risk nodes to be able to apply appropriate mitigations to reduce the likelihood of disease transmission. Other data quality issues identified within this study include the potential underrepresentation of both smaller poultry holdings in the UK, and the number of company links, through the GBPR.

Contact structures and interactions between company clusters is also important regarding disease outbreak measures that are implemented after the confirmation of an IP. Using data from October 2021 to July 2022, we found a positive correlation between the area distance covered between premises and the number of premises within a company ($r_s = 0.6527$, $p < 0.0001$). In the case of an IP being confirmed on the average company cluster premise, 61% of all other related premises would not be covered by any associated PZ or SZ restrictions. Only 29% of company cluster related premises are within 3km of each other. This spatial data may help in trying to establish how premises interact with each other within a company cluster, and highlights that in the case of an IP the majority of the other premises within the company are potentially a higher exposure risk due to not being required to implement zone-associated restrictions. However, as it is estimated that 50% of the overall disease risk is within 3km of an IP (EFSA Panel on Animal Health and Welfare, 2021) it could be discussed that siting company-linked premises further away from each other will reduce the risk of secondary disease occurrence within the company. A caveat to this would be that the risk is only reduced if personnel/resources are not shared, and that there are no other significant risk factors. Based on our risk data, the probability of a second IP occurring within a company cluster is almost double that of initial infection within the company cluster. Therefore, those that are outside of zonal restrictions associated with an IP (61% of premises within a company cluster) should put in place additional biosecurity measures to mitigate those risk pathways involving human mediated routes, in addition to those risk pathways covered by the restriction zones. Indeed, in most company clusters where there was more than one IP, the first and second IPs were in close proximity.

The results from this study suggest that the patterns we observe with farms from the same companies being infected is unlikely to only occur due to random chance or from contact with infected wild birds, but could in some cases be a result of lateral spread. We cannot draw any more specific conclusions about what potential factors may be the cause of the company clusters from this analysis, and therefore further investigation is required. One possibility may be that the farms from the same company share similar management or biosecurity practices that might make them more likely to be subject to incursion from wild birds. Another could be that fomite transmission has more of a role to play in the transmission of HPAI within company clusters than first thought. Spatial clustering of infection in geographic areas may also explain some occurrence of multiple IPs within a company-cluster. Tracking and controlling a wild-animal mediated disease such as HPAI will always be difficult, but identifying high risk factors for the spread of disease that are not wild bird related will aid in reducing transmission, through identifying more effective biosecurity measures.

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INTERVENTION MODELLING

REVIEWING THE PERFORMANCE OF R_0 ESTIMATION METHODS USING OUTBREAK DATA: INSIGHTS FOR FMD VACCINATION PROGRAMMES

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SUMMARY

We performed a sensitivity analysis across a range of standard tools that quantify the basic reproduction number R_0. This was based on simulation studies of both within- and between-farm outbreaks with parametrisations based on foot and mouth disease (FMD) dynamics in endemic regions. Choice of method requires consideration of both the level at which data are generated and understanding of local epidemiology. Poor estimation of R_0 or using estimates from different settings may result in inappropriate or ineffective control measures being designed and/or implemented. Our work therefore suggests that before designing vaccination programmes, simulation studies should be carried out to better understand the potential impact of scenario-specific factors on estimation of R_0.

INTRODUCTION

The basic reproduction number R_0 is a key metric in epidemiology used to characterise infectious diseases and their potential to generate epidemics (Heesterbeek, 1996; Keeling and Grenfell, 2000; Heffernan et al., 2005). R_0 is defined as the average number of individuals infected by a given case in a fully susceptible population. In the absence of infection control, R_0 can be used to predict if an outbreak will likely take off, with $R_0>1$ indicating that disease would have potential to spread through the population whereas $R_0< 1$ would indicate that it will die out.

Vaccination is potentially the most efficient method for controlling the spread of foot and mouth disease (FMD) in endemic settings but remains sub-optimal. The effective vaccination coverage (V_C) is the proportion of the population at risk that needs to be immune for R_0 to be less than 1. As V_C is typically directly computed from R_0, biased estimation of R_0 result in populations being over- or under- vaccinated, leading to inefficient or ineffective control.

Several estimates of R_0 for FMD have been reported, ranging from 2.52 to 88 (Perez et al., 2004; Orsel et al., 2005, 2007; Bravo de Rueda et al., 2014; Kim et al., 2016; Hayer et al., 2018), but there is no standard method of estimation. The value of R_0 for FMD has been estimated from both field (Hagenaars et al., 2011) and experimental settings (Orsel et al., 2005; Bravo de Rueda et al., 2014) or derived from outbreak case records, either recorded at the animal level or at the farm level such as those from the 2001 UK outbreak (Chis Ster et al.,

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2012). While these variations can be explained by the impact of heterogeneities in livestock industry structures, the background level of immunity to specific serotypes in different populations, the epidemiology of the disease itself, or different levels and types of underreporting in the data, it is as yet unclear if the choice of estimation method for R_0 also affects the derived estimates. Evaluating the performance of different methods to estimate R_0 from outbreak data, and their robustness to background epidemiological and surveillance variations, is therefore key to improving the design of vaccination strategies in FMD endemic regions.

To reach this goal, we conducted a simulation study in which five easily available methods are used to compute R_0 estimates from pre-defined simulated sets of data from individual- (i.e., within farm using an SEIR model) and farm-level (i.e. between farm using an SIR model) outbreaks representative of FMD in endemic settings. In particular, we have in mind outbreaks amongst pastoralist small holdings in sub-Saharan African countries (Bronsvoort *et al.*, 2003, 2006; Sumption et al., 2008; Casey-Bryars et al., 2018; Nyaguthii et al., 2019).

MATERIALS AND METHODS

In this study, we made use of simulated data to assess the performance of simple commonly used R_0 estimation methods from outbreak information. The focus is on assessing R_0 estimation performance from individual epidemics that occurred at individual (i.e., within farm) and farm level (i.e., between farm). Over each individual simulated outbreak, performance was measured by comparing the analytic formulation of R_0 for the underlying disease transmission model, referred to as 'true R_0', with the values of R_0 estimated using each method assessed.

Modelling framework

Two compartmental models were used to generate outbreak data representative of individual- (i.e., within farm using an SEIR model) and farm-level (i.e., between farm using an SIR model) spread. Both models were stochastic and Markovian and assumed that time spent in each state followed an exponential distribution, with average residence time given by the reciprocal of the rate of transition out of the given state. Population turnover was not accounted for in either of these simple models as it was assumed negligible during an outbreak. The models used implementation of the Gillespie direct method (Gillespie, 1976) and were coded in the statistical software *R* version 3.6.3 (R Foundation for Statistical Computing, 2020) with embedded C++ language, making use of the *Rcpp* package version 1.0.4 (Eddelbuettel and Francois, 2011).

In these models, we defined β as the transmission parameter and σ_I as the recovery rate, i.e. the per-capita rate of transition from the infectious state (I) to the recovered state (R). In the SEIR model, the per-capita rate of transition from the exposed (E) to the I state is specified by λ. For simplicity, we defined γ^{-1} as the mean time between infection of a given case and recovery, and specified $\gamma = \lambda + \sigma_I$.

In specific situations, the SEIR within-herd model framework was further extended, introducing a carrier state C (McLachlan et al., 2019). In this model, we proposed that a proportion θ of recovered individuals enter the C state and remain in it for a mean period $1/\sigma_C$, where σ_C is the per-capita rate of recovery from the C state. In all cases, individuals in the C state can transmit the disease with a rate $\omega\beta$, where ω is the ratio of transmission from carriers relative to that from infectious individuals. We further assumed that the outbreak is much shorter than the lifespan of individual. As such, death of individuals was not included in the models and the mortality rate μ was set to 0.

From these models, we analytically derived the value of the 'true R_0' using the Next Generation Matrix (NGM) approach (Diekmann et al., 2010). In both SIR and SEIR models, the true value of R_0 was computed to be $R_0 = \beta/\sigma_I$, whereas, in situations where a carrier state was present, its value was established as $R_0 = \beta/\sigma_I + \omega\theta\beta/\sigma_C$.

R_0 estimation methods

In this study, we tested five simple methods commonly used to estimate R_0 from real-life outbreak data. These methods were grouped into two groups: those that estimate R_0 based on epidemic growth, and time-dependent methods.

Epidemic growth estimation methods: Estimation methods of R_0 from the early phase of an outbreak can assume that the depletion of susceptible individuals is sufficiently small that growth can be considered to be independent of density and exponential in nature. Based on these assumptions, we implemented the doubling time T_d method (referred to as Method 1) and estimated the rate of exponential increase r (Bjørnstad, 2018) (Method 2) to estimate R_0 using the relations

$$R_0 = 1 + (\ln(2)/T_d)D = 1 + Gr \tag{1}$$

where $D=\sigma_I^{-1}$ is the duration of the infectious period (Anderson and May, 1991), and G is the mean generation interval, that is, the average time between infection of a given case and infection of its secondary cases.

When using Method 1, D is likely to be unknown. As such, G can be used as an approximation of D when estimating R_0 (Ferguson et al., 2005, 2006). To test the impact of this approximation on the estimation of R_0, we implemented Method 1 using both D (Method 1a) or G (Method 1b) in its calculation.

In Method 2, r is estimated by regressing the log-transformed cumulative incidence on time which, via Eq.(1), is used to estimate R_0. The value of G is difficult to estimate in real world situations but may be approximated by the mean serial interval V, the average time between the onset of symptoms of a given case and the onset of symptoms of its secondary cases. Since this is a simulation study, with all infection timings recorded, both the mean serial interval and mean generation time can be computed. As in Method 1, we tested the impact of this approximation on the estimation of R_0 by Method 2 using either V (Method 2a) or G (Method 2b) in its calculation.

We further estimated R_0 using the relationship between r and the moment generating function M (Method 3), such as

$$R_0 = 1/M(-\ln(r)) \tag{2}$$

The moment generating function $M(z)$ in Eq.(2) characterises the discretised generation time distribution (Wallinga and Lipsitch, 2007) and follows a Poisson distribution with a mean z = -ln(r), where ln(r) is the epidemic growth rate. Here, we used the 'est.R0.EG' function from the *R0* package version 1.2.6 (Boelle and Obadia, 2015) to implement Method 3.

Time dependent estimation methods: An estimate of R_0 can also be inferred using a likelihood-based estimation approach based on observed dates of newly detected cases (Wallinga and Teunis, 2004), determining who infects whom. However, rather than inferring a complete infection network, this method identifies the most likely pairs of cases (the parent and child pair) based on the difference in the time between onset of signs of disease, basing inference on the (assumed) single chain of transmission. Here, we used two different implementations of this R_0 estimation method based on inferring chains of transmission: the 'est.R0.TD' function in the *R0* package version 1.2.6 (Boelle and Obadia, 2015)(Method 4), and the 'estimate_R' function in the *EpiEstim* package version 2.2.3 (Cori, 2020)(Method 5), both freely available in the statistical software *R*.

Simulation studies

Here, performance of R_0 estimation was tested for a broad range of parameter values reflecting reported parameters for FMD: the secondary transmission rate β; the recovery rate σ_I and (when applicable) the per-capita E-to-I transition rate λ. As such, we considered β ranging from 1 to 5 infectious contacts per day while σ_I and λ were set to vary between 1 and 7 days (Mardones et al., 2010; Charleston et al., 2011; Yadav et al., 2019). These represent variability in true R_0 between values of 1 to 35.

For each combination of parameters (β, σ_I, and when applicable, λ) and model structure, 500 simulated outbreaks were independently initiated by introducing a single infectious individual in a population of N=1000 fully susceptible individuals/individual farms. For each outbreak, disease progression was recorded on each day and simulations were run until there was no disease present in the population.

Due to the stochastic nature of disease spread, outbreaks may not be of sufficient size to estimate R_0 values. In this work, only outbreaks of sufficient size were considered to evaluate the performance of R_0 estimation methods. The estimated values of R_0 were compared with the appropriately calculated true R_0 value to evaluate the coverage properties for each method and scenario.

For some methods, estimates of V and $M(z)$ were required. For each combination of parameters, the serial interval was obtained from 500 additional simulations. In these simulations, the initial index case was infectious but secondary cases were unable to transmit thus allowing parent-child transmission pairs to be identified. In this way, we recorded the number of secondary cases and the time at which they became infectious to estimate the mean serial interval V. From these records, we computed the generation time distribution $M(z)$ using 'est.GT' and 'generation.time' functions from the *R0* package version 1.2.6 (Obadia et al., 2012; Boelle and Obadia, 2015).

Robustness testing

We further tested the robustness of the assessed R_0 estimation methods for various scenarios of herd size, reporting bias, susceptibility at the onset of the outbreak, and transmissibility of FMD carriers. These scenarios were chosen as representative of FMD outbreaks occurring in endemic settings (Bronsvoort *et al.*, 2003, 2006; Sumption et al., 2008; Casey-Bryars et al., 2018; Nyaguthii et al., 2019).

In this analysis, we considered outbreaks generated from an SEIRC transmission process similar to that of McLachlan et al. (2019), in which a proportion of θ infectious individuals passed into a carrier (C) state instead of recovering to the R state. Individuals in the C states were allowed to transmit the disease with a rate $\omega\beta$. In this analysis, we fixed β=1 and considered 3 epidemiological scenarios, based on variations of λ and σ_I:

- Scenario 1: $1/\lambda = 4$ days and $1/\sigma_I = 4$ days, hence $R_0 = 4$.
- Scenario 2: $1/\lambda = 3$ days and $1/\sigma_I = 7$ days, hence $R_0 = 7$.
- Scenario 3: $1/\lambda = 4$ days and $1/\sigma_I = 2$ days, hence $R_0 = 2$.

For each scenario, 500 outbreaks were independently generated in each combination of conditions (i.e., herd size, susceptibility at the onset of the outbreak, reporting bias, and ω) and scenario, and R_0 was estimated using each tested method and compared to the true (analytically calculated) R_0 as detailed above. When ω was being explored, we fixed θ=0.5 and $1/\sigma_C$=6 months. Otherwise, θ=0 and the outbreaks were generated from an SEIR transmission process.

RESULTS

Overall assessment

In general, the accuracy of R_0 estimates did vary depending on the method used, with the coverage properties consistently being below the notional 95% value; and the performance of the methods was found to be dependent on the epidemiological process used to generate the outbreak. When outbreaks were generated by an SIR model, methods based on the doubling time T_d (i.e., Methods 1a and 1b) showed good performances, with the 95% range of the estimated R_0 including the true R_0 value for almost all the explored parameter space. In this situation, poor performances of Methods 1a and 1b were only recorded when the true $R_0 \leq 3$ and β=1, for which R_0 were, on average, overestimated (Table 1). On the other hand, Methods 2, 3 and 4 consistently underestimated the true R_0 value for >80% of the considered parameter space, only performing well in estimating the true value of R_0 where true $R_0 \leq 3$. Performance of Method 5 was variable, estimating the true R_0 value well for 54% of the considered parameter space, but underestimating the true R_0 value in the situations where the true $R_0 \geq 15$.

Table 1. Performance of the different tested R_0 estimation methods in capturing the true R_0 computed over outbreaks simulated with an SIR model. Here, percentage of simulated outbreaks for which estimated R_0 is below, within and above 95% Confidence Interval (CI) is given for the explored parameter combinations

Method	True R_0 above 95% CI	True R_0 within 95% CI	True R_0 below 95% CI
Method 1a	0.0%	91.4%	8.6%
Method 1b	0.0%	91.4%	8.6%
Method 2a	88.6%	8.6%	2.9%
Method 2b	88.6%	8.6%	2.9%
Method 3	85.7%	14.3%	0.0%
Method 4	82.9%	17.1%	0.0%
Method 5	34.3%	54.3%	11.4%

When implementing the different R_0 estimation methods for outbreaks generated by an SEIR model, performance results were more complex, with all methods capturing the true R_0 value in some parts of the explored parameter space (Table 2), but with overall estimates of coverage being relatively low. However, Method 5 showed the best performance, providing useful coverage of the true R_0 value for 92% of the explored parameter space.

In general, R_0 is overestimated when the true R_0 value is low (true $R_0 \leq 2$) and underestimated for larger R_0 values. In fact, the 95% range of the estimated R_0 computed using most methods would capture the true R_0 value where the latter ranges between 2 and 4. However, the duration of the latent period ($1/\lambda$) impacted on the performance of the R_0 estimation methods. For example, when β=1, the 95% range of R_0 estimates computed using Method 1a captured the true $R_0 \geq 4$ well when $1/\lambda \leq 2$ days but R_0 was underestimated when $1/\lambda > 2$ days. Similarly, the 95% range of R_0 estimates computed using Method 4 underestimated most of the situations where true $R_0 \geq 5$ and when $1/\lambda \leq 4$ days but captured the true R_0 when $1/\lambda \geq 5$ days.

Detailed assessment of a specific scenario

We now consider a specific scenario to illustrate how performance of R_0 estimation is impacted by key epidemiological characteristics. Figure 1 shows the performance of all R_0 estimation methods assessed, when varying the background outbreak conditions under Scenario 1 (i.e., R_0=4). Few differences in the relationship between performance and tested conditions, or in the relative performance between methods, were found between Scenarios 1, 2 and 3.

Overall, all R_0 estimation methods showed little variations in their mean estimates when increasing the population size and reporting bias (Figs.1A and 1B), whereas the mean estimates of R_0 were (unsurprisingly) generally closer to the true R_0 value when the susceptibility of the herd prior to an outbreak was higher, leading to larger outbreaks (Fig. 1C). Of all conditions tested, varying ω impacted R_0 estimation the most, showing progressively large differences between mean estimates of R_0 and the true R_0 value as ω increases (Fig. 1D).

Table 2. Performance of the different tested R_0 estimation methods in capturing the true R_0 computed over outbreaks simulated with an SEIR model. Here, percentage of simulated outbreaks for which estimated R_0 is below, within and above the 95% confidence interval (CI) is given for the explored parameter combinations

Method	True R_0 above 95% CI	True R_0 within 95% CI	True R_0 below 95% CI
Method 1a	30.6%	55.1%	14.3%
Method 1b	0.0%	83.7%	16.3%
Method 2a	36.7%	49.0%	14.3%
Method 2b	40.8%	44.9%	14.3%
Method 3	59.2%	26.5%	14.3%
Method 4	26.5%	67.3%	6.1%
Method 5	8.2%	91.8%	0.0%

Even in situations where mean R_0 estimates were far from the true value of R_0, uncertainty around estimates (as informed by the width of their 95% confidence intervals) ensured that most methods frequently provided coverage of the true R_0 values. From our results, however, both Methods 3 and 4 performed the worst of all methods considered, consistently underestimating the true R_0 value in situations with increasing levels of under-reporting, background immunity at the onset of the outbreak, herd size and transmissibility of FMD carriers. Finally, consistent with the overall pattern shown in Table 2, estimates of R_0 computed from Methods 1b and 5 were the closest to the true R_0 values and the least sensitive to changes in background conditions and scenarios.

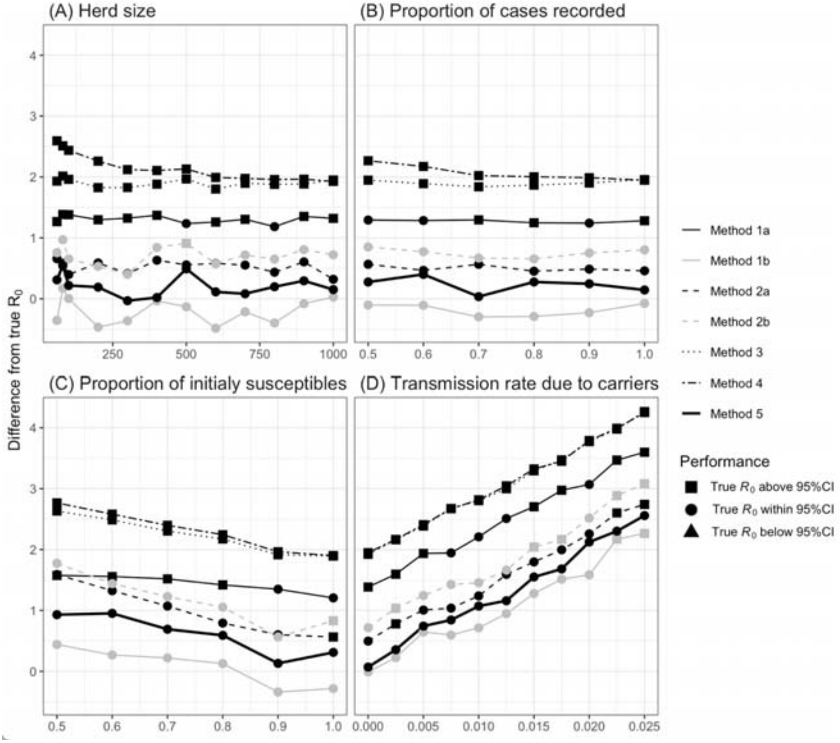

Figure 1. Performance of R_0 estimation methods over outbreaks following SEIRC dynamic. Mean difference of estimates relative to the true R_0 in situations where (A) the herd size, (B) the proportion of cases recorded, (C) the proportion of susceptible individuals prior to the outbreak, or (D) the transmission rate, ω, due to carrier individuals increase. Here, outbreaks were generated considering $\beta=1$ and both latent (λ^{-1}) and infectious (σ_I^{-1}) periods = 4 days (Scenario 1). The shape of the points reflect whether the 95% range of estimates from the R_0 estimation methods includes (circles), underestimates (square) or overestimates (triangles) the true R_0 value. Positive values represent underestimation of R_0 while negative values represent overestimation of R_0

DISCUSSION

Estimation of R_0 from outbreak data is common but there is no agreed single standard method. As such, it remains unclear how estimates of R_0, computed by analysing outbreak records, reflect the true R_0. This uncertainty will undermine control efforts, such as, whether estimated vaccination thresholds are sufficient to provide protection.

Overall, performance in estimating R_0 from outbreak data were not consistent between methods, with some methods typically underestimating R_0 whereas others overestimate it. Over all scenarios and conditions tested, R_0 tended to be overestimated when the true R_0 values were smaller and underestimated when the true R_0 value was larger. It is important to remember that the sample size for inference is only one outbreak, both in this simulation exercise and typically in real-world usage. The underestimation bias is likely to be due to bias in the data, in that when R_0 is low, and the disease system has an appreciable non-zero probability of not giving rise to a large outbreak (as established via various threshold results), the data available for analysis will tend to be unrepresentatively drawn from the more 'infectively active' realisations. The overestimation bias may arise from systematic breach of the underlying assumptions of the inference models, in that larger values of R_0 lead to larger outbreaks over a shorter period of time, where there is a higher probability of the density independence assumption being breached. Situations in which the assumption of an approximate pure birth process is breached will give rise to underestimation. However, as the former effect is intrinsic to the sampling properties of the observation process, it will affect all methods equally. However, the former effect, and others which may be present, will impact differentially for different methods, which suggests that this assessment exercise is indeed worthwhile.

Best performing methods also differ depending on whether observations are of outbreaks between farms or at the individual level within farms. Among all methods tested, the simple "doubling time" estimation method (Method 1) performed best on data from between farm outbreaks. For such a scenario, this method is the least sensitive to variations in transmission parameters and infectious periods, capturing true R_0 values in 91% of all combinations of parameters tested. On the other hand, for within-farm outbreaks, the presence of a latent period of at least 2 days impacts performance of R_0 estimation methods, with the best performance being that based on chains of transmission (*EpiEstim* package in R, Method 5). In this case, this method gives rise to confidence intervals containing true R_0 values in 92% of all the combinations of parameters tested. In both situations, however, Methods 1b and 5 were the best performing methods to estimate R_0.

The performance of the R_0 estimation methods strongly depends on γ and β, with most methods performing well when γ was small and when $R_0<3$. This is consistent with work carried out to evaluate the performance of the methods implemented in the *R0* package (Methods 3 and 4), with little bias observed when simulating outbreaks with both $1/\lambda=1.6$ and $1/\sigma_I=1$ and R_0 ranging from 1.5 to 3, values typical of H1N1 influenza (Obadia et al., 2012; Nikbakht et al., 2019). In the case of FMD, estimates of $1/\lambda$ range from 1.5 to 4.6 days, whilst estimates of $1/\sigma_I$ range from 1.7 to 10.8 days (Mardones et al., 2010; Charleston et al., 2011; Yadav et al., 2019). Together, these studies suggest serial interval values for FMD range between 6.3 and 12.2 days, much longer that those used previously to test performance of R_0 estimation methods. Hence, our results, highlighting the poor performance of Methods 3 and 4 for broader parameter ranges, are not inconsistent with those from these previous studies.

In this study, we have in mind outbreaks of FMD amongst pastoralist small holdings in sub-Saharan African countries, for which herd size as well as the level of under-reporting and background immunity of the population may be variable. In particular, the background immunity of these populations may be extremely variable as previous exposures from multiple serotypes may have occurred prior to outbreaks. In addition, vaccination against FMD is not common in Equatorial Africa but is used in some circumstances to reduce local transmission. However, the administration of FMD vaccines is not always optimal, with vaccine strains not matching the field virus (Paton et al., 2005; Parida, 2009) and the number of doses sometimes insufficient to provide yearly protection. As the level of immunity of the population may vary over time, outbreaks can occur despite vaccination (Hayer et al., 2018). Although corrections exist to estimate R_0 from outbreaks where there is partial immunity, these require prior knowledge on background immunity that is most often unknown.

Accordingly, we explored the impact of transmission from carriers on the estimation of R_0. Transmission from carriers has only been shown under artificial conditions or anecdotally reported (Salt, 1998; Arzt et al., 2018) and their role in the persistence of FMD in endemic regions remains controversial. However, if carriers can transmit infection, even at low levels, they have the potential to significantly extend the duration of the infectious period and may appreciably affect estimates of R_0 (McLachlan et al., 2019).

Here, we found that Methods 1b and 5 were the most robust to changes in background immunity of the population, under-reporting, herd size, and transmission due to carriers. As poor estimation of R_0 or using estimates from different settings may result in inappropriate or ineffective control measures being designed and/or implemented, using these methods may be preferred compared to the other considered methods.

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EVALUATION OF FOOT AND MOUTH DISEASE CONTROL MEASURES IN ENDEMIC AREAS OF THAILAND

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SUMMARY

A stochastic epidemiological model was constructed to evaluate FMD control measures in two areas of Thailand: Lamphaya Klang subdistrict and Bo Phloi district. The transmission parameters and farm types were based on the FMD outbreaks occurring between 2016 and 2017. The control measures consisting of culling, ring vaccination, animal movement restrictions and infected farm isolation were evaluated by the number of secondary infected farms and outbreak duration. The model showed that all four control measures were capable of preventing major outbreaks, supposing that the important related parameters (vaccine efficacy in ring vaccination and transmission kernel reduction in animal movement restrictions and isolating) were adequate. In the densely populated areas, stringent control measures, such as culling or ring vaccination with high vaccine efficacy, were required to prevent a major outbreak. Conversely, less stringent control measures might be chosen in areas with sparse population density with usually minor outbreaks.

INTRODUCTION

Foot and mouth disease (FMD) is a contagious viral infectious disease in cloven-hoofed animals (Grubman and Baxt, 2004). It is considered to be the most economically important animal disease because of the enormous costs of outbreaks and of the associated control and preventive measures. Many epidemiological models have been developed to evaluate the consequences of FMD outbreaks and control options in FMD-free countries, such as the United Kingdom (Keeling et al., 2001), the Netherlands (Backer et al., 2009), Japan (Hayama et al., 2013) and Peru (Martínez-López et al., 2014). However, the FMD models developed for FMD epidemic countries are unsuitable for applying to the endemic situation because of the difference in immunity and transmission dynamics (Knight-Jones et al., 2016). In the past decades, a number of studies on the evaluation of FMD control strategies in endemic areas have been published. The majority of studies were modelled by using historical FMD incidence and focusing on the country level. For example, Young et al. (2016) on the vaccination program in Cambodia, Nampanya et al. (2016) in Lao PDR and Jemberu et al. (2016) in Ethiopia. A study in Vietnam incorporated spatial features to calculate the transmission between communes (Do et al., 2022). However, so far, there still has been a gap in endemic-FMD models at the individual farm level.

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FMD is endemic in Thailand. Even though Thailand has adopted routine vaccination as the main FMD preventive measure, 980 FMD outbreaks were reported throughout the country from 2016 to 2021 (WOAH, 2022), reflecting that the current preventive measures are not sufficient to prevent the outbreaks. The main outbreak control measures consist of animal movement restrictions and ring vaccination, which are implemented in the outbreak zone (Arjkumpa et al., 2020). These control measures are set as general regulations for every area. However, one-size-fits-all control measures might not be suitable as many studies showed that the FMD transmission dynamic is affected by multiple factors such as the farm density (Keeling et al., 2001; Boender et al., 2010) and animal network (Dubé et al., 2009). These factors highlight the requirement for area-specific FMD control measures.

The objective of this study was to evaluate the four different FMD control measures by comparing the number of secondary infected farms and outbreak duration. We used a previously developed model for FMD in an endemic area (Chanchaidechachai et al., 2021) and the estimated parameters from FMD outbreaks occurring between 2016 and 2017 in two areas of Thailand. The results showed the FMD transmission dynamics in the endemic situation and evaluated the effect of control measures in areas with different livestock species and densities.

MATERIALS AND METHODS

Data collection

The first study area was Lamphaya Klang subdistrict, located in the central region of Thailand. The area is densely populated with dairy cattle farms. The second area was Bo Phloi district, located in the western region of Thailand. This area is sparsely populated. The FMD outbreaks happened in these two areas between 2016 and 2017. From the official record, no control measures were executed during the outbreak. The outbreak data were collected by research staff by interview. The data consisted of the farm location, animal species, farm size, animal trading history and the history of FMD outbreaks in the farms between 2016 and 2017. The interviews started at the centre of each study area, i.e., a milk collection centre in Lamphaya Klang subdistrict and the local veterinary office in Bo Phloi district, then included farms further away until approximately 500 farms were included. The size of the study area in Lamphaya Klang subdistrict was 12.5 × 8.4 km^2 covering 502 dairy farms. The FMD outbreak happened from 15 September 2016 to 8 August 2017 and affected 273 out of 502 dairy farms. For Bo Phloi district, the size of the study area was 30.8 × 25.5 km^2 covering 346 beef cattle farms, 104 goat farms and 51 pig farms. The FMD outbreak happened from 13 October 2016 to 15 December 2016 and affected 15 beef farms.

Parameterisation

The between-farm transmission was calculated from two mechanisms. The first one is the spatial transmission kernel, which is a function describing the relation of the transmission rate between farms depending on the distance between the farms (Boender et al., 2010), as shown in Eq.(1).

$$k(r_{ij}) = \frac{k_0}{1 + \left(\frac{r_{ij}}{r_0}\right)^{\alpha}} \qquad (1)$$

where $k(r_{ij})$ is the transmission rate exerted by infectious farm j on susceptible farm i, r_{ij} is the Euclidean distance between susceptible farm i and infectious farm j and k_0, r_0, and α are three parameters that determine the height and the shape of the transmission kernel.

The second transmission function is the trade network transmission. The trade network was constructed from the interview data. When the farms are infectious, they can spread the disease to other susceptible farms that share the same trader with a constant rate δ per day. The transmission parameters were estimated from outbreak data in two study areas together using the maximum likelihood method (Chanchaidechachai et al., 2021). The model parameters are summarised in Table 1.

Table 1. Summary of foot and mouth disease outbreak model parameters

Parameters	Value	Sources
Transmission kernel parameters	k_0 = 0.0054 day^{-1} r_0 = 0.171 km α = 1.50	Estimated from real outbreak data using the maximum likelihood method (Chanchaidechachai et al., 2021).
Trade transmission rate	δ = 0.0006 day^{-1}	Estimated from real outbreak data
Latent period	3 days	Mardones et al., 2010
Farm Infectious period in Lamphaya Klang subdistrict	Gamma (shape =3.02, rate = 0.137), mean = 22	Estimated from real outbreak data
Farm Infectious period in Bo PhloiBo Phloi district	Gamma (shape =1.87, rate = 0.126), mean = 15	Estimated from real outbreak data
Detection time for dairy farm	5 days	Compartment model with the transmission rate = 0.67 day^{-1} (Bravo de Rueda et al., 2015) and the number of detection cases = 2
Detection time for beef farm	7 days	Compartment model with the transmission rate = 0.67 day^{-1} (Bravo de Rueda et al., 2015) and the number of detection cases = 3
Detection time for pig farm	8 days	Compartment model with the transmission rate = 0.59 day^{-1} (Eblé et al., 2006) and the number of detection cases = 3
Detection time for goat farm	18 days	Compartment model with the transmission rate = 0.21 day^{-1} (Orsel et al., 2007) and the number of detection cases = 3

Model outline

The model was structured using the farm as the individual unit. Each day, the model appraised and updated the farm state, which consisted of susceptible, latent, undetected infectious, detected infectious and recovered states. The model started with the index cases (3 farms in Lamphaya Klang subdistrict and 4 farms in Bo Phloi district based on the interview data) being in the latent state and other farms in the susceptible state. The same set of index cases was used in every simulation. Regarding the between-farm transmission, the probability of infection of the susceptible farm i on day t was calculated from the sum of the transmission kernel and trade transmission (Eq.(2)), and then the infection state was stochastically randomised from the probability of transmission by the binomial distribution.

$$p_{inf} = 1 - e^{-(\lambda_{kernel}(t)+\lambda_{trade}(t))} \tag{2}$$

After infection, the farms were in the latent state for 3 days before changing to the undetected infectious state. The undetected infectious farms transitioned to the detected infectious state after the detection time, which was estimated from a population-based model. The outbreak in the farm was assumed to be detected when the number of infected animals on the farm was more than the case limit number. The infected farms recovered after the infectious period and stayed in a recovered state until the end of the simulation. The simulation started from the first day that index cases were in the undetected infectious state to the day that the last infected farm was recovered, and run for 500 iterations in each scenario to account for stochasticity. The outputs from the model were the number of secondary infected farms, excluding the index cases, and the outbreak duration. The model programming and simulation were conducted using R program version 4.2.1 (R Core Team, 2022).

Control measures

Culling infected farms: Culling has never been used to control the FMD outbreak in Thailand. Thus, we wanted to investigate the impact of culling on the FMD outbreak in Thailand. Several assumptions were made for the culling. First, the farms were assumed to be culled 1, 7 or 14 days after the disease was detected on the farms. We set various variable culling dates to test the consequences of delayed culling. Second, the culling process was finished in 1 day, irrespective of the farm size. Third, the culling completely stopped the disease transmission immediately, and no new animals were reintroduced into the culled farms during the outbreak.

Ring vaccination: The ring vaccination is defined as the vaccination of the susceptible farms in delineated areas surrounding the infected farms. We assumed that the ring vaccinations were implemented to all farms within a 10-km radius of the detected infected farms on that day, with a maximum vaccination rate of 40 farms per day and executed from the outside inwards. The first ring vaccination focused on the farms around the index case and was implemented the day after the index case was detected. The second ring vaccination started 7 days after the index case was detected and concerned the farms located around the newly-detected infected farms. The susceptibility and infectivity of vaccinated farms depended on the vaccine efficacy. For example, suppose the vaccine efficacy was x %, then the susceptibility and infectivity of vaccinated farms were $100 - x$ %. To consider parameter uncertainty, we tested the model with various combinations of the onset of immunity (7, 14, 21 or 28 days) and vaccine efficacy (0 – 100%). Lastly, we assumed that the vaccine-induced immunity lasted for 6 months.

Animal movement restrictions: The regulation of animal movement restrictions followed the Animal Epidemic act, which prohibited the movement of animals and animal products in the outbreak zone, in our case the infected subdistricts. We assumed that the animal movement restrictions were announced one day after the first infected farm was detected, and it was enforced until the last infected farm was recovered. After the implementation of animal movement restrictions, trade transmission became zero. However, the effect of animal movement restrictions on the FMD transmission kernel has never been shown in any literature before. We found one study on bluetongue disease showing the reduction of long-distance transmission after animal transport restrictions (de Koeijer et al., 2011). In this model, we assumed that other transmission routes besides animal and animal product movements, such as the movement of people, vehicles and fomites and the over-the-fence transmission between the adjacent farms, was not affected by animal movement restrictions. These kinds of transmissions are likely to happen between farms close to each other. Therefore, we assumed that the local transmission kernel below a specific cut-off distance from the infectious farm remained the same. In contrast, above the cut-off distance from the infectious farm, the long-distance transmission kernel was assumed to be reduced by a certain percentage, resulting from lower animal movement activities. We tested the model with various combinations of cut-off distances from 0 to 1 km and the percentage decrease of long-distance transmission kernel from 0 to 100%.

Infected farm isolation: Due to the high economic impact and animal welfare problems from animal movement restrictions, we proposed infected farm isolation as another option with less impact. The concept is to restrict animal movement exclusively on isolated farms. In this model, we assumed that infected farms were isolated one day after detection until they recovered. During the isolation, the trade transmission from isolated farms became zero. However, the isolation did not completely stop the spatial transmission kernel since people and vehicles still needed to move for farm maintenance. We used the same effect as animal movement restrictions on the spatial transmission kernel of the isolated farms.

Sensitivity analysis

A global sensitivity analysis was conducted on the model parameters concerning the number of infected farms and the outbreak duration. For each control measure, 500 parameter sets were sampled from their distributions (Table 3) using Latin hypercube sampling. For each parameter set, the simulation was run for 100 iterations from which the median number of infected farms and the median outbreak duration were saved. We used a regression-based method to analyse the parameter variance contributions (Burgers et al., 2010). In brief, the regression model was fitted between the output and input parameters. As long as the fitted regression model can explain more than 90% of output variance, any type of regression model (e.g., linear regression, polynomial regression, spline regression) can be applied. The sensitivity of parameters was presented as the top marginal variance (TMV) and the bottom marginal variance (BMV) extracted from the regression model. TMV was defined as the variance reduction that would occur if the parameter became fully known. It was calculated as the variance explained by the regression model with only that parameter. Bottom Marginal Variance was the variance that the regression model could not explain without that parameter (Jansen et al., 1994). The sensitivity analysis was performed on 15 input parameters (Table 3) using the simulation outbreaks in Lamphaya Klang subdistrict. We selected the parameters with TMV of more than 25% and made scatter plots to show the effect of selected parameters on the median number of infected farms and the median outbreak duration.

RESULTS

Baseline model

The baseline model without control measures from Lamphaya Klang district showed that the predicted median number of secondary infected farms, excluding index cases, was 293 (95% prediction interval of [1, 345]), and the median outbreak duration was 312 days (95%

prediction interval of [26, 506]). The results from the baseline model were consistent with the real outbreak data. The baseline model in Bo Phloi district showed that the predicted median number of secondary infected farms, excluding index cases, was 3 (95% prediction interval of [0, 13]), and the median outbreak duration was 42 days (95% prediction interval of [16, 116]). In comparison, the number of secondary infected farms from the real outbreak was 11 and the outbreak duration was 68 days. Despite the slightly underestimated outbreak in Bo Phloi district, the real outbreak was in the 95% prediction interval. Thus, the baseline model can still depict the real outbreak.

Control measures

Due to the small baseline outbreak in Bo Phloi district, the difference between control measures is subtle in Bo Phloi district. In Lamphaya Klang subdistrict, all four control measures can potentially control the outbreak, but culling is the most effective in reducing the number of infected farms and the outbreak duration. A longer culling delay resulted in more infected farms and a longer outbreak duration (Table 2).

Table 2. The median and 95% prediction interval of the number of secondary infected farms (excluding index cases) and outbreak duration from the foot and mouth disease outbreak model of baseline and culling control measures in Lamphaya Klang and Bo Phloi district

Scenarios	Lamphaya Klang subdistrict		Bo Phloi district	
	Median number of secondary infected farms [95% prediction interval]	Median outbreak duration (day) [95% prediction interval]	Median number of secondary infected farms [95% prediction interval]	Median outbreak duration (day) [95% prediction interval]
Baseline	293 [1, 345]	312 [26, 506]	3 [0, 13]	42 [16, 116]
Culling with the delay of 1 day	1 [0, 7]	15 [10, 32]	1 [0, 5]	17 [14, 36]
Culling with the delay of 7 days	4 [0, 35]	34 [16, 106]	2 [0, 7]	27 [17, 54]
Culling with the delay of 14 days	21 [0, 164]	100 [23, 329]	2 [0, 11]	33 [16, 80]

The outputs from ring vaccination were affected by the vaccine efficacy and the onset of immunity after vaccination. Higher vaccine efficacy and the shorter onset of immunity resulted in fewer infected farms and a shorter outbreak duration. If the vaccine efficacy was greater than or equal to 60%, ring vaccination could limit the number of secondary infected farms to fewer than 21, for any given onset of immunity. The effect is comparable to the outcome of culling with a delay of 14 days (Fig.1). In Bo Phloi district, ring vaccination could reduce the outbreak outcomes as well.

Regarding the animal movement restrictions and isolation, a greater reduction of the transmission kernel and a smaller cut-off distance resulted in fewer infected farms and a shorter outbreak duration. Both the animal movement restrictions and isolation could limit the number of secondary infected farms to fewer than 21, comparable to the outcome of culling with a delay of 14 days, if the reduction of transmission kernel was greater than or equal to 60%. If the reduction of transmission kernel was greater than or equal to 90%, the animal movement restrictions could limit the number of secondary infected farms to fewer than four (Fig.1), which was comparable to culling with a delay of 7 days. The median number of secondary infected farms and outbreak duration from imposing animal movement restrictions is slightly lower than that achieved by the isolation of the infected farms given the same parameters.

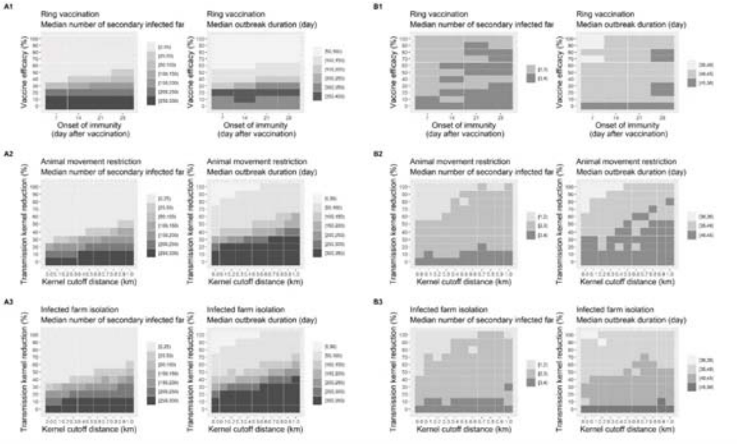

Figure 1. The median number of secondary infected farms (excluding index cases) and outbreak duration from the foot and mouth disease outbreak model. A1, A2 and A3 represent ring vaccination, animal movement restrictions and infected farm isolation in Lamphaya Klang subdistrict. B1, B2 and B3 represent ring vaccination, animal movement restrictions and infected farm isolation in Bo Phloi district

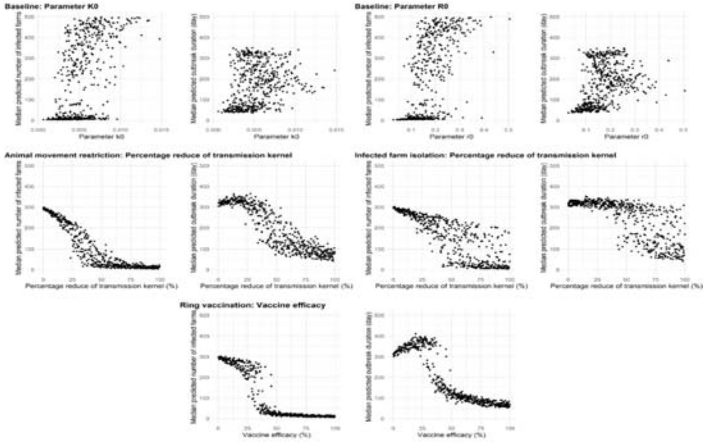

Figure 2. The scatter plots of the median predicted number of infected farms (left) and median outbreak duration (right) against the parameters from the foot and mouth disease outbreak model in Lamphaya Klang subdistrict

Sensitivity analysis

We performed the sensitivity analysis with only the model from Lamphaya Klanag subdistrict because of the limited outbreak in Bo Phloi district. For the baseline model, the parameters k_0 and r_0 explained most of the outcome variance (Table 3), while transmission via the trade network (δ) barely affected the outcome variance. For the ring vaccination, most outcome variances were explained by the vaccine efficacy. For the animal movement restrictions and infected farm isolation, the outcome variance was mostly explained by the percentage of decrease of the transmission kernel. From the scatter plot in Fig.2, the increase of k_0 and r_0 resulted in a higher number of infected farms and in longer outbreak durations, but at a certain point, the outbreak duration was shorter because the high transmission rate rapidly accelerated the outbreak leading to the early depletion of susceptible farms. The outcome variance from the infected farm isolation was larger than animal movement restrictions given the same set of parameters. For ring vaccination, the low vaccine efficacy resulted in a longer outbreak duration compared to the zero vaccine efficacy because the low vaccine efficacy can halt disease transmission. However, it is not effective enough to stop the outbreak until the vaccine efficacy reaches approximately 50%, at which point it is adequate to prevent a major outbreak.

Table 3. Sensitivity analysis of the foot and mouth disease outbreak model in Lamphaya Klang subdistrict. Top Marginal Variance (TMV) is the variance reduction if the parameter is fully known. Bottom Marginal Variance (BMV) is the variance not explained by the parameter.

Control Measures	Parameters	Distribution	Median number of infected farms		Median outbreak duration (days)	
			TMV(%)	BMV(%)	Top (%)	BMV (%)
Baseline	k_0	Gamma (shape=5.25, scale=0.001)	30.7	42.7	10.4	55.6
	r_0	Gamma (shape=5.63, scale=0.03)	39.8	53.6	23.2	71.8
	A	Gamma (shape=118.97 , scale=0.012)	9.6	7.8	3.1	28.6
	Δ	Gamma (shape=2.18, scale=0.0002)	1.1	0.1	0.8	0
Ring vaccination	Vaccine efficacy (%)	Uniform (min=0, max=100)	86.6	87.2	93.2	90.3
	Vaccination rate (farms per day)	Uniform (min=20, max=80)	0	0.2	0	0.3
	Onset of immunity (days after vaccination)	Uniform (min=7, max=28)	0	0.1	3.3	0.4
	Immunity protection duration (days)	Uniform (min=90, max=240)	2.1	2.1	0.9	0.4
Animal movement restrictions	Transmission kernel cut-off distance (km)	Uniform (min=0, max=1)	0.5	2.9	1.8	4.8
	Decrease of transmission kernel (%)	Uniform (min=0, max=100)	91.9	94.5	81.2	85.9
	Delay in animal movement restrictions (days after detection)	Uniform (min=1, max=30)	0.5	0.5	1.9	1.8
Infected farm isolation	Transmission kernel cut-off distance (km)	Uniform (min=0, max=1)	2.6	4.1	4.1	8.9
	Decrease of transmission kernel (%)	Uniform (min=0, max=100)	70.8	75.2	59.8	65.6
	Delay in isolation (days after detection)	Uniform (min=1, max=14)	12.6	13.0	14.1	21.5

DISCUSSION

Overall, all four control measures had the potential to prevent a major outbreak in both Lamphaya Klang and Bo Phloi districts. In Lamphaya Klang subdistrict where the baseline outbreak size was large, the control measures needed to be more rigid to effectively control the outbreak compared to Bo Phloi district where the baseline outbreak size was small. However, control measures were still required for Bo Phloi district to reduce the possibility of a major outbreak escalation.

Although culling infected farms appeared to be the most effective control measure, the decision on culling should consider the economic cost and benefit. If the risk of outbreak recurrence is high, the culling cost might outweigh the benefit of outbreak control. It is necessary to mention that we assumed an unlimited culling capacity and 100% culling effectiveness to stop transmission. In reality, these factors might not be perfect, and they might hamper the effectiveness of culling.

From the model, the typical FMD vaccine produced by the Thai government, which induces an expected 75% of protection at 4 weeks (WOAH, 2021), provides enough protection to control the outbreak by ring vaccination, given our assumptions. However, multiple extrinsic factors, such as vaccine matching, vaccine logistics, vaccination schedule and vaccine coverage, could interfere with, and lower, vaccine efficacy in the field (Ferrari et al., 2016). To ensure adequate field vaccine effectiveness, we proposed the use of a high potency FMD vaccine ($\geq 6PD_{50}$ dose) in outbreaks in high-risk areas, or where vaccine matching is unknown, since the high-potency FMD vaccine can induce early protection and provide better protection against heterologous virus strains (Barnett and Carabin, 2002; Cox and Barnett, 2009),

As the spatial transmission kernel quantifies the transmission rate by subsuming all transmission routes, we cannot individually quantify how much animal movement contributed to the transmission. In this study, we decided to model the effect of animal movement restrictions by defining a cut-off distance from infected farms, below which the local transmission kernel remained the same and above which it decreased faster. These parameters are affected by multiple factors. The cut-off distance is affected by the farm types and the relationship between the farms. For example, the cut-off distance from the small extensive farms should be higher than that for the intensive farms with strict biosecurity since the small extensive farms are expected to have more contact with their neighbouring farms. The reduction of the transmission kernel depended on the contribution of animal movement to the overall transmission and the stringency level of animal movement restrictions. For example, strictly enforcing animal movement restrictions in an area with high animal movement should immensely decrease long-distance transmission and vice versa. We do not intend to conclude a clear-cut parameter value from the model. The results were presented in various combinations of cut-off distance and transmission kernel reduction to let local authorities and experts choose the most suitable parameters for their area and interpret the results to reflect their situation.

Even though the median number of infected farms and outbreak duration from isolation were slightly larger than from animal movement restrictions, the isolation was associated with a much higher risk of a major outbreak than the animal movement restrictions. The decision on the implementation of isolation control measures should consider this risk. For the sake of simplicity, we assumed the same cut-off distance and kernel reduction in every farm in this model, but in reality, the effect of animal movement restrictions and isolation might be heterogenous depending on multiple underlying factors, such as farm types, biosecurity and farm contact.

This study is one of the few FMD models in endemic areas that incorporated spatial features and that was defined at the farm level. This study provided insight into FMD modelling in endemic areas, and the results highlighted the necessity for area-specific control measures. In the high farm density area, stringent control measures, such as culling or ring vaccination with high vaccine efficacy, were required to prevent a major outbreak. In contrast, less stringent control measures might be chosen in areas with low farm density with usually minor outbreaks, as the outbreak impact is limited.

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HOW CAN EPIDEMIOLOGICAL MONITORING AND MODELLING CONTRIBUTE TO MANAGEMENT DECISIONS? LESSONS LEARNED FROM TEN YEARS OF BRUCELLOSIS IN FRENCH WILDLIFE

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SUMMARY

Epidemiological monitoring and modelling are tools to inform management decisions. However, whether research actually feeds field actions depends on how actors from both fields interact. We propose feedback on the outbreak of brucellosis due to *Brucella melitensis* detected in 2012 in the French Alps in humans, cattle and ibex. Based on changes in the category of papers published, we identified three phases in epidemiological knowledge: descriptive epidemiology was performed in 2012-2014, analytical studies in 2015-2020, and evaluative epidemiology emerged since 2021. Management phases followed knowledge with a one-year lag. However, changes in management decisions were not primarily related to changes in knowledge, but to the societal reaction to management and to the discovery of a new infected herd. Having identified the factors promoting or limiting the interaction between science and management, we propose several ways for improving the scientific approach and its use in health management.

INTRODUCTION

Evidence-based decision-making has become a general rule, in particular concerning health. Epidemiological research is intrinsically designed to play a central role in informing decision in health policies. Describing the importance and distribution of diseases, analysing their drivers and evaluating management actions are the main ways by which epidemiology helps improve health management. However, as in other fields, researchers may be frustrated by the inadequate use of science (Stephen, 2017). The way scientific knowledge is used by stakeholders to define or justify action is not straightforward, as the context plays a major role in the interpretation and the willingness to account for scientific evidence (Dobrow et al., 2004).

A first major aspect in the context of health management at the wildlife-livestock-human interface is the presence of numerous stakeholders, each focused on specific and sometimes conflicting issues. The main issues at stake are human health, livestock health and farming, wildlife health and conservation, and the economic consequences of each of them. Moreover,

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lack of knowledge, risk persistence, system unpredictability and limited feasibility of management operations in natural ecosystems make the appropriate use of evidence more difficult. Such situations require adaptative management schemes, *i.e*., a systematic approach for improving management by learning from management outcomes (Williams and Brown, 2016). In particular, the management cycle concerning wildlife diseases should ideally include risk assessment, definition of management objectives, action and evaluation of the action efficacy, all being performed in parallel with the monitoring of the outbreak and including all the relevant stakeholders (Portier et al., 2019). Adaptive management and wildlife disease schemes are both based on strong exchanges and a deep understanding between scientists and decisions makers. Here, we used the case of brucellosis in Alpine ibex *Capra ibex* to study how these exchanges were performed, and what were their outcome in terms of decision making.

While France was officially free of brucellosis since 2005, infection by *Brucella melitensis* was discovered in 2012 in the French Alps, around the Bargy massif. Infection was successively identified in humans (2 cases), in cattle (1 herd) and in local chamois *Rupicapra rupicapra* and Alpine ibex populations (Mailles et al., 2012; Garin-Bastuji et al., 2014). While seroprevalence was low in chamois (1/55 tested in 2012), high seroprevalence levels were observed in ibex (close to 50% in females), which was an unprecedented situation in European wildlife (Garin-Bastuji et al., 2014). This specific finding at the wildlife-livestock-human interface raised many issues. In particular France has been declared officially free from ruminant brucellosis after decades of efforts from farmers. Therefore, farmers were strongly defending eradication in the wildlife compartment. On the other hand, nature protection associations highlighted the need for conservation of the Alpine ibex, a formerly highly threatened species now emblematic of nature conservation all over the Alps, and rejected any hypothesis of culling, especially without preliminary testing of animals.

Faced with this unprecedented situation, management scenarios had to be created at the same time as the process of knowledge acquisition, or even before. A combined monitoring of epidemiology, demography and spatial ecology was initiated in 2012. Each year, some ibex were captured and tested for the presence of brucellosis antibodies (laboratory analyses before 2015, on-field tests since then). Seropositive ibex were euthanised as part of management measures. Seronegative ibex were visually marked, some were equipped with VHF or GPS collars, and all were released and monitored. Population abundance was estimated through capture-mark-resight methods based on standardised counts of marked and unmarked individuals in the area, repeated several times per year, every year. Female reproductive success was estimated through the repeated observation of marked, known-aged females. Depending on the year, authorities chose management strategies that combined capture/test/removal of seropositive individuals and culling of individuals with unknown health status, with variations in the numbers of ibex, sex-age classes and areas targeted by each of them (Lambert et al. 2021). However, the application of these decisions was limited due to field constraints and to opponents performing field and legal actions, leading to differences between the policy makers' strategy and the action actually implemented in the field.

Ten years after the emergence of the outbreak, our objective was to determine the main management phases and to analyse the extent to which management decisions were driven by changes in the field situation, progress in the understanding of disease dynamics or other considerations. We also searched for ways to improve research itself and how to use the results in order to improve decision-making. We particularly studied the role of epidemiological models and the ways modelling could be improved.

MATERIALS AND METHODS

We first described the progress of the outbreak in terms of the field situation (ibex population size and seroprevalence of brucellosis), progress in epidemiological understanding of the outbreak (publications in international papers, reports from collective expertise) and main management measures (number of ibex captured and culled). Although the study of the system led to a continuous progress in the understanding of the outbreak epidemiology, we distinguished between descriptive, analytical (search for causes), evaluative (assessing the efficacy of management measures) or modelling epidemiological studies, since each type of study brings distinct levels of information to management decisions. We also determined changes in management phases, corresponding to different trends in decision-making. Based on the authors perception and on meeting minutes, we tracked the main arguments that conducted to changes in management decisions and analysed how they were related to the field situation, to changes in general knowledge on disease epidemiology or other arguments.

RESULTS

Outbreak history

The Bargy massif is a small mountain range (15 kilometres long) located in the Northern French Alps, Haute-Savoie. Based on the follow-up of GPS-collared females (that play a major role in brucellosis epidemiology – see below), five socio-spatial units were identified in 2015, and then grouped into two areas showing contrasting epidemiological patterns (Fig.1).

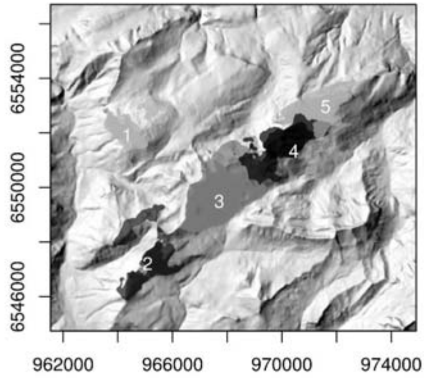
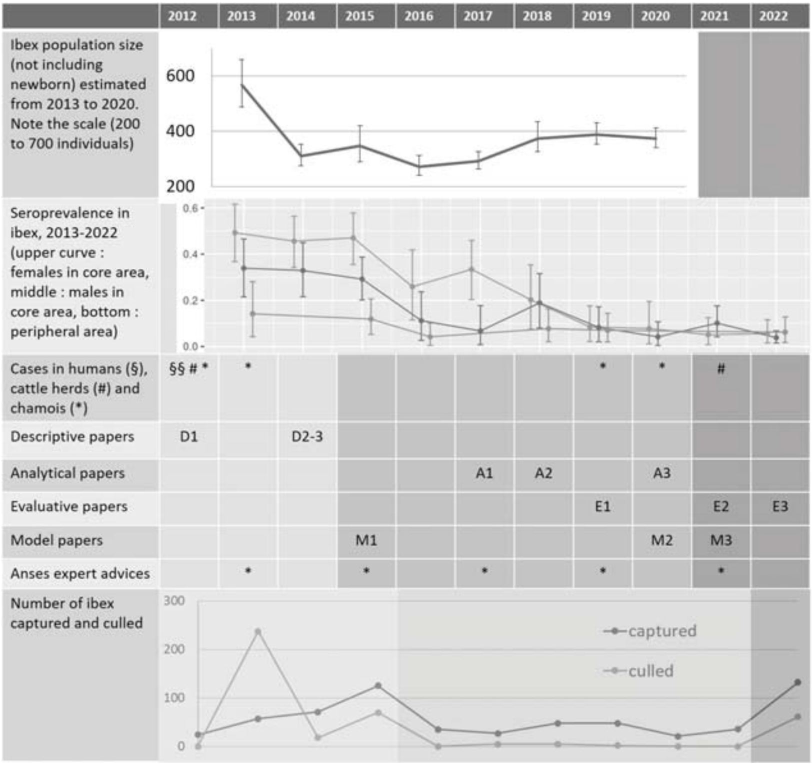


Figure 1. Socio-spatial and epidemiological structure of the Alpine ibex population in the Bargy massif (Lambert et al., 2020). Axes indicate Lambert 93 coordinates of the range. Each greyed area represents the distributional range of a socio-spatial unit, as identified by the GPS monitoring of females, that plays a major role in brucellosis epidemiology - see text. Socio-spatial units 1 and 2 correspond to the peripheral area, with low seroprevalence in 2013-2015, while units 3-5 constitute the core area, with high seroprevalence in 2013-2015 (Marchand et al., 2017)

The main results of the demographic and epidemiological monitoring are represented in Fig.2, shown with the progress in the knowledge and understanding of the epidemiological situation and with the management actions implemented. The ibex population, estimated to be 570 individuals in 2013 (95% confidence interval: 487-660), sharply decreased following the massive culls in autumn 2013- spring 2014 and in 2015 (251 and 70 ibex culled, respectively). The population then increased to around 380 in 2018-2020 (no estimates are available for more recent years). Since 2013, seroprevalence has decreased dramatically. While it was close to 50% in females in the core area, 35% in males in the core area and 15% in the peripheral area in 2013, seroprevalence decreased to 4-6% in 2022 (updated from Calenge et al., 2021). Other field discoveries included 2 cases in humans, 2 in cattle herds and 4 in chamois.



	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Cases in humans (§), cattle herds (#) and chamois (*)	§§ # *	*						*	*	#	
Descriptive papers	D1		D2-3								
Analytical papers						A1	A2		A3		
Evaluative papers								E1		E2	E3
Model papers				M1					M2	M3	
Anses expert advices		*		*		*		*		*	

Figure 2. Calendar of the main field discoveries, progress in knowledge and management actions implemented. The main epidemiological studies are: D1 : Mailles et al., 2012, D2 : Mick et al., 2014, D3 : Garin-Bastuji et al., 2014, A1 : Marchand et al., 2017, A2 : Lambert et al., 2018, A3 : Quéméré et al., 2020, E1 : Ponsart et al., 2019, E2 : Calenge et al., 2021, E3 : Lambert et al., 2022, M1 : Thébault et al., 2015, M2 : Lambert et al., 2020, M3 : Lambert et al., 2021. The three phases of knowledge and management are identified by distinct shades. D = Descriptive; A = Analytical; E=Evaluative; M = Modelling

Three phases of knowledge and management

2012 – 2014 (knowledge) and 2012-2015 (management): Papers published define three knowledge phases (Fig.2). In 2012-2014, no prior information on the ibex population was available and only sporadic cases of brucellosis had been identified before in other populations of ibex. The first publications described the emergence of the outbreak in humans and cattle (Mailles et al., 2012), the discovery of brucellosis infection in ibex and chamois (Anses, 2013; Garin-Bastuji et al., 2014), identified the strain circulating in ibex as *Brucella melitensis biovar 3* and attributed its origin to a spillover from domestic herds before the last bovine case in the area that occurred in 1999 (Mick et al., 2014). The first raw seroprevalence estimates were highest in male ibex aged more than 5 years old (Anses, 2013).

The management of brucellosis is regulated by laws concerning both the disease and the host. Brucellosis is a notifiable disease and its eradication is required according to European and national laws. On the other hand, Alpine ibex is considered a near-threatened species in France and its protection status is guaranteed by international and national regulations. Decisions had to be taken following both regulation systems, and are handled by ministries of Agriculture and Environment, respectively. To capture or cull ibex, managers must ask the opinion of the Conseil National pour la Protection de la Nature (CNPN), the national council for nature protection, an independent council managed by the ministry of environment. They may also rely on the scientific opinion arising from independent collective scientific expertise coordinated by the Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (Anses), that may be solicited by ministries or other structure like associations. Both the CNPN opinion and the scientific opinion from Anses are consultative only, meaning that policy makers do not necessarily follow their recommendations.

During the first phase, management decisions were taken with virtually no information. After the first captures in 2012-2013, the situation was considered an emergency (Anses, 2017), and the methods applied were directly derived from management strategies used in domestic herds. The Ministries of Agriculture and Environment asked Anses to urgently provide their first scientific opinion in August 2013: conclusions were limited due to time constraints (only one month between the request and the due date) and lack of knowledge. Because ibex older than 5 years old were considered as the most probable sources of infection, due to their high apparent seroprevalence, the option taken by policy makers was to cull all ibex aged more than 5 years old, and in practice 251 were culled in autumn 2013 and spring 2014. During the cull, no information was collected on the culled ibex. The extent of the operation alarmed the local and national nature protection associations. Awareness campaigns alerted public opinion against the cull and from then, both field and legal actions were taken each year when culls were planned.

In 2015, the paradigm of the "healthy core group" emerged. The proposed strategy was to intensively capture and test ibex and release the seronegative ones, followed by rapid culling of the remaining, untested animals. The idea was to keep a substantial group of ibex with known seronegative status to preserve the local population, while rapidly achieving eradication of brucellosis. This change of strategy was probably due to the difficulty in reaching all individuals in the field, to the topography and harsh meteorological conditions, to the lack of acceptability of massive culls and to the absence of evidence of their efficacy. The method was implemented in 2015, however with uncomplete realisation (125 captures, 70 culls), due to both difficulties in reaching animals in the field and to the protest actions from nature protection associations who rejected the culls without preliminary testing of animals.

2015 – 2020 (knowledge) and 2016-2021 (management): In 2014, nature protection associations asked Anses to design and evaluate alternative strategies for managing brucellosis in ibex. The working group worked for nine months, summarised previous knowledge and introduced management scenarios that were compared qualitatively and quantitatively using a first epidemiological model (Anses, 2015; Thébault et al., 2015). The model was based on the literature on the demography and ecology of ibex, and on the knowledge of brucellosis in domestic species, with a cost (impact on ibex population)-benefit (probability of extinction of brucellosis) approach. The report also listed knowledge gaps, that were progressively filled during the following years. First, socio-spatial structure was identified as a strong determinant of brucellosis seroprevalence (these findings were first highlighted in 2015 and later published in Marchand et al., 2017), suggesting a contrasting disease dynamic between the peripheral versus the core area. The main routes of transmission were identified using serological and bacteriological investigations (Lambert et al., 2018) and the genetic structure of the population was investigated (Quéméré et al., 2020). In parallel with these investigations, an epidemiological model accounting for up-to-date knowledge was elaborated, analysed and used to unravel main routes of transmission and at-risk classes (Lambert et al., 2020) and to compare management scenarios (Lambert et al., 2021). Altogether, these studies concluded that transmission occurred mainly by exposure to infectious births and abortions, followed by venereal transmission. Females were the source of 90% of infections, while males played the role of disseminating infection between socio-spatial units. Specifically, socio-spatial units located in the core area of the massif (especially units 3 and 4, Fig.1) were the source of transmission to other units (Lambert et al., 2020). As a consequence, management scenarios were predicted to be more efficient when targeting females, and especially young females, in the core area (Lambert et al., 2021).

Interestingly, management decisions were not synchronous with phases of knowledge but were delayed by one year. The second management phase thus lasted from 2016 to 2021. At this time, management strategies relied both on captures and culls, mostly targeting the core area, with 20-50 culls planned each year. However, nature protection associations consistently brought legal actions each year and justice generally suspended the culling operations (but not the captures) in emergency. On the other hand, farmers protested against this management strategy that contrasted with the whole culling of infected herds, which is mandatory in domestic ruminants. Finally, 215 captures and 12 culls were performed between 2016 and 2021.

Since 2021 (knowledge) and since 2022 (management): An experimental assay of vaccination on captive ibex revealed a high risk of *Brucella* shedding in the environment (Ponsart et al., 2019). This information and the lack of evidence for ibex protection by vaccination precluded the use of vaccination for ibex (Anses, 2019). The management actions to be evaluated were thus test-and-remove and culling. In 2020, the amount of data generated allowed for estimates of adjusted seroprevalence, accounting for the high proportion of marked animals and the fact that most captures occurred on unmarked individuals. It also allowed determination of the force of infection and its variation (Calenge et al., 2021; Lambert et al., 2022). These results suggested that the force of infection was divided by approximately 10 in 2015-2016, i.e. during management phase 2. This drop probably resulted both from management actions and natural changes in infection dynamics.

In October 2021, a new case of brucellosis was discovered in a large cattle herd, generating a strong reaction among farmers. Local and national authorities were asked to eradicate brucellosis as soon as possible, generating strong discussions. New advice was requested from

Anses by the ministries of Agriculture and Environment, with a very short delay (2.5 weeks). The request explicitly asked for the use of epidemiological models to compare six pre-defined management scenarios (Anses, 2021). The management strategy that was adopted by policy makers was again in line with the idea of a healthy core group, with as many captures as possible followed by a cull of all remaining unmarked animals. Finally, 135 captures and 61 culls were performed in 2022.

Arguments for change and factors limiting or promoting the science-decision interaction

Examining the arguments that led to changes in management decisions, we identified that they relied both on new knowledge and on social reactions to field discoveries. Changes from phase 1 to phase 2 probably relied on the following elements: (1) the massive cull in 2013-2014 did not result in a clear decrease in prevalence (Marchand et al., 2017), and some results suggested counter-productive effects (Lambert et al., 2022); (2) massive culls led to strong reactions from nature protection associations, including legal actions, thus nearly precluding the use of culling during management phase 2; (3) no new cases of brucellosis were observed in domestic herds or humans between 2013 and 2020. Between 2016 and 2021, only limited culls were planned, probably because managers aimed to avoid protest by nature protection associations, with all decisions being taken to court and broken. The drastic change between 2021 and 2022 was clearly determined by the discovery of a new infected cattle herd, and by the strong reactions of farmers following this discovery, and the culling of the whole infected herd.

Factors that we believe promoted or limited integration between science and decision are summarised in Table 1. In our opinion, five factors acted to better integrate science into decisions. First, the Anses scientific opinions, although not mandatory, were read by most stakeholders and were used to build or to counteract management strategies. Confidence in Anses opinions relied on the fact that each of them was elaborated by an ad-hoc interdisciplinary working group, fulfilling the rules of independent collective expertise. Anses groups were the main occasion for scientists to formally interact with requesters (Ministry of Agriculture or associations). Second, CNPN opinions also fed the debate, although exchanges with scientists working on brucellosis were limited. Third, institutions involved in the outbreak management included both research teams and field or laboratory actors. At the French Office for Biodiversity (OFB), contact occurred between the local field agents and the national research group; in Anses, the expertise groups included agents from the Anses national reference laboratory for brucellosis in ruminants who conducted diagnostics on ibex. The personal knowledge and mutual acculturation among OFB or Anses groups contributed to exchanges between science and management action, and to exchanges between national and local actors. The first three factors lead to a fourth and fundamental aspect facilitating the use of science, which is interpersonal knowledge within and between the structures involved. Beside the formal exchanges within groups working on opinions, and between these groups and ministries asking for opinions, numerous informal interactions took place, including with decision-makers who directly asked individual scientists to clarify specific points. These contacts contributed to the transmission of new results to decision-makers, often before Anses reports were elaborated. Finally, the Ministry of Agriculture funded both management actions and research, which helped to design relevant research programs and to communicate research results to decision-makers.

Table 1. Factors limiting and promoting interactions between scientific advances and management decisions

Promoting interactions	Limiting interactions
1. Collective scientific expertise advices (Anses)	1. View of the crisis as an emergency and belief in rapid crisis resolution
2. Mandatory consultation of the council for the protection of nature (CNPN)	2. Opposing views on the aims of management, feasibility, efficacy and the cost-benefit of management tools
3. Structures mixing scientific teams and field/laboratory actors (Anses, OFB)	3. Divergent and untold ethical principles
4. Interpersonal knowledge between scientists, decision makers and field actors	4. Absence of place for discussion
5. Funding of monitoring and research by policy makers	5. Turnover of persons in charge
	6. Memory of previous situation or interpretation

On the other hand, we identified six factors limiting the use of research by policy makers. First, many stakeholders considered the situation as an emergency, not only during the first phase, but also, some of them even at later stages. Most actors also considered that the issue could be solved rapidly, i.e. in 1-2 years. Scientific opinions were thus asked in very short time frames, which limited the possibility to integrate multidisciplinary and to consider long-term scenarios. The need for long-term research was not recognised before 2015 and the time frame for decision-making was often too short to incorporate research results. This sense of emergency explained why no information was taken on culled ibex in 2013-2014, which then precipitated the opposition of nature associations and deepened the crisis. Second, strong oppositions emerged concerning the aim of management action and the feasibility, efficacy and cost-benefit of management tools. The first aim of farmers was to eradicate brucellosis, which included using massive culling of ibex, applying to wild populations the same principles that are used in livestock management of brucellosis. On the other hand, the first objective of nature protection associations was to protect the ibex, thus no cull of ibex was conceivable, especially concerning non-tested animals. Moreover, mass media intervention often oversimplified, crystalised and stiffened the positions of all actors, including scientists. Behind these oppositions, a third factor was the divergence about the values that should be considered to manage the outbreak. Although not explicitly stated, principles of animal ethics (not killing and not harming) and/or environmental ethics (respecting ecosystem integrity, non-interventionism as a precaution) probably guided most of the opponents against the culls, while ethical principles of public health (possibility of constraint to avoid damage caused to others, proportionality of means, Upshur, 2002) likely motivated the authorities in charge of managing the outbreak. Fourth is the absence of a place for discussion between scientists and decision makers, and among actors, i.e. local and national authorities from different ministries. During the most intense crisis times, interactions were distorted. Local politicians, farmers and nature association representatives directly solicited cabinet ministers to defend their positions, while services in charge of health policy were not involved in the discussions. Due to this lack of concertation, in 2015 and 2022, decisions were taken at the national and political level. Fifth, the concertation was discontinued due to the turnover of persons in charge in all public services at the local and national levels. Last, we observed that some stakeholders often set their mind on a first impression. For example, after the 2013 cull, raw seroprevalence in ibex aged less than 5 years old was higher than before the cull. This was interpreted as a rebound of incidence due to social perturbation, with young males replacing old males for reproduction and being massively exposed to the disease. This interpretation was demonstrated to be erroneous, as the change in prevalence was instead due to sampling bias that was year-dependent (Marchand et al., 2017). However, the apparent rebound in prevalence was still considered to have occurred by some actors. The massive cull of 2013 and 2015 also convinced some stakeholders to consider that management was mainly based on massive culling, even after several years with few or no culls.

DISCUSSION

"Wildlife Health 2.0 research teams will need to be as adept at providing the scientific justification for options to respond to wildlife health threats as they will need to be in producing the social evidence to identify implementation strategies that are feasible, sustainable, understandable, and acceptable to decision makers" (Stephen, 2017). The case of brucellosis in ibex offered us the occasion to apply this recommendation and to propose ways to improve science-based management, a much-needed change for wildlife health (Vicente et al., 2019).

We first advocate that research activities may be improved by considering questions emerging from stakeholders. For example, about brucellosis, post-assessment of management measures is limited, and basically consisted of appreciating the temporal dynamics of the prevalence and the force of infection (Calenge et al. 2021; Lambert et al., 2022). The specific effects of each action have not been assessed, in terms of efficacy as well as unwanted effects, e.g., on ibex disturbance or population dynamics. The efficacy of each action could be assessed through modelling, using "what if" scenarios. The current situation of low prevalence also raises the question of whether brucellosis may fade out (and with what probability or when), or alternatively whether the outbreak may start again and result in a similar situation as in 2012 if management stops being efficient. Finally, the routes of transmission between ibex, chamois and cattle herds have still to be identified and deserve further attention.

We aimed to identify how to improve modelling in the context of decision-making. First, realistic models are hard to explain to a non-scientific audience. However, the 2021 request to Anses showed that at least some stakeholders assimilated model results, as long as outputs relevant to them could be obtained and visualised. Complex models thus may not be a limit to science-decision interaction. Second, models should be flexible enough to test alternative scenarios and to be revised regularly, integrating new field data and epidemiological knowledge. In the case of brucellosis, decisions are taken on a yearly basis as population biology and management actions are highly seasonal. Thus, yearly cycles of modelling are relevant, provided the model is available at the time of reflection. The modelling process should thus become a continuous effort during the whole period of interest. Models also raise the question of which scenarios to consider: although all may be useful for a better understanding, scenarios that were considered as non-realistic or not acceptable were rejected, which limited model use. For example, a scenario of more than 50 captures per year was considered unrealistic in 2021 (Anses, 2021). However, 135 animals were captured in 2022, thus model predictions were not comparable to field results. For the results to be assimilated by stakeholders, scenarios should be defined in concertation with them. Models should also consider the costs and benefits of management. Here, the total number of ibex culled and captured during the whole simulation period was estimated for various scenarios (Lambert et al., 2021) to provide elements to estimate the feasibility, the financial and organisational costs and the impact on the population. Lastly, the ethical bases that serve to identify the chosen scenarios should be clarified, so that debate is possible on the conflict between values.

Research in social and political sciences could also be further developed. In the case of brucellosis, although some preliminary studies have been conducted, the position of stakeholders, their interplay and possible avenues for change have not been identified. Finally, philosophical values and ethical principles underlying management actions should also be identified, as well as their conflicts in such a complex system.

Finally, the main way to improve the use of research results by policy makers, field actors and the general public is to improve communication among them. Communicating model results on a complex system is challenging: for example, point estimates are more likely to be remembered than credible or confidence intervals, although such intervals are necessary to avoid the overinterpretation of point estimates. In this respect, the progressive acculturation of epidemiology by all actors is an essential issue, that implies a "de-appropriation" of knowledge by specialists. The accessibility of knowledge could also be increased and publicised, through French-speaking texts in the case of brucellosis. In particular, the outbreak monitoring is expected to generate transparent information on the epidemiological situation. However, this principle is limited by the necessary time to conduct investigations. Moreover, each structure may have its own definition of what should remain confidential. A French-speaking OFB web page was updated for this purpose (https://professionnels.ofb.fr/fr/article/point-foyer-brucellose-dans-massif-bargy). A major challenge is to include uncertainty in communication and to avoid oversimplification. For example, models estimate the probability of extinction, while policy makers ask for a yes/no answer. The message that the future situation depends on stochastic, non-controllable events such as the place of abortion or the death of a few individuals is frustrating for some actors. As mentioned in the results, a key point for improvement is to define a place for concertation, and to organise a dialogue between scientists and stakeholders, as required for management cycles of wildlife diseases (Portier et al., 2019).

As a conclusion, brucellosis in ibex is a relevant model to learn how to manage diseases at the interface between wildlife, livestock and human health. The need for a long-term approach and for a permanent place for discussion between scientists, decision-makers and stakeholders are the main ways for improvement and may also serve for other host-pathogen systems.

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COMMENSAL BACTERIA

TRANSMISSION RATES OF VETERINARY AND CLINICALLY IMPORTANT ANTIBIOTIC RESISTANT *ESCHERICHIA COLI*: A META- ANALYSIS

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SUMMARY

Resistant bacteria are endemic in livestock. The transmission rate between hosts is a key parameter for simulating transmission dynamics of antibiotic-resistant bacteria, and might differ among antibiotic resistance genes, animal species, and antibiotic usage. We conducted a Bayesian meta-analysis of resistant *Escherichia coli (E. coli)* transmission in broilers and piglets to obtain insight in factors determining the transmission rate. We included extended spectrum beta-lactamase (ESBL), carbapenem-resistant (CPE), colistin-resistant, and fluoroquinolones-resistant *E. coli*. Transmission rates of different resistant *E. coli* between young broilers ranged between $0.3 \cdot 10^{-3}$ h^{-1} and $9.4 \cdot 10^{-3}$ h^{-1}. The range in piglets was between $0.4 \cdot 10^{-3}$ h^{-1} and $2.5 \cdot 10^{-3}$ h^{-1}. In groups without antibiotic treatment, the transmission rate of resistant *E. coli* in broilers was almost twice the transmission rate in piglets. The effect of other factors, antibiotic treatment, resistance gene and inoculation dose, were inconclusive.

INTRODUCTION

Transmission dynamics of antibiotic-resistant bacteria between livestock hosts are widely unknown despite the damaging impact of therapeutic failure due to antibiotic resistance in all animal species including humans. Cases of resistant bacteria against important last resource antibiotics such as carbapenem-resistant *E. coli* (CPE) have been occurring worldwide in livestock since 2010 (Köck et al., 2018). However up to date, CPE has not spread as extensively among livestock as other beta-lactamase producing *E. coli* such as extended spectrum beta-lactamase *E. coli* (ESBL) (Dahms et al., 2015).

Simulation modelling is a helpful tool to assess antibiotic-resistant bacteria transmission dynamics and to evaluate intervention programs. We can simulate transmission dynamics in various conditions that cannot be studied in the real-world setting, but require parameters for these simulations. The transmission rate (β) is a crucial parameter in these simulations and must be determined accurately because it largely determines the model outcome and thus predictions (Kirkeby et al., 2017). Transmission rates are best calculated from transmission experiments in which animals are inoculated and the infection is allowed to spread to susceptible contact animals. The infection status of individual animals is tracked over time, and

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used to calculate transmission rate. Still, these longitudinal experimental studies have their limitations.

Despite being the often optimal way to acquire transmission rate information, transmission experiments are restricted of size, few treatment groups, housing and management conditions and limited sampling times due to costs (labour intensive), and ethical reasons (Hu et al., 2017). Consequently, we lack transmission experiments for resistant *E. coli* that test other relevant factors such as antibiotic treatment, locations of the gene, and animal species.

Bayesian meta-analysis can improve the accuracy of the estimations of transmission rates from longitudinal experimental study via combining multiple studies and producing probabilistic prediction that is informative of the data and the model (McElreath, 2020). Meta-analysis increases sampling power by joining small scale studies with partial pooling, while penalising against overfitting by using regularising priors (McElreath, 2020). Bayesian inference is flexible and intuitive due to its adjustable prior and likelihood components (McElreath, 2020). This flexibility is important in our model as we included an SIS model with environmental transmission in the likelihood function. Bayesian inference produces a non-uniform probabilistic prediction in the form of a posterior distribution which is more informative of the model and data than an uniform probabilistic confidence interval (Vilares and Kording, 2011; Gelman et al., 2021; Hiura et al., 2021). The posterior distribution reflects the variability of the data, likelihood model and prior information while the confidence interval assumes that the entire range of the confidence interval of a uniform distribution has equal opportunity to be the true value.

Here, Bayesian meta-analysis was employed to infer transmission rates of *E. coli* with different resistance genes in both piglets and broilers from transmission experiments. Environmental transmission was assumed, because bacteria such as *E. coli* are transferred between animal hosts through the faecal-oral route and can survive in a farm environment as long as 30 days (Lister and Barrow, 2008; van Elsas et al., 2011; van Bunnik et al., 2014). We aim to identify factors determining the transmission rate.

MATERIALS AND METHODS

A systematic review was conducted following the PRISMA protocol. Transmission events and infectious periods were extracted from longitudinal experimental transmission studies. Transmission events were fitted to an SIS model with environmental transmission (Gerhards et al., 2022) using a Bayesian hierarchical inference model to obtain transmission rates.

Systematic literature review and data extraction

Key words related to ‘meat-producing livestock’+ ‘resistant bacteria’+ ‘longitudinal data’ were collated and applied to online database PubMed to identify suitable studies. Figure 1 demonstrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) applied in the review (Fig.1). We included the unpublished data of our own experiment for which an extended publication is being drafted.

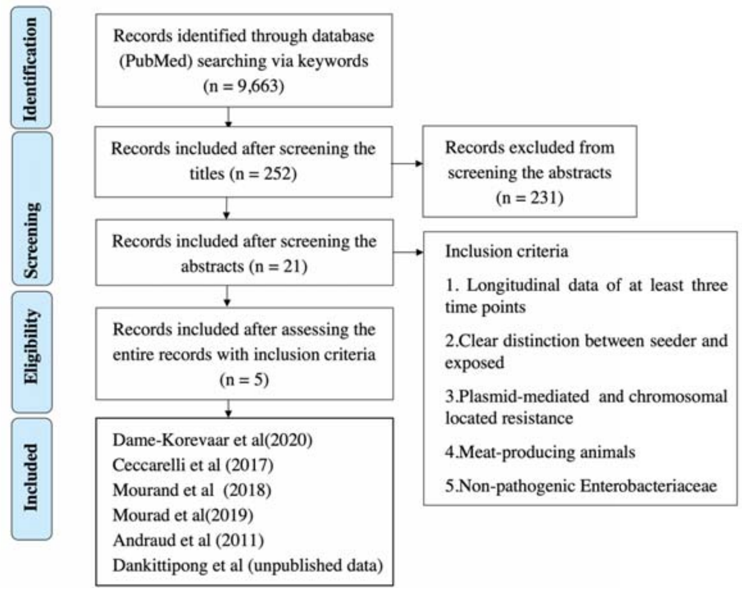

Figure 3. PRISMA protocol for systematic literature review to collect longitudinal data of resistance genes transmission between meat-producing animals

The excreting status (positive or negative for resistance markers) of individual animals were extracted at each sampling time point. In each individual animal, we extracted the pen information, the inoculation strain, any antibiotic treatments (yes/no), and the inoculation status (inoculated animal versus contact animal). Contact animals were assigned to the transmission model as susceptible animals and could become a case and subsequently become an infectious animal, whereas the inoculated animals could only become infectious but were not counted as cases.

Transmission model

We used an SIS transmission model with environmental transmission (Gerhards et al., 2022). We extracted the number of susceptible and infectious animals at each sampling time point from longitudinal data. Within the same pen, susceptible animals (S_t) may become infectious (I_t) through infectious material deposited in the environment (E_t) and can subsequently recover and become susceptible again. Infectious material deposited in the environment (E_t) is the source of indirect transmission where infectious animals are excreting infectious material into the environment. The excreted bacteria decay with a constant rate (δ_t) and the viable bacteria are picked up and colonize with rate (β_t) by susceptible animals (unpublished data). Because we do not know the exact number of bacteria excreted by a broiler chicken or pig, we scaled this excretion into one unit of excreted bacteria by one broiler chicken per hour (and by one pig per hour) (Gerhards et al., 2022). In contrast to Gerhards et al. (2022), we used a fixed decay rate because of a lack of sampling moments without excreting animals to enable estimation of the decay rate.

Bayesian hierarchical inference for transmission rate

We applied Bayesian inference for the parameters of the transmission model. The transmission rate parameter of each pen (β_i) was calculated in two steps. The number of new cases during a time interval is binomially distributed with the number of trials equal the number of susceptible animals in the pen (S_i) and the probability of transmission (p_i), where i is index for pens (clusters). The probability of transmission during an interval is quantified by calculating a pen specific transmission rate β_i via two parameters, the mean log population transmission rate ($\log(\bar{a})$) and the variation of transmission rate between pens (z_i). The probability of transmission is multiplied by the environmental contamination (E_t). Because we are not able to quantify the exact amount of bacteria excreted by the animals, E_t represents the instantaneous hazard of colonisation given a standardised day of excretion transmission (Gerhards et al., 2022). The slightly informative prior for the log mean transmission rate ($\log(\bar{a})$) follows a normal distribution with a mean of -10 and a standard deviation of 10. Whereas the prior for the variation of transmission rates between pens (z_i) follows a normal distribution with a mean of 0 and a standard deviation of 1.

The entire posterior distributions were extracted as output. The posterior distribution of the transmission rate in each pen (β_i) was extracted, and for comparisons grouped and averaged by the resistance gene in the inoculation, host species and antibiotic treatment. The posterior distributions are either presented in figures or by the Maximum A Priori (MAP) and 97% Highest Probability Density Interval (97% HDPI).

To compare two transmission rates for different factors such as animal species, we determined the entire posterior distribution of ratios between the transmission rates of two factors by dividing the rates in each sample of the posterior distribution. A ratio of one means the transmission rates are equal for the two factors. Therefore, we calculated the probability that the ratio is higher than one (P>1) by summing iterations that resulted in ratios higher than one and dividing the sum by the total number of iterations.

All analyses were done in R version 4.1.2 (R development Core Team, 2022) and Bayesian inference was done in RStan 2.21.5 (Stan Development Team, n.d.) with 14 tree depth, 0.99 acceptance rate and four chains, each chain with 10,000 iterations.

RESULTS

Transmission experiment data

We extracted three longitudinal experimental studies in broilers, which contained a total of 170 one-day old conventional broilers and 36 five-day old specific-pathogen free (SPF) broilers. Dame-Korevaar et al. (2018) tested the transmission rate of *E. coli* carrying *bla*$_{\text{CTX-M-1}}$ resistance gene with $0.5 \cdot 10^1$ and $0.5 \cdot 10^2$ cfu/animal inoculation doses in one-day old conventional broilers. Ceccarelli et al. (2017) inoculated five-day old SPF broilers with *E. coli* carrying *bla*$_{\text{CTX-M-1}}$ genes of $0.5 \cdot 10^6$ and $0.5 \cdot 10^8$ cfu/animal dosages. We added the data of an unpublished study, which evaluated the transmission of *E. coli* carrying *bla*$_{\text{OXA164}}$, *E. coli* carrying *bla*$_{\text{CTX-M-2}}$, and *E. coli* carrying *catA1* inoculated at $0.5 \cdot 10^3$ cfu/animal in one-day old conventional broilers and included amoxicillin treatment (20 mg/kg of broiler) for five days (unpublished data). Inoculation with *E. coli* carrying a resistance gene was conducted on the fourth day of amoxicillin treatment. Within the three studies, all inoculated and susceptible chicks acquired *E. coli* carrying resistance genes except for one pen of conventional broilers inoculated with $0.5 \cdot 10^1$ cfu/animal of *E. coli* carrying *bla*$_{\text{CTX-M-1}}$ in Dame-Korevaar et al. (2018).

For piglets, the three longitudinal experimental studies contained a total of 101 SPF piglets between seven to eight weeks old. Two experiments were conducted by Mourand et al. (2018, 2019) to test the transmission rate of *E. coli* carrying *mcr-1* resistance genes with $2.5 \cdot 10^5$ and $2.5 \cdot 10^8$ cfu/animal inoculation doses. In the Mourand et al. (2019) study, colistin was administered at a dosage of 12,500 IU/kg live weight (which is 4 mg/kg) for three consecutive days either seven days before inoculation or one hour before inoculation. The eight week old piglets were then inoculated with $2.5 \cdot 10^8$ cfu/animal inoculation doses. We excluded two pens treated with colistin seven days before inoculation from the final results because we wanted the antibiotic treatment in piglets to be comparable with that of the broilers (where the inoculation events overlapped with the antibiotic treatment events). In Mourand et al. (2018) study, *E. coli* carrying *mcr-1* resistance genes with $2.5 \cdot 10^5$ and $2.5 \cdot 10^8$ cfu/animal inoculation doses were inoculated to seven weeks old piglets. The two pens inoculated with $2.5 \cdot 10^5$ cfu/animal did not result in any colonisation and thus were excluded from the model input. Point mutated fluoroquinolone resistant *E. coli* transmission between the seven weeks old piglets was conducted (Andraud et al., 2011) with 10^{10} cfu/animal inoculation dose. In this study, all piglets in the seven pens became colonised with *E. coli* carrying the fluoroquinolone resistance gene.

Transmission rate of resistant bacteria within the same animal species

Overall transmission rates of *E. coli* carrying resistance genes in piglets were between $0.4 \cdot 10^{-3}$ h^{-1} to $2.5 \cdot 10^{-3}$ h^{-1} (lowest to highest value of 97% HPDI). Transmission rates of *E. coli* carrying resistance genes in broilers ranged from $0.3 \cdot 10^{-3}$ h^{-1} to $9.4 \cdot 10^{-3}$ h^{-1}. We found on average higher transmission rates for *E. coli* carrying *bla*$_{\text{CTX-M-1}}$ or *bla*$_{\text{CTX-M-2}}$. which explains this wide variation (Table 1).

Furthermore, the studies with *E. coli* carrying *bla*$_{\text{CTX-M-1}}$ included multiple inoculation doses ranging from $0.5 \cdot 10^1$ cfu/animal to $0.5 \cdot 10^8$cfu/animal. The low dose of $0.5 \cdot 10^1$ cfu/animal resulted in a lower transmission rate, compared to other inoculation doses. Nevertheless, upon inoculation with this small dose of *E. coli* carrying *bla*$_{\text{CTX-M-1}}$, the transmission rate was already higher than observed for the other resistance genes at higher doses (Table 1).

Table 1. Transmission rate per hour from different animal species, status, mode of transmission, resistance genes, and antibiotic treatment. MAP denotes Maximum a priori and 97% HPDI denotes 97% higest posterior density distribution

Species	Status	Resistance (genes)	Antibiotic	Number of animals	Inoculated dose (cfu/animal)	MAP (h^{-1})	97% HPDI	Reference
Broilers	Specific pathogen free animals	*bla*$_{\text{CTX-M-1}}$	No	20	$0.5{\cdot}10^{6}$	$2.5{\cdot}10^{-3}$	$1.2{\cdot}10^{-3}$, $9.4{\cdot}10^{-3}$	Ceccarelli et al., 2017
		bla$_{\text{CTX-M-1}}$	No	16	$0.5{\cdot}10^{8}$	$1.6{\cdot}10^{-3}$	$0.9{\cdot}10^{-3}$, $3.3{\cdot}10^{-3}$	Ceccarelli et al., 2017
	Conventional	*bla*$_{\text{CTX-M-1}}$	No	20	$0.5{\cdot}10^{1}$	$0.4{\cdot}10^{-3}$	$0.1{\cdot}10^{-3}$, $2.4{\cdot}10^{-3}$	Dame-Korevaar et al., 2020
		bla$_{\text{CTX-M-1}}$	No	30	$0.5{\cdot}10^{2}$	$2.4{\cdot}10^{-3}$	$1.4{\cdot}10^{-3}$, $4.6{\cdot}10^{-3}$	Dame-Korevaar et al., 2020
		bla$_{\text{CTX-M-2}}$	No	20	$0.5{\cdot}10^{3}$	$0.7{\cdot}10^{-3}$	$0.4{\cdot}10^{-3}$, $1.1{\cdot}10^{-3}$	unpublished data
		bla$_{\text{OXA-48}}$	No	18	$0.5{\cdot}10^{3}$	$0.4{\cdot}10^{-3}$	$0.3{\cdot}10^{-3}$, $0.8{\cdot}10^{-3}$	unpublished data
		catA1	No	20	$0.5{\cdot}10^{3}$	$1.0\ {\cdot}10^{-3}$	$0.6{\cdot}10^{-3}$, $1.6{\cdot}10^{-3}$	unpublished data
		bla$_{\text{CTX-M-2}}$	Amoxicillin	20	$0.5{\cdot}10^{3}$	$2.6{\cdot}10^{-3}$	$1.4{\cdot}10^{-3}$, $4.3{\cdot}10^{-3}$	unpublished data
		bla$_{\text{OXA-48}}$	Amoxicillin	20	$0.5{\cdot}10^{3}$	$0.6{\cdot}10^{-3}$	$0.3{\cdot}10^{-3}$, $1.3{\cdot}10^{-3}$	unpublished data
		catA1	Amoxicillin	20	$0.5{\cdot}10^{3}$	$0.8{\cdot}10^{-3}$	$0.3{\cdot}10^{-3}$, $3.3{\cdot}10^{-3}$	unpublished data
Piglets	Specific pathogen free animals	*mcr-1*	No	20	$2.5\text{-}9{\cdot}10^{8}$	$0.8{\cdot}10^{-3}$	$0.5{\cdot}10^{-3}$, $1.4{\cdot}10^{-3}$	Mourand et al., 2018
		Fluoroquinolone	No	51	$1.0{\cdot}10^{10}$	$0.7{\cdot}10^{-3}$	$0.5{\cdot}10^{-3}$, $1.1{\cdot}10^{-3}$	Andraud et al., 2011
		mcr-1	Colistin	10	$2.5\text{-}9{\cdot}10^{8}$	$0.9{\cdot}10^{-3}$	$0.4{\cdot}10^{-3}$, $2.5{\cdot}10^{-3}$	Mourand et al., 2019

Comparing the transmission rates between groups with and without antibiotic treatment

Amoxicillin accelerated the transmission of *E. coli* carrying *bla*$_{\text{CTX-M-2}}$ resistance genes but had no effect on the transmission rates of the other resistance genes. Figure 2 shows the 3.34 fold higher transmission rate for *E. coli* carrying *bla*$_{\text{CTX-M-2}}$ in the group treated with amoxicillin compared to the untreated group (Fig. 2). Amoxicillin and colistin seem to increase the transmission rate of *E. coli* carrying *bla*$_{\text{OXA-48}}$ and *E. coli* carrying *mcr-1*. However, their ratio between 0.26-3.39 (97% HPDI) cannot decisively show an effect from antibiotics on *E. coli* carrying *bla*$_{\text{OXA-48}}$ and *E. coli* carrying *mcr-1*. For *E. coli* carrying *catA1* genes we found on average a lower transmission rate with amoxicillin treatment, but this was even less conclusive as approximately half (0.54) of the posterior distribution has higher transmission rates (Fig.2).

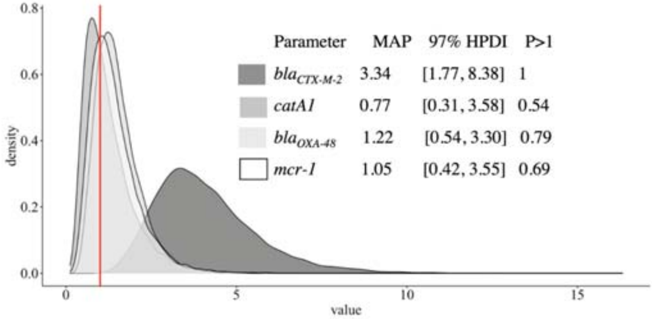

Figure 4. Posterior distributions of the ratio of transmission between antibiotic treatments (no antibiotic vs. with antibiotic treatment) for different resistance genes in broilers and piglets

Comparing the transmission rate in broilers versus piglets

Without antibiotics, the transmission rate between broilers was higher (probability of 0.99) than that between piglets, and this was on average two-fold higher. In contrast under antibiotic treatment, the same transmission rate was found for piglets and broilers (Fig. 3).

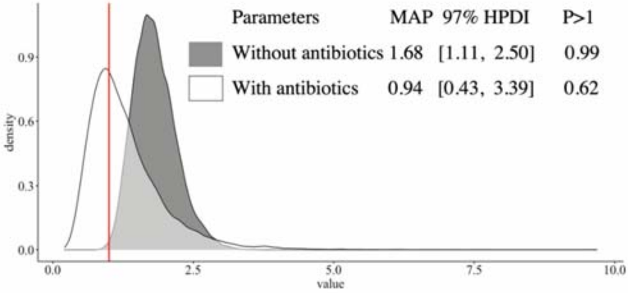

Figure 5. Posterior distributions of the transmission rate ratio of broilers and piglets when treated and not treated with antibiotics

DISCUSSION

We considered three possible explanations for our findings that in the absence of antibiotics the transmission rate is higher among broilers than among piglets: the gut microbiome of animals, fitness costs of bacteria, and differences in experimental set-up between the studies.

First, the piglets were older than the broilers. The stability of the gut microbiome of piglets and broilers increases with the age of the animals (Ranjitkar et al., 2016; Guevarra et al., 2019). A stable gut microbiome has a preventive effect against resistant bacteria invasion (Lozupone et al., 2012; Sorbara and Pamer, 2019). Exogenous and potentially resistant bacteria will readily colonise an unstable gut microbiome (Kim et al., 2017; Rochegüe et al., 2021). Diverse bacteria species in a stable gut microbiome establish complex interactions to achieve homeostasis within the gut, which results in a preventive effect against invasion of exogeneous bacteria (Lozupone et al., 2012; Awad et al., 2016; Rochegüe et al., 2021). In our meta-analysis, broilers were one to five day olds at the start of the experiment while piglets were at least seven weeks old. Young broilers of less than one week old typically have a volatile gut microbiome and are most vulnerable to *E. coli* colonisation (Zhu and Joerger, 2003; Ranjitkar et al., 2016). The microbiome of 7 week old piglets is more stable than that of the broilers which reduces the opportunity for resistant *E. coli* to colonise (Chen et al., 2017; Guevarra et al., 2019; Zhou et al., 2021).

Secondly, specific resistance genes, or the mobile elements with which these are associated, could impose a different fitness cost to *E. coli* thereby determining the transmission rate (Melnyk et al., 2015). Some genes are even associated with an improved fitness of bacteria without antibiotic treatment (Luo et al., 2005; Andersson, 2006; Borrell et al., 2013; Melnyk et al., 2015). Betalactamase producing genes (in our study $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-2}}$) are known to rapidly colonise host populations and diversify worldwide due to their highly mobilised genetic characters which suggests a low fitness cost in acquiring these genes (Cantón et al., 2012; Palmeira et al., 2020). Transmission rates of *E. coli* carrying $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-2}}$ genes were highest in our meta-analysis (Table 1). This indicates a low fitness cost of $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-2}}$ genes incurred to *E. coli* and as evidenced by the high transmission rate of $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-2}}$ *E. coli* between broilers. Although we did not have transmission experiment data of *E. coli* carrying $bla_{\text{CTX-M-1}}$ between piglets, we believe that *E. coli* carrying $bla_{\text{CTX-M-1}}$ would have a fast transmission rate in piglets as well. This would be in line with consistently high detection of $bla_{\text{CTX-M-1}}$ *E. coli* in Dutch pigs (MARAN, 2020).

Thirdly, variation of experimental settings, specifically housing, affects transmissibility of bacteria from the environment to the animal. In this meta-analysis, piglets were all housed in pens in a stable. Piglets inoculated with *E. coli* carrying fluoroquinolone resistance were housed on a slatted floor. Slatted floors may reduce transmission rate as part of the excreted faeces contaminated with resistant bacteria is sieved through the slatted floors (Andraud et al., 2011). Though the type of floor was not mentioned in Mourand et al. (2018 and 2019), it is possible that their piglets were housed in a similar setting given both teams complied to the same French regulations on animal welfare in experimentation (Mourand et al., 2018, 2019). This removal of faeces through housing was not present in the experimental setting for broilers in isolators or pens without slatted floors (Ceccarelli et al., 2017; Dame-Korevaar et al., 2020), and could contribute to faster transmission rates between broilers than between piglets.

Small scale transmission experiments of resistant bacteria have limited sampling power and often only include one host species. This meta-analysis identified that antibiotic treatment and hosts species are important factors. Even though the transmission rate of piglets treated with antibiotics was based on only two pens. Consequently, there is a wide uncertainty in the ratio between animal species. To reduce the uncertainty around these estimates, it is valuable to include more transmission experiments especially with regard to transmission in piglets. Furthermore, the flexibility of the Bayesian framework allows for incorporating data from both field experiments and observational studies. Such additions would also allow for an estimation of the difference between experimental and field settings.

We believe our results are already useful for simulating the modelling of transmission dynamics of resistant bacteria in piglets (7-8 weeks old) and broilers (less than one week old), especially because in the Bayesian framework we have obtained a posterior distribution that can be used to include the uncertainty of the parameter estimates in such simulation models.

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EARLY COLONIZERS OF THE CALF INTESTINE AND THEIR CONSEQUENCES FOR DAIRY COW PERFORMANCE: A PILOT STUDY

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SUMMARY

Although the microbiota diversity and composition are responsive to changes in environment, diseases, treatments, and other factors, the intestinal bacteria present in the critical first weeks of life may affect an animal's fitness even beyond the neonatal period. This study aimed to identify relationships between faecal microbiota in two-week-old dairy calves and their first lactation performance using 16S rRNA sequencing, random forest, and regression analysis. Abundances of the inflammation-inducing genera *Peptostreptococcus* and *Fusobacterium* were negatively associated with weight gain up to one year. Abundance of [*Ruminococcus*] *torques* group was negatively associated with 305-day milk yield, and a higher abundance of *Fusobacterium* was associated with an increased risk of reproductive issues. High abundance of the anti-inflammatory genus *Collinsella* was associated with a shorter calving-conception interval. These results indicate that specific bacterial genera present in faeces already in the second week of life may affect immune development and subsequent performance of dairy cows.

INTRODUCTION

The intestinal microbiota has been of growing interest in various scientific fields. As it has been shown in humans, the composition and diversity of faecal microbiota can give hints at the overall health status, and certain patterns are even connected to specific diseases or conditions (Chen et al., 2020; Salosensaari et al., 2021; Aasmets et al., 2022). To support a microbiota composition related to good health and productive performance may be a way to improve animal health and welfare while improving the farmer's financial situation. Microbiota can adjust in response to various factors, such as infections, antibiotic treatments, or changes in the environment (Oultram et al., 2015; Meale et al., 2016). While some bacterial species reduced or eradicated by antimicrobials return within weeks after discontinuation of antibiotic treatment (Suez et al., 2018; Holman et al., 2019), others may never recover from the intervention or remain substantially changed (Jakobsson et al., 2010; Dethlefsen and Relman, 2011; Li et al., 2019).

In humans, particularly during the early life, the faecal microbiota composition is highly flexible, and the human microbiome becomes adult-like at the age of three (Arrieta et al., 2014).

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During their first three weeks of life, calves can be considered monogastric animals, as only their abomasum is completely functional (Guzman et al., 2016). Before weaning, the microbiota are diverse between individuals (beta-diversity) and seem to be easily influenced, while after weaning, beta-diversity is low, and changes in composition seem to be more temporary (Dill-McFarland et al., 2017). Alpha-diversity, the diversity within an individual, increases with age (Dill-McFarland et al., 2017; Dorbek-Kolin et al., 2022). The neonatal period is highly influential for the future of the animal, as it adapts to its environment outside the uterus; the foundation for growth, health, and performance is laid. During these first three weeks, fluctuations in the concentrations of inflammatory markers, namely acute phase proteins (APPs), occur in multiple ruminant species, with serum amyloid A (SAA) concentrations peaking in the first week, and haptoglobin (Hp) concentrations peaking around the second week (Orro et al., 2006; Seppä-Lassila et al., 2017; Niine et al., 2018; Peetsalu et al., 2019). After the second week of life, the concentrations of these APPs decrease in serum (Peetsalu et al., 2019, 2022). This indicates that during the first two weeks of life, an immunological adaptation process may be taking place, as this age-related pattern in the APPs has been observed in healthy as well as in infected animals (Seppä-Lassila et al., 2018; Peetsalu et al., 2019). The concentrations of SAA and interleukin-6 (IL-6) in calf serum are associated with the same markers' concentrations in colostrum, during the first week, but only the IL-6 association continues in the second week (Peetsalu et al., 2022). Interestingly, SAA in colostrum is negatively associated with calf serum SAA concentration, while IL-6 concentrations are positively associated in colostrum and serum (Peetsalu et al., 2022). This sparks interest in processes happening during the second week of life, when the colostrum influence has decreased. It has been shown that microbiota colonisation is related to increased SAA production (Murdoch et al., 2019). SAA concentration measured in the second week of life, on the other hand, has been linked to differences in weight gain in ruminants (Orro et al., 2006; Seppä-Lassila et al., 2017; Peetsalu et al., 2019, 2022). Higher SAA concentrations in the second week were associated with lower weight gain up to nine months of age (Peetsalu et al., 2022). It can be hypothesized that microbiota colonization of the ruminant gastrointestinal tract especially during the second week of life may influence future performance, with immunomodulation being a possible mechanism. This hypothesis is supported by the negative association of genus *Peptostreptococcus* abundance with average daily weight gain (ADWG) up to nine months of age (Dorbek-Kolin et al., 2022). High abundance of this genus in faeces of two-week old dairy calves was associated with higher levels of SAA and Hp, which in turn were negatively associated with 9-month ADWG (Dorbek-Kolin et al., 2022; Peetsalu et al., 2022). Associations of APP concentrations during the first three weeks of life extend beyond early weight gain (Loch et al., 2022, unpublished), so effects of microbiota composition might similarly persist.

The aim of this study was to investigate associations between individual microbiota genera abundance in faeces of two-week old dairy calves with the performance of these animals in their first lactation.

MATERIALS AND METHODS

This observational cohort study was conducted based on ethical permission issued by the Ethical Committee of Animal Experiments in the Estonian Ministry of Agriculture (no. 7.2-11/2). The study was conducted on a large dairy farm in Central Estonia, and all female calves born from January 21st to March 16th, 2015 were included (n = 144). At the time, approximately 2000 milking cows lived on the farm, each producing an average of 10,270 kg of milk per year (Estonian Livestock Performance Recording Ltd, Tartu).

Immediately after birth, the calves were removed from their dams, and weighed on a digital scale (MS4 PW, Excell Precision Co., Ltd, Vilnius, Lithuania). Colostrum was milked from their dams and the quality examined visually and with a colostrum densimeter (Jørgen Kruuse A/S, Langeskov, Denmark). In one case, the colostrum quality was deemed poor (specific gravity <1,035), so deep-frozen colostrum from another cow was used. The calves received 3 L of colostrum within two hours after birth.

During the first four weeks of their lives, the calves were housed individually on a wooden floor with straw bedding, after which they were moved to group pens of 8-10 calves with sawdust bedding on concrete floor. In addition to *ad libitum* access to hay and starter feed (Prestarter, Agrovarustus OÜ, Tartu, Estonia), the calves received 2-3 L of warm unpasteurized raw milk twice per day during the first two weeks of life. After that, they were fed the same amount of milk replacer (Josera GoldenSpezial, Josera GmbH & Co. KG, Kleinheubach, Germany) for one week. At one month of age, the milk replacer was switched (Josera IgluStart, Josera GmbH & Co. KG) and decreased by 0.5 L per feeding each week, until they were weaned at around ten weeks old. After this, the calves had continued free access to starter feed.

The farm employed their own veterinarians, who were responsible for the calves' health on a daily basis. During the sampling period, acute cryptosporidiosis was diagnosed as the cause of increased mortality, and a treatment protocol with halofuginone lactate (HL; Halocur, Intervet International B. V., Boxmeer Netherlands) was implemented. Retrospectively, the animals were divided into three groups, according to *Cryptosporidium* spp. oocyst count per gram of feces (opg) by week of age: no oocysts found, low opg (below median of the week in question), and high opg (above median of that week). Similarly, based on their treatment, the calves were retrospectively divided into groups: no treatment, incorrect treatment (i.e. not according to the manufacturer's recommended protocol), and correct treatment (according to protocol). The manufacturer's treatment protocol consisted of daily administration of HL over the course of seven days, starting within 48 h after birth. As the treatment protocol was implemented for all calves younger than two weeks and after the study had already begun, some calves received their first dose of HL later than the manufacturer recommended (incorrect treatment group). Other than cryptosporidiosis, the veterinarians diagnosed no diseases in the calves during the sampling period. However, this infection and its treatment may have masked other diseases.

The animals were weighed again at approximately 12 months of age. The first artificial insemination was performed when the heifers had reached a body weight of 370 kg and were at least 365 days old. All performance and health data were recorded using DairyComp (VAS, Tulare, CA, USA). Diagnoses of health problems and their treatment(s) were recorded by the farm veterinarians.

Data and sample collection

All samples were taken on the same day, allowing for an age span of 8 to 14 days of age between different animals. Faeces were collected directly from the rectum using clean disposable gloves and kept at 4°C for up to 48 h until further analysis. Serum samples for analysis of APP concentrations were taken concurrently with the faecal samples, and the data used in this study are the results presented in Peetsalu et al. (2022).

After the first lactation, the following data was retrieved from the farm's recording system: weight at one year (to calculate ADWG), age at first calving (AFC), 305-day milk yield of the first lactation, number of antibiotic treatments administered, diagnosed health problems and their treatment in timely relation with the first lactation (first insemination to second calving), occurrence of reproductive issues during this period (recorded diagnoses: endometritis, retained placenta, abortion), and calving-conception interval. All animals that had faecal samples from the second week available and survived until their first insemination were included for statistical analysis (n = 95). Depending on the animals' survival, a different sample size for each outcome was available.

Laboratory analysis and sequencing

An immunofluorescence method was used for *Cryptosporidium* spp. oocyst count in faeces; additional details can be found in Niine, et al. (2018). Results were measured as approximate number of oocysts per gram of faecal matter. Hp and SAA in blood serum were measured with a haemoglobin-binding assay and a commercial ELISA kit, respectively (see Peetsalu et al., 2022).

DNA was extracted from 200 µg of each faecal sample using the PSP® Spin Stool DNA Kit (STRATEC Biomedical AG, Birkenfeld, Germany). The V3-V4 region of the 16S rRNA gene amplicons was then sequenced using the Illumina MiSeq platform in the same manner as in previous studies (Alipour et al., 2018; Husso et al., 2020; Dorbek-Kolin et al., 2022). Pre-amplification was performed in 12 PCR cycles. A ZymoBIOMICS Microbial Community Standard (Zymo Research, USA) and an in-house adult cow faecal standard were sequenced as no-template controls. Read quality was checked with FastQC and MultiQC, leftover primes and spacers were trimmed with Cutadapt v1.10.

A mapping file was created for QIIME2 v2018.4, validated with Keemei, and the FASTQ-files were imported. The DADA2 plugin was used to denoise and quality filter the reads, call amplicon sequence variants (ASVs) and generate a feature table. A naïve Bayes classifier was trained in QIIME2 against SILVA v132 97% database, extracted to include only the V3-V4 reference region and used to assign taxonomy to ASVs. Sequences derived from chloroplasts or mitochondria were removed and singletons were filtered.

Statistical analysis

As a first step, the microbial genera found (n = 228) were pre-selected based on a relative abundance of >0.01% in ≥10% of the samples. These genera (n = 62) were defined as the core microbiota, comparable to studies in humans (Salosensaari et al., 2021; Aasmets et al., 2022). Correlation analyses were used to explore possible relationships between the genera, and correlations between selected genera (based on the results of the present study) are presented in Fig. 1B. The abundances of the core genera were to serve as predictors in the statistical models. Apart from defining the core microbiota, the absolute abundance of genera was analysed, as the focus was on investigating effects of true differences in abundance between calves, not in their relation to other genera (Kodikara et al., 2022).

Outcomes were as follows: ADWG at 12 months old (continuous; n = 95), AFC (continuous; n = 93), 305-day milk yield (continuous; n = 85), calving-conception interval (continuous; n = 82), and occurrence of reproductive issues in the first lactation (binary; n = 95). Based on previous results by the same authors, genera were further preselected: genera that were associated with APP concentrations during the second week of life (Dorbek-Kolin et al., 2022) were chosen as predictors of highest interest for outcomes associated with the APP concentrations (Loch et al., 2022, unpublished).

Secondly, regression analysis was performed to adjust for possible confounding variables for the outcomes: *Cryptosporidium* spp. oocyst count group, HL treatment group, parity of the dam (multiparous/primiparous), exact age at sampling (days), exact age at weighing (days), and antibiotic treatments administered before measuring of the outcome.

Based on these regression results, model residuals for the outcomes were then included as response variables in individual random forest analysis, to account for confounder effects on the outcomes. The core genera were independent variables. The genera that were among the top five most influential genera for the confounder-adjusted outcome in these models, and had previously shown a relationship with APP concentrations, were selected for further analysis.

Finally, genus abundance was included as independent variable in linear regression in order to calculate effect sizes. Each outcome/genus-abundance-pair had its own model. One genus was included as explanatory variable into each univariate model to investigate the possible effect of individual genera on the outcome. Calving-conception-interval was logarithmically transformed to follow normal distribution. For reproductive issues, logistic regression was used. Confounders as named above were included into each model, and the final models were constructed with stepwise backward elimination of variables. A variable was considered a confounder if it affected the response coefficient by more than 10%. Linearity of the relationship was confirmed by lowess smoothing curve graphs.

Statistical analysis was performed in R version 4.2.0 (http://www.R-project.org/), with package ‘randomForest’ (Liaw and Wiener, 2002) for the random forest analysis. Basic data management was performed using Excel 2016 (Microsoft, Redmond, WA, USA) and Python 3.5.1 (Anaconda 4.0.0, Continuum Analytics, Austin, TX, USA). The results were interpreted as significant if $p \leq 0.05$, and borderline significant if $0.05<p<0.1$.

RESULTS

Alpha diversity, reported as Shannon index, ranged from 0.92 to 5.77, with a median of 4.15 and a mean of 3.86. On phylum level, the core microbiota consisted of *Firmicutes, Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria,* and *Verrucomicrobia* in decreasing order (Fig. 1A). *Firmicutes/Bacteroidetes* ratio ranged from 0.15 to 19230.00, with a median of 2.06 and a mean of 630.42. No significant associations with any of the outcomes were found. The following are results of univariate models that included confounders. The abundance of genus *Peptostreptococcus* in faeces was negatively associated with ADWG up to one year (-0.04 g/d per ASV; 95% CI: -0.076; -0.009; p = 0.013), as was *Fusobacterium* abundance (-0.003 g/d per ASV; 95% CI: -0.005; -0.001; p = 0.003). The abundance of *Fusobacterium* was furthermore positively associated with occurrence of reproductive issues (OR 1.0001; 95% CI: 1.00005; 1.0003; p = 0.011). Abundance of [*Ruminococcus*] *torques* group was negatively associated with 305-day milk yield (-1.29 kg per ASV; 95% CI: -2.22; -0.36; p = 0.007). *Collinsella* abundance was negatively associated with calving-conception interval (-0.0001 d per ASV; 95% CI: -0.0002; -1.64; p = 0.046). Correlations between the genera that were significantly associated with outcomes are presented in Fig 1B.

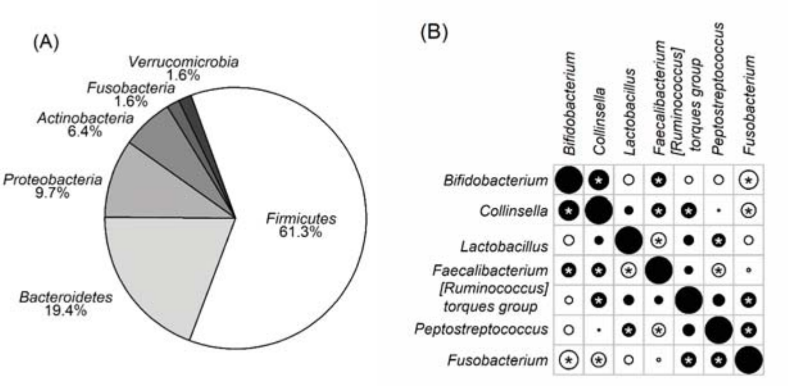

Figure 1. (A) Distribution of core genera relative abundance (n = 62) in faeces of 95 dairy calves among bacterial phyla. (B) Correlations between absolute abundances of selected genera of the faecal microbiota of 95 two-week-old dairy calves. Black circles indicate positive correlation, white ones negative correlation. Size of circle represents correlation coefficient size. Asterisk (*) indicates statistically significant correlation ($p \leq 0.05$).

DISCUSSION

The abundances of genera *Peptostreptococcus* and *Fusobacterium* were associated with lower weight gain and a higher risk of reproductive issues, and [*Ruminococcus*] *torques* group with decreased milk yield. Abundances of all three genera were also positively associated with serum concentration of APPs in two-week-old calves (Dorbek-Kolin et al., 2022), and among each other, they were positively correlated. When generalizing these results, a high abundance of genera that are associated with increased inflammatory response may lead to decreased performance of the animals later in life.

The genus *Fusobacterium* includes several opportunistic bacterial species, such as *Fusobacterium nucleatum*, that has been considered as a biomarker for colorectal cancer in humans and seems to be a driving force in chronic inflammation in the gastrointestinal system (Quaglio et al., 2022). Both *Fusobacterium* and *Peptostreptococcus*, the genera seeming to have negative effects on the animals in the present study, have been shown to be overrepresented in intestinal mucosa of human colorectal cancer patients (Li et al., 2022).

Other genera may have beneficial effects on their hosts when high in abundance. During the first days of life, the genera *Bifidobacterium* and *Lactobacillus* dominate the calf intestine, and their interactions with the mucosa may promote the development of tight junctions, as the epithelial permeability decreases soon after birth (Gomez et al., 2019). These two genera may also play a role in the control of the inflammatory response to other microbiota, as their presence stimulates the synthesis of interleukin-10 (IL-10), which inhibits the production of pro-inflammatory cytokines (Gomez et al., 2019). *Lactobacillus plantarum*, for example, has been found to stimulate toll-like receptor-2 and increase scaffold proteins near tight junctions in the human duodenum (Karczewski et al., 2010), as well as to maintain optimal somatic growth of otherwise germ-free mice during chronic undernutrition, hinting at its potential to increase weight gain of animals (Schwarzer et al., 2016). Patients with anorexia nervosa (a multifactorial disorder connected to low levels of appetite-inducing hormone ghrelin and increased pro-inflammatory cytokines) have been found to have a shifted gut microbiota with decreased abundance of *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium* (Smitka et al., 2021). *Faecalibacterium* also correlated with higher daily weight gain in seven-week-old calves (Oikonomou et al., 2013). Through its production of butyrate, the colon's preferred energy source, *Faecalibacterium* may be an important energy-harvesting commensal of the calf intestine (Foditsch et al., 2014), and also seems to mitigate intestinal inflammation through direct anti-inflammatory effects as well as induction of IL-10 and regulatory T-cell production (Qiu et al., 2013). Generally, it seems that a high abundance of the genera *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus* is beneficial for weight gain and immune homeostasis, whereas higher abundances of *Peptostreptococcus* and *Fusobacterium* may have more harmful consequences for their hosts. Although the present study did not find significant associations of these beneficial genera with favourable outcomes, both *Peptostreptococcus* and *Fusobacterium* abundances were negatively correlated with the abundances of *Faecalibacterium* and *Bifidobacterium*, hinting at antagonistic effects of these genera (Fig. 1B).

Another genus of interest is *Collinsella*. It had previously shown a non-linear association with SAA: *Collinsella* abundance was lower in calves with moderate SAA concentrations than in those with low or high SAA levels (Dorbek-Kolin et al., 2022). In the present study, a negative association of *Collinsella* abundance with calving-conception interval was found, as well as a linear negative association of *Collinsella* abundance with SAA serum concentration (data not shown). *Collinsella* and *Fusobacterium* abundances are negatively correlated, and *Collinsella* and *Bifidobacterium* positively (Fig. 1B). This study found no significant association between abundance of *Collinsella* and ADWG, but a study in humans showed that infants that acquired a faecal microbiota high in *Collinsella* earlier (before the age of six months) had a higher skinfold thickness at 18 months of age compared to children that reached this microbiota cluster later (Dogra et al., 2015). This indicates that early acquisition of a high abundance of *Collinsella* might be connected to increased weight gain. In the case of production animals, this would make *Collinsella* a favourable genus, as does the association with shorter calving-conception interval.

Future research may investigate how the microbiota composition can be influenced in a way that supports development and performance of dairy cows without compromising health and welfare of the animals. As shown here, APPs have the potential to be used as markers for understanding microbiota-host interactions. Colonization of the intestines with microbiota has previously been shown to increase concentrations of SAA (Murdoch et al., 2019), and certain early colonizers of the calf intestine are associated with increased acute phase response (Dorbek-Kolin et al., 2022). It can be hypothesized that this process plays an important role in the immune development and consequently performance and overall fitness of an animal.

This observational study has some limitations. Performing it on one farm only does come with the advantage that management and environment did not differ between the animals, but causalities may not be clear, and some interfering factors may not have been measured. APPs measured in the first month of life were not significantly associated with survival beyond the pre-weaning period, so possible associations between the microbiota abundances with survival was not analysed in this study. However, the dropouts may have influenced the results of the outcomes that were analysed. It can be hypothesized that the animals that did not survive to the point when the outcome was measured may have performed worse than the heifers that remained in the herd and if they had survived, they would have strengthened the results. Furthermore, as this study investigated associations with outcomes by individual bacterial genera, interactions between the different genera may affect their relationship with the outcomes, which should be the focus of future research.

The first lactation serves as indicator for productive life length of dairy cows. For example, multiple episodes of mastitis during the first lactation seem to decrease productive lifespan (Heravi Moussavi et al., 2012). More generally, milk yield and reproductive performance depend on body weight (Zanton and Heinrichs, 2005; Chuck et al., 2018). Body condition, milk productivity, and fertility during the first lactation indicate how well dairy cows adapt to change without decreasing their performance, which also hints at a long productive lifespan (Roche et al., 2018; Mendes et al., 2021). Thus, microbiota related to a successful first lactation may be beneficial for following lactations as well.

In conclusion, specific bacterial genera found in the faeces of two-week-old calves may be harmful for immune development when high in abundance, as shown through increased inflammatory response and subsequent lower performance, such as *Peptostreptococcus, Fusobacterium*, and [*Ruminococcus*] *torques* group. Others, potentially antagonistic to the ones named, may be beneficial for immune development and future success of their hosts as production animals, such as *Collinsella*. This pilot study shows how APPs can aid in the deciphering of such microbiota-host relationships.

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HEALTH AND PRODUCTION

REDUCING CAMEL YOUNG STOCK MORTALITY IN ETHIOPIA

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SUMMARY

Mortality of young stock is a challenge for livestock producers globally. This pilot study, part of a Government-led Young Stock Mortality Reduction Consortium project was undertaken to identify and evaluate interventions to reduce camel young stock mortality in pastoral production systems in Ethiopia. Key interventions were selected in alignment with national objectives in the Ethiopian Livestock Master Plan. Pastoralists were enrolled by convenience sampling across two regions. The pilot study findings demonstrated highly significant reductions in mortality, risk of diarrhoea and respiratory disease, and death from malnutrition post-intervention, with the greatest impact in larger herds. These findings should contribute to improved livestock productivity in Ethiopia. Indeed, activities from a wider study also piloted are now being scaled up for bovine calves, and it is anticipated that this will be extended to camel and small ruminant young stock as well.

INTRODUCTION

In Ethiopia, all camels are owned by pastoralists and, like cattle and small ruminants, they are a source of milk, meat and hides and are financial investments, contributing to pastoralist livelihoods (Dawo, 2010). Ethiopia has the largest livestock population in Africa, including 8 million camels (Central Statistical Agency of Ethiopia, 2021), with livestock production contributing significantly to the national economy (Bekele et al., 2018). However, livestock morbidity and mortality, particularly in young stock, are production constraints in Ethiopia (Fentie, 2016; Mayberry et al., 2018). The mortality estimates for the 2020 fiscal year, excluding nomadic areas, were 3.43 million cattle (4.9%), 6.51 million (15.1%) sheep, 8.74 million (16.5%) goats, and 0.53 million (6.6%) camels (Central Statistical Agency of Ethiopia, 2021).

Pastoralism is the most extensive farming system in Ethiopia (Amede et al., 2017), and considered one of the two major agricultural systems of the country along with mixed crop-livestock (Getahun, 1978), yet little information is available for the system. In the limited number of recent studies of young stock mortality, mean camel calf mortality rates of 14.9-35.6% have been reported (Megersa et al., 2008; Awoke and Ali, 2015). More than 60% of camel calf mortalities are reported as being in calves less than three months of age (Megersa, 2014), and most deaths are predominantly due to infectious diseases (Khalafalla and Hussein,

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2021), specifically respiratory problems (Zeleke and Bekele, 2000; Megersa, 2014; Fentie, 2016). Keskes et al. (2013) reported high disease prevalence to be the predominant cause of camel calf mortality, with camel pox, trypanosomiasis, diarrhoea and respiratory disease the most common diseases.

Management practices have previously been shown to contribute to camel mortality (Megersa, 2014; Awoke et al., 2015). To contribute to understanding and addressing young stock mortality in Ethiopia, the Young Stock Mortality Reduction Consortium (YSMRC) was formed under the auspices of the Ethiopian Ministry of Agriculture (MoA), as a collaborative effort between Addis Ababa University's College of Veterinary Medicine and Agriculture (AAU-CVMA); Aklilu Lemma Institute of Pathobiology (AAU-ALIPB); University of Gondar; the National Animal Health Diagnostic and Investigation Centre (NAHDIC); Tufts University; the University of California, Davis (UCD); and Supporting Evidence Based Interventions in Livestock (SEBI-Livestock). Together with the Ethiopian MoA, the YSMRC represented an innovative collaboration with a tripartite funding mechanism.

The YSMRC set out to design, implement and monitor interventions targeted for pastoralists in Ethiopia. This pilot study describes mortality and morbidity risks in camel young stock and a series of interventions implemented to reduce young stock losses.

MATERIALS AND METHODS

Study Design

The interventions were developed to align with national objectives detailed in the Ethiopian Livestock Master Plan i.e., they were designed to be appropriate and sustainable for the locale. The study expanded on previous health intervention packages developed by the MoA and Tufts University, arising from a previous assessment of young stock mortality causes (Fentie, 2016). Originally highly detailed and comprised of many interventions, the packages were focused down to key interventions, selected for impact and reproducibility potential. Staggered baseline evaluations were conducted across the study areas from March to August 2019, prior to the introduction of the interventions. The year-long pilot interventions were implemented, with farmer training conducted by government livestock extension agents, and followed by staggered final evaluations from March 2020 to July 2020, timed to match baseline evaluations where possible, in order to minimise seasonal variations.

Study Area and household selection

Two study regions, Afar and Somali, representing the pastoral production system in Ethiopia were selected, with selection criteria including livestock population density and accessibility. Study districts were selected across the two regions, consisting of two pastoral districts: Awash Fentale and Gursum.

Within each of the two study districts, three kebeles were selected per district (kebeles generally have three villages, each with 150 households). Within each kebele, one village was purposively selected, with 50 households from that village then randomly selected, resulting in 150 households per district. To avoid substantial differences in traditional practices during the implementation phase, neighbouring kebeles within a district were selected. In total, 300 households were invited to enroll in the study, representing six villages from six kebeles, in two districts.

Households were identified from regional livestock office registers and households were eligible if they owned at least one of the following: pregnant camels, or camel with camel-calf of < 6 months of age. Households in which no animals were born in the past 12 months, either at baseline or final evaluations, were excluded.

Interventions

Questionnaires and Standard Operating Procedures (SOPs) were developed to guide the interventions. The aim of this government-implemented pilot study was to assess applicability for scaling up. Farmer training for a total of 22 interventions was provided but it was not possible to monitor all so a subset of eight interventions were selected for monitoring purposes. A monitoring and evaluation plan was developed, with a results framework, through which indicators were selected to monitor intervention uptake and change. Participants were trained to carry out interventions and supported by extension officers over the year.

Data collection

Trained enumerators used questionnaires to collect data. Data were standardised and stored on a bespoke Bases & Datos server, created by Ijaki Albizu (Zaragoza, Spain) using database engine FileMaker Pro software (version 12, Claris International Inc., Cupertino, CA, USA). Data were exported to and cleaned in Microsoft Excel (version 2013, Microsoft, Redmond, WA, USA) and statistical summaries were produced using Excel and R (version 4.0.3) via RStudio (version 1.3.1093, RStudio, Boston, MA, USA).

Changes in practice between baseline and final evaluation were assessed, where households were evaluated as having 1) made an improvement to practices; 2) made no change but were already practising the recommended practice; or 3) made no change and were not practising the intervention as recommended or had a negative change.

Only households present for both the baseline and final evaluations, with sufficient data to calculate mortality risk, were included in the subsequent summaries and analyses. We analysed the change in mortality and morbidity using a generalised linear mixed model with a Poisson distribution and farm ID as random effect (Croissant, 2021). The relatively low number of households in Gursum prohibited any analysis of whether the effect of the intervention was modified by district.

Outcomes

Data were collected at baseline and final evaluations, and included reproductive parameters (e.g. birth and death of young stock), health outcomes (e.g. incidence of diarrhoea and respiratory disease) and intervention uptake. Baseline and final mortality, diarrhoea and respiratory disease risk, and risk of death from malnutrition for camel calves were calculated (Table 1). Morbidity and mortality risks are the outcome indicators, comparing baseline with final median risk to give a measure of success.

Table 1. Definitions used in the calculation of risk parameters. All parameters are calculated for the previous 12-month period

Parameter	Numerator	Denominator
Mortality risk	Total no. camel calves born alive but died	Total no. of camel calves born alive
Risk of diarrhoea	Total no. camel calves with diarrhoea	Total no. of camel calves born alive
Risk of respiratory disease	Total no. of camel calves with respiratory disease	Total no. of camel calves born alive
Risk of death from malnutrition	Total no. of camel calves that died from malnutrition	Total no. of camel calves born alive

RESULTS

At the study baseline, a total of 160 households were enrolled in the study, with 129 households enrolled in Awash Fentale, and 31 in Gursum; at final evaluation there were 115 households in Awash Fentale and 20 in Gursum. After excluding those households with no animals born in the past 12 months, there were 100 households in Awash Fentale and 13 in Gursum, giving a total of 113 households included in the subsequent descriptive statistical summaries and analysis.

Intervention uptake

Households were counted as performing an intervention if the response was anything greater than the minimum level. At baseline, households were practicing an average of 5.1 interventions (standard deviation (SD) 1.5) in the previous 12 months. At final evaluation, households were practicing an average of 7.7 interventions (SD 0.5).

Six of the eight monitored interventions had a high level of uptake (> 50% of households), with the largest improvements seen in the use of calf supplementary feed (89% households improved their practices), and supplementary feeding of pregnant camels (87% improved). This was followed by households starting calf supplementary feeding early (75% improved), having sick calves examined (70% improved), and increasing the frequency of water provision (66% improved). For the practice of separating pregnant camels, 53% of households improved, while 21% had no change as they were already optimal. A similar situation was seen with giving calves colostrum: 50% of households improved their practices, while 27% of households had no change due to optimal practices. For two of the interventions, a relatively larger proportion of households reported either no change or a negative change in practices – these were the frequency of water provision (35% households reporting no or negative change) and the volume of milk fed (67% of households).

Mortality, diarrhoea and respiratory disease risk, and death due to malnutrition

Median risk at baseline and final evaluations are presented in Fig.1, showing decrease in the prevalence of all parameters at final evaluation. Pre-intervention in Awash Fentale, on average two calves died in every herd, ranging from a total of zero to nine calves. Post intervention, on average only one calf died, with a quarter of all herds reporting zero deaths. A similar trend was seen in Gursum, with median number of deaths reducing from one calf per herd pre-intervention, to zero calves post intervention.

More than three quarters of pastoralists pre-intervention had at least one calf with diarrhoea, more than a half had at least one calf with respiratory disease, and more than a half had at least one calf that died from malnutrition. Pastoralists in Gursum reported lower numbers of morbidity and mortality in calves.

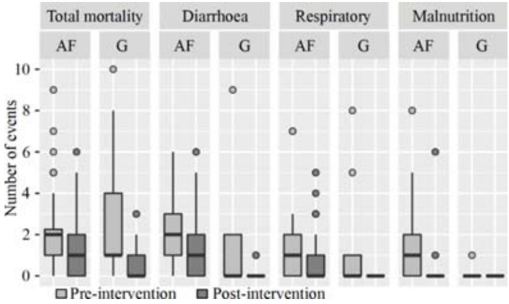

Figure 1. Box and whisker plots showing median mortality risk and prevalence of diarrhoea, respiratory disease and death from malnutrition in camel calves, in each pastoral area. Baseline measures are represented in light grey and post-intervention represented in dark grey. AF = Awash Fentale; G = Gursum

This represents an overall baseline median mortality risk, prevalence of diarrhoea and respiratory disease, and death from malnutrition of 40%, 44%, 20% and 20%, respectively. Post-intervention, median mortality risk, prevalence of diarrhoea and respiratory disease, and death from malnutrition reduced to 10%, 8%, 0% and 0%, respectively.

In both study areas, the average herd experienced a reduction of one fewer calves dying over the study period, post-intervention (Fig.2). Mortalities ranged from up to 10 fewer deaths to six additional calves dying after the intervention. A quarter of all herds either had no change in mortality or at least one additional death post intervention.

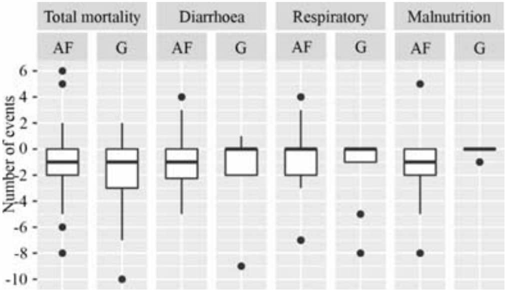

Figure 2. Box and whisker plots showing change in median mortality risk and prevalence of diarrhoea, respiratory disease and death from malnutrition in camel calves, in each pastoral area. AF = Awash Fentale; G = Gursum

Rate ratios for mortality risk, prevalence of diarrhoea and respiratory disease, and death from malnutrition post-intervention compared to the baseline were 0.43, 0.40, 0.37 and 0.02, respectively. All reductions were statistically significant ($p < 0.01$).

DISCUSSION

The intervention packages selected for camels (and cattle, previously described (Wong et al., 2022)) were successful in significantly reducing the prevalence of young stock mortality, diarrhoea, respiratory disease, and death from malnutrition. The interventions included a range of basic health and husbandry practices, selected by local and visiting experts, and did not require advanced technologies. As such, they should be relatively straightforward, cost-effective and impactful if implemented on a broader scale. However, different interventions had different levels of uptake in different areas of pastoral production. Therefore, scoping studies are recommended for future applications to ascertain a) what pastoralists are already doing in any particular area, b) what pastoralists and local livestock experts think would be most useful to implement, and c) how many additional interventions pastoralists would be willing and able to perform, in order to select appropriate interventions for new areas.

However, despite the overall success of the interventions, not all households benefitted from the interventions, with a few households reporting increased mortality and morbidity. This is a concern, especially for those pastoralists with very few animals, or those with very low mortality pre-intervention, where no improvements in mortality, or indeed increased losses during the period of the interventions would lead one to interpret the interventions as a failure. Only over a longer period would benefit be expected, but this would require investment which would be unlikely to occur if the interventions were not already seen as beneficial.

This latter outcome likely also relates to the main limitation of the study, in that it was conducted over a single year, without a control group, therefore between-year effects could not be accounted for in the changes observed. Additionally, the contribution of each individual factor is difficult to ascertain as the interventions were implemented in a combined package rather than individually, and only a selection of interventions were monitored. Furthermore, the contribution of the different management improvements to a decreased mortality might have varied depending on the area; in pastoralist areas in particular, the environment could have played a role in feed availability and animal survival, however the weather differences between the previous year and the study year were unremarkable. Flooding in early 2020 in Ethiopia was considered the most severe in a decade (European Commission, 2020), but flooding in the Awash River basin is a common occurrence (Achamyeleh, 2003; Wondim, 2016) and pastoralists local to this region may already practice adaptation strategies. The improved management of the interventions might have reduced the environmental influences by producing more resilient young animals.

There are limited published studies of baseline camel mortality and morbidity in Ethiopia. Ahmed and Hedge (2007) observed similar mortality (39%) to our study, but a lower mortality due to pneumonia (7%). Also similarly, malnutrition has also been found to contribute to mortality in camel calves (Fentie, 2016), and diarrhoea has been reported as the predominant cause of morbidity in camel calves (Ahmed and Hedge, 2007; Gebru et al., 2018; Abraha et al., 2019).

There were some conceptual and methodological limitations with the study. A large number of households were excluded from data analysis due to inaccuracies in pastoralist recall or enumerator error. Examples include where the number of animals born exceeded the possible number that the number of adult reproductive females could produce, or where the total number of animals born dead or alive, the number of stillborn animals, and the number of animals that died or lived did not ‘add up’. There is the potential for bias in the loss of these data, however we can only speculate on how this could affect the outcomes. Future field data collection could be improved by training enumerators to check data during interviews, or use of digital data collection tools with automatic checking. Many households had very few animals which made it challenging to measure impact.

Administrative support from all levels of the Ethiopian government was instrumental in the successful implementation of this project. Additionally, use of local language translations for SOPs, pastoralist training and data collection tools was important to pastoralists and helpful for enumerators. Involvement of NAHDIC in the consortium helped with availability of laboratory diagnostic capability domestically and should aid the sustainability of the activity during scaling up. Some inputs for veterinary care and management were provided specifically by the study, such as weighing scales, drugs and drug delivery systems. These inputs facilitated the animal health care, however providing free veterinary drugs during scaling up would be challenging, as the cost has to be recovered. It is important to assess the financial cost and benefits of the interventions, and a cost-benefit analysis is presented in a poster by Kirk *et al.* at SVEPM 2023.

Targeted interventions for improving knowledge and uptake of basic animal husbandry, feeding and housing are recommended strategies for the reduction of morbidity and mortality in Ethiopian young stock. These findings should contribute to improved livestock productivity in Ethiopia. Indeed, the authors are aware that the activities from a wider study piloted are currently being scaled up for bovine calves by the MoA, and it is hoped that this will be extended to camel and small ruminant young stock as well.

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ESTIMATING DISEASE BURDEN IN SMALL RUMINANTS IN ETHIOPIA: APPLICATION OF THE GLOBAL BURDEN OF ANIMAL DISEASES (GBADS) FRAMEWORK

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SUMMARY

The Global Burden of Animal Diseases Program (GBADs) has developed a framework to estimate economic burden of animal disease in a population. In this framework, overall disease burden is enveloped as a difference in income between the current and ideal health situations of a livestock population, and this is called the animal health loss envelope (AHLE). This framework was used to estimate the economic burden of diseases in small ruminants in Ethiopia. The AHLE was estimated at USD 3.22 billion for the year 2021 (3% of national GDP). Of this burden, 68% was due to morbidity (production losses) and 32% to mortality. Expenditure on animal health accounted for less than 1% of the overall burden. The estimated high economic burden and small expenditure on animal health relative to the losses indicate potential for substantial improvement in animal health and reduction of the burden of ill health through appropriate animal health interventions.

INTRODUCTION

Small ruminant production is an important economic activity in Ethiopia. It supports the livelihood of millions of households in the country. The small ruminant population was 95.4 million head in 2020, constituting 13% of the total livestock biomass in the country and contributing to 2% of the national GDP (Jemberu et al., 2022). Most small ruminants in the country are kept in two major production systems: the crop livestock mixed (CLM) system and the pastoral system. Small ruminants are kept by up to 60% of households in the crop-livestock mixed production system of the highlands and 95% of households in the pastoral production system of the lowlands across the country (Gebremedhin et al., 2017; ILRI, 2020). The CLM systems contain 58% of the national sheep population and 42% of the national goat population while the pastoral system contains 42% of the national sheep population and 58% of the national goat population (Jemberu et al., 2022).

Despite the importance of small holder livestock production for livelihoods and economic welfare, a substantial yield gap has been reported for small holder livestock production in Ethiopia (Herrero et al., 2016). Inadequate animal health is a major contributor to yield gaps and improving animal health through increased veterinary expenditure has been shown to improve profitability of small holder goat production (Mayberry et al., 2018). Animal health problems affect livestock production in different ways, mortality takes away the production

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asset, morbidity reduces production and productivity, and disease prevention and control expenditure increases production costs. Understanding and quantifying the burden of animal disease and health loss is thus essential for prioritising disease control interventions that will most efficiently reduce the yield gaps. Estimates for the economic burden of animal diseases are scarce, particularly in Ethiopia, and economic impact estimates are often only available for individual diseases. One may be tempted to sum up individual disease impacts to calculate overall disease burden within a sector, however this approach has several limitations. One of the main problems is that independent individual disease impact studies do not consider occurrence of comorbidity and a linear addition of them would lead to overestimation (Torgerson and Shaw, 2021). This approach also tends to ignore health problems which are studied less such as predation, injuries, and malnutrition. The Global Burden of Animal Diseases program (GBADs) has developed a framework to overcome these limitations. In this framework, overall disease burden is enveloped as the difference in farm income comparing the current situation to an ideal situation where there are no health or nutritional problems (Torgerson and Shaw 2021). This animal health loss envelope (AHLE) encapsulates the overall burden due to poor health and nutrition, and includes losses due to mortality, morbidity (production loss) and animal health expenditure. Having quantified the AHLE, losses are then attributed to individual diseases, disease groups or other causes of health loss. In this study we estimated the overall economic burden of the small ruminant health problems in CLM and pastoral production system in Ethiopia using the GBADs framework.

MATERIALS AND METHODS

Estimating the animal health loss envelope (AHLE)

The animal health loss envelope is the difference in the income from livestock kept under the current state of health and livestock kept under an idealised perfect health situation where there are no health or nutritional problems. This envelope represents the overall economic burden of diseases in that livestock population. The income from a livestock farm or population can be calculated using enterprise budgeting. In this study enterprise gross margin (enterprise profit before fixed costs) was used instead of enterprise budget (net profit). The main reason for this was that disease burden has little effect on fixed costs and decisions on improvement of animal health are often operational management measures that take place within the scope of the fixed costs. The other reason was that the fixed costs under traditional extensive small ruminant production are not significant. Hence the AHLE was estimated as the difference in gross margin under the current health conditions (with current disease and nutritional problems, and veterinary expenditure) and ideal health condition (with no disease or nutritional problems, and no veterinary expenditure) in small ruminant production systems.

Calculating gross margin using herd model

Livestock herd models are useful to assess production and herd growth (Upton, 1989). These type of models have also been extensively used for simulation of the effect of disease on production (Shaw et al., 2014). In this study a dynamic herd growth model was developed in R (R Core Team, 2021). The model simulated the herd growth based on demographic (birth and death rates) and offtake rates. While demographic and offtake rates were entered on an annual basis, a monthly time interval was used for removing the competing risks problem between the different demographic events. The simulation of the model produces production offtakes (live animals, milk, skin, and manure) and their respective monetary values (revenue) based on price inputs for these production outputs. It also estimates cost of production inputs;

feed, labour and animal health care based on the price of these inputs. These revenue and cost outputs of the model enable calculation of gross margin for the simulated population. The model was parametrised with stochastic values for the main inputs of the model and simulated for 10,000 iterations. The R herd model used to calculate gross margins can be obtained on request to the authors.

Current condition: All data used for calculating the gross margin for the current conditions were derived from secondary data including statistical databases, reports, and the literature. The data that were needed for parametrising the herd model for calculating gross margin included 1) the year's initial population structure in terms of sex and age category, 2) reproduction parameters such as proportion of adult females giving birth and prolificacy rate, 3) mortality for each sex category, 4) production outputs such as net live animal offtake, milk production (daily yield and lactation length), manure and skin ouputs, 5) production inputs; labour, purchased feed, and animal health care, and 6) price of live animals, production outputs and inputs. A systematic literature search was done for parameters that were expected to have published information such as mortality, live animal weight and reproduction parameters. A random effect meta-analysis was used for pooling the estimates collected through systematic literature search (Harrer et al., 2022). For parameters where there was no sufficient published literature for meta-analysis, the best available single estimates were used. The list of parameters (distribution) values used by the model for the crop livestock mixed and pastoral production systems can be found in Table A1 and Table A2 of the annex of the online version available at https://animalhealthmetrics.org/estimating-disease-burden-of-small-ruminants-in-ethiopia-application-of-the-global-burden-of-animal-diseases-gbads-framework/.

Ideal condition: The parameter values of the herd model that changed for calculating the gross margin under ideal conditions were those related to mortality (zero in the idealised scenario) and improvements in live weight gain, milk production and reproduction parameters. The ideal values for these parameters were derived from structured expert elicitation.

The structured expert elicitation was done using the classical (Cooke's) method. Briefly, the classical model is an approach for eliciting and mathematically aggregating expert judgments, with validation incorporated as a core feature (Colson and Cooke, 2018). In this method, experts quantify their uncertainty for two types of questions: target questions and calibration questions. The target questions are the ones used to elicit the needed parameter values that are unknown by other means. The calibration questions are those whose true value are known or can be known to the researchers but not to the expert and are used to validate/calibrate the experts' judgments. The experts are asked to quantify their uncertainty about quantities asked both in the target and calibration questions, by providing subjective assessments for percentiles of the distributions, usually the 5th, 50th and the 90th percentiles. The best estimate is denoted by the 50th percentile and a credible interval provided by the 5th and 95th percentiles. The experts' judgments are then linearly pooled by giving weights to their estimates for the target questions based on their performance (statistical and information score) for the calibration questions (Colson and Cooke, 2018). This combined estimate is called the decision maker and once calculated the decision maker acts as a virtual expert representing the combined judgments of real experts.

In the expert elicitation for this study, first some experts were identified based on their research/publication in the subject matter i.e., production and reproduction of small ruminants in Ethiopia. Additional experts were included by snowballing from the identified experts. In total 10 experts participated in a half day elicitation workshop at ILRI in Addis Ababa. In the structured expert elicitation questionnaire, the current production and reproduction parameter values were used as calibration questions and the required ideal parameters values were the target questions. There were 12 questions about the current liveweights of sheep and goats, in the different age-sex groups that were used as calibrating questions and the corresponding liveweights under ideal conditions were the target questions for elicitation of ideal growth (liveweight) parameter values. Similarly, six questions on current age at first parturition, parturition proportion and litter size for sheep and goats were used as calibrating questions and the corresponding questions for ideal conditions were the target questions for elicitation of the ideal reproduction parameters. This elicitation was done separately for CLM and pastoral systems.

The elicited data were analysed by the EXCALIBUR software (EXALIBURE v.1.6.1 pro, 1989-2018 T.U., Delft, In development by Lighttwist Software). The experts' judgments were combined using global weight performance measures in which the experts are weighted based on their average score across all calibration questions as described in Aspinall (2008). The ideal parameter values derived from expert elucidations were used as a beta pert distribution in the herd gross margin model. The 50th percentiles estimate of the decision maker (combined experts' judgment) was used as the most likely values, and the minimum and maximum values of the ranges for the target variables were used as minimum and maximum values of beta pert distribution.

The parameters values used by the ideal models for the CLM and pastoral production systems can be found in Table A3 and Table A4 of the annex of the online version available at https://animalhealthmetrics.org/estimating-disease-burden-of-small-ruminants-in-ethiopia-application-of-the-global-burden-of-animal-diseases-gbads-framework/.

RESULTS

The AHLE (ideal gross margin minus the current gross margin) which represents the national burden of poor animal health and nutrition for small ruminants in Ethiopia was estimated at 129.1 billion Ethiopian birr (95% CI 128.9 – 129.2) or 3.227 billion USD (95% CI 3.222 - 3.230) for 2021. This is equivalent to 1,340 birr (33.5 USD) per head/year. This loss is 86% of the potential gross margin which could be gained under the ideal conditions of no disease or nutrition problems. The ideal and the current gross margins, and the entries used for calculating them are indicated in Fig. 1.

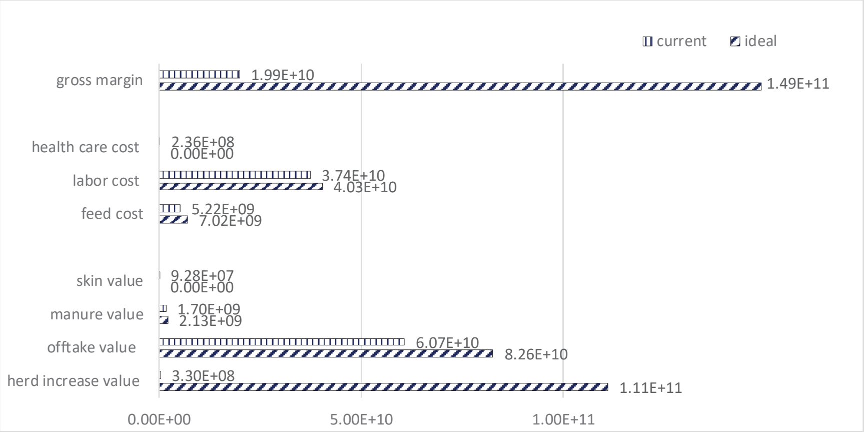

Figure 1. Gross margin and different entries of gross margin under current and ideal conditions in Ethiopian birr. (Note that the values of some entries such as skin value, health care cost and herd increase value under current conditions are so small that their bars are barely or not visible at the scale of the graph)

The AHLE has three major components: loss due to mortality, loss due to morbidity (production loss) and animal health expenditure (AH expenditure). Morbidity causes the major loss contributing about 68% of the overall burden. The AH expenditure not only contributes the least to the overall burden (less than 1%) but also is insignificant relative to the morbidity and mortality losses (Fig. 2).

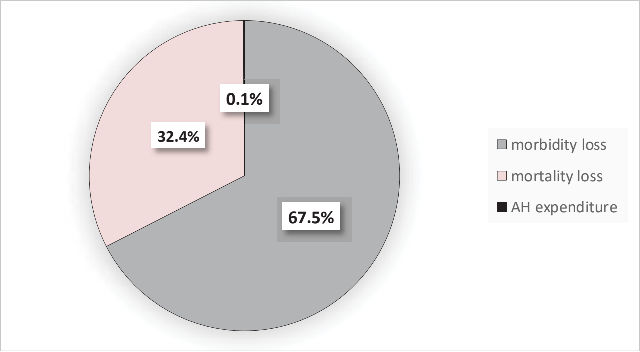

Figure 2. Relative share of the different components of the AHLE

The distribution of AHLE by production system and species is presented in Table 1. Larger AHLE per head of animal was estimated for goats and the largest was for goats in the CLM system. The least AHLE was for sheep in the pastoral system.

Table 1. The distribution of AHLE across production systems and species

Production system and species	Morbidity loss (birr)	Mortality loss (birr)	AH expenditure (birr)	AHLE (birr)	Population	AHLE/ head (birr)
CLM - sheep	2.41E+10	9.99E+09	6.36E+07	3.42E+10	24.7E+06	1380
CLM - goat	1.86E+10	1.98E+10	5.21E+07	3.84E+10	22.2E+06	1730
Pastoral – sheep	7.42E+09	5.04E+09	4.81E+07	1.25E+10	18.2E+06	687
pastoral - goat	3.22E+10	1.15E+10	7.23E+07	4.37E+10	30.3E+06	1440
Overall	8.23E+10	4.63E+10	2.36E+08	1.29E+11	95.4E+06	1340

DISCUSSION

In this study we used the GBADs framework to estimate animal health loss in the small ruminant population of Ethiopia. This is the first worked example of estimating the burden of diseases (sub optimal health) in a specific livestock sector. This estimate gives an insight on the scale of economic loss due to suboptimal health in the sector and the level of loss that can potentially be averted by implementation of interventions that improve animal health. By using the AHLE approach (overall disease burden estimate) all causes of health loss can be included in the burden estimate, including nutritional problems and external forces such as predation, accidents and injuries which are not usually represented in the animal health economics literature. This approach also addresses the potential overestimation problem which is encountered through linear summation of individual disease losses which do not account for co-morbidities (Honeycutt et al., 2011; Torgerson and Shaw, 2021).

In the AHLE framework, the ideal situation represents a utopian scenario where animals are free from any disease or nutritional insufficiencies. We recognise that in reality these problems exist, but through interventions these problems can be minimised or avoided. Irrespective of their efficiencies these interventions would incur a cost i.e., the animal health expenditure, which is component of the AHLE. This means the AHLE as estimated in this analysis cannot be made zero. What can realistically be achieved is employment of efficient animal health interventions that reduce the burden of ill health on livestock production and resource use to its lowest possible level. This is what has been achieved by some sectors and countries where livestock keepers have access to improved animal health technologies and access to good animal health care resources.

The small ruminant disease burden estimated in this study (3.22 billion USD per year, which is about 3% of the national GDP), appears very high. Given high disease prevalence and nutritional problems in the country with reported crude mortality reaching up to 18% in the small ruminant population (CSA, 2021) and up to 40% in lambs and kids (Fentie et al. 2016), this estimated burden is not surprising. Nevertheless, this high estimated burden may also be partly accounted for by some assumptions made in the analysis. The estimated burden is a loss in gross margin, which is the revenue derived from the sector minus the variable cost. The main variable cost in livestock operations (especially in intensive systems) is feed. The systems involved in this analysis are traditional extensive systems where the main source of feed is communal grazing, with little or no supplementary feeding. In this analysis feed cost was considered only for the purchased supplement feed which was zero in the pastoral system and about 12.5% in the CLM system. This would exaggerate the gross margin derived from increasing herd size in the ideal scenario and without much or no increase in feed cost. This exaggerated ideal gross margin results in exaggerated AHLE. The exclusion of non-purchased feed was done for two main reasons. One reason was the difficulty to estimate the cost of grazing feed and the other reason was from the individual farmers perspective the feed derived from communal grazing has no opportunity cost. But at community level the grazing feed resources do have opportunity costs and if this cost was considered the estimated burden could have been lower.

Looking into the distribution of the burden across different production system and species, both overall and per head disease burden was higher in goats. This can be partly explained by the higher mortality reported in the literature and used in the models of the goat production systems. The lowest burden was observed in sheep in the pastoral system. Looking closer into the input data for the model of this system, there are low estimates for some ideal parameter values. The experts estimated low ideal liveweight for sheep in this system, for some sex-age classes they estimated lower body weight under ideal conditions compared to under current conditions. This could happen due to various factors. One could be that the experts were not able to estimate the ideal values correctly and another could be that the current parameter values used from existing data sources were overestimated. There were more data gaps in the pastoral system and for some parameter inputs, including liveweight, either single estimates from literature were used or the same values were used from the CLM system. Either way, this analysis shows that better data are needed at production system specific levels, potentially for multiple breeds kept within the different production systems, if more specific and sensitive results are required at production system level.

An import insight shown in this AHLE burden estimate is the relative contribution of each of the three components: mortality, morbidity and health expenditure. The proportion of burden due to animal health expenditure relative to the direct disease losses (morbidity (production loss) and mortality) was miniscule, highlighting the existing low level of investment in the animal health sector. If the relationship between disease losses and investment/expenditure on disease control is represented in a loss-expenditure frontiers (McInerney et al., 1992), the small ruminant sector is operating on the left end of the frontier where the expenditure is very low relative to loss. This is far from the optimum point in the frontiers curve which is usually around the inflection point of the curve. This implies that there is a great potential to reduce the high burden of disease losses by investing in animal health, gleaning significant returns, until the optimum point in the frontiers is achieved (i.e., until the return from a unit of additional investment is no greater than the cost of that additional unit of investment).

There are some limitations included in this analysis which will need to be smoothed out in future versions of the model. Estimation of production and reproduction parameters for the dynamic herd and flock models under ideal health conditions was a difficult task. An ideal situation of no mortality is straight forward, it is simply setting the premature (unplanned) mortality to zero. The impact of zero morbidity and nutritional problems is reflected in many production and reproduction parameters and it is not straightforward to estimate these parameters in the ideal situation. For this study, production and reproduction parameters under the ideal scenario were derived from expert opinion but this aspect of the estimation might lack sufficient rigour. More robust data generation is needed in this aspect to support or complement estimates from expert elicitation.

In conclusion, we estimate a high economic burden of small ruminant diseases and nutritional problems. While this high economic burden seems plausible due to the high levels of infectious and non-infectious diseases and nutrition problems facing small ruminants in the country, some further model fine tuning is required to improve some assumptions that may exaggerate results. Ultimately however, the estimated AHLE shows very little investment in animal health relative to the morbidity and mortality losses which indicates a potential to reduce the burden of livestock ill health by employing appropriate disease control interventions.

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COMMUNICATION AND BEHAVIOUR

USING SOCIAL PRACTICE THEORY TO UNDERSTAND THE DIGITAL AND DATA DIVIDE: A FOCUS GROUP STUDY OF UK CATTLE FARMERS

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SUMMARY

Inequalities in access and skills to use data and technology exist on cattle farms. Our study aims to understand the digital and data divide by drawing on social practice theory (SPT) to recognise the emergence, linkages, and reproduction of data practices on cattle farms in the UK. Eight focus groups were completed with 34 cattle farmers. The transcribed data were analysed using reflexive thematic analysis with a SPT lens. Four data practices were generated from the analysis: routine data collection, observation, data administration, and data analysis. The data administration practice broke the connection between data collection and use. Data was often not used because farmers did not have the appropriate materials (e.g. infrastructure), attached negative meanings (e.g. time-wasting) or lacked competencies (e.g. using technologies). Instead of focusing on individual behaviours, data use on farms can be improved through transformation of practices by altering materials, competencies and meanings towards practices.

INTRODUCTION

Appropriate management decisions are key for sustainable and profitable beef and dairy farming (Boulton et al., 2017; Palczynski et al., 2021). Technology adoption on farms may improve decision making and is often suggested to increase profitability and improve animal health and welfare (Duncan et al., 2021; Barrett and Rose, 2022). However, there is variable uptake of technologies on cattle farms, with particularly low uptake on beef farms (Läpple et al., 2015; Groher et al., 2020).

Many farm technologies aim to collect data. For example, weighing scales can collect data automatically. Some technologies are also data-driven and use algorithms or changes in data signals to detect events. Thus, there is an increasing level of "datafication" on farms, in which various factors on the farm are translated into numbers. A consequence of this is the emergence of the "data divide", which is described by Marshall et al. (2022) as a "gap between the generation and application of farm data". A "digital divide", where there are inequalities between those who have access and skills to use data technologies, and those who do not, has also been described (Hennessy et al., 2016).

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The emergence of the digital and data divides generates two key questions: (1) how do these divides come to exist? and (2) how can these divides be reduced? (Rotz et al., 2019). These questions require an exploration of the social and ecological context of data collection and technology use (Rose et al., 2018; Marshall et al., 2022). Social practice theory offers a lens for focusing on routine practices. This is particularly suitable for understanding data and technology activities as they are often carried out as mundane, everyday practices on the farm.

Social practice theory uses practices as the unit of analysis rather than individual behaviours or human interactions. Shove et al. (2012) conceptualise practices as requiring the connection of three elements: materials, competencies, and meanings. Materials refer to objects, technologies, or bodies (Maller, 2016). Competencies are the skills, background knowledge, and understanding of practices. Meanings are the symbolic meanings, motivations, and beliefs. If connections between the three elements of practice are broken, then the practice can no longer be performed as it once was, and it must be adapted (Shove et al., 2012). One of the key problems around studies of farmers' behaviours or practices is that they tend to focus on one behaviour (or practice) and this does not take into account the complexity of the enmeshment of practices (Hidano et al., 2018).

This study aims to further understand the data and digital divides by drawing on social practice theory to recognise the emergence, linkages, and reproduction of data practices on cattle farms in the UK. Furthermore, the study explores why these data and digital divides exist and how the generation and application of data can be connected.

MATERIALS AND METHODS

Ethics

The study was approved by the University of Nottingham School of Veterinary Medicine and Science Ethics Committee (no. 3509 211202). Participants provided written, informed consent by completing a form.

Study sample

Participants were recruited through adverts on social media, through researcher networks and mailing lists. The only criteria were that farmers had to rear calves and be based in the UK. The focus groups were split into two types: dairy farmer and beef farmer. Four focus groups were held with nineteen dairy farmers and four focus groups were held with fifteen beef farmers. The size of the focus groups ranged from two to six participants. The concept of information power was used to determine the sample size (Malterud et al., 2016).

Data collection

Focus group discussions were held between December 2021 and June 2022. The focus groups were held online on Microsoft Teams and lasted 60-90 minutes. A topic guide was used to guide the discussion around the subjects of data use, technology use, disease management in youngstock, and goals for their future farm. All focus groups were audio and video recorded with the participants' consent. The recordings were transcribed verbatim by an independent transcription company and the transcriptions were checked against the audio recordings.

Data analysis

The transcribed data were analysed using reflexive thematic analysis (Braun and Clarke, 2019, 2020). The primary author (CD) first familiarised herself with the transcripts. The transcripts were then coded using an inductive and semantic approach. This later shifted to a deductive and latent approach as it was decided that the data was suited towards a social practice lens. This was because many of the codes generated were related to materials, competencies and meanings. The codes were clustered together to generate themes which represented socially shared practices.

RESULTS

Four routine data practices were generated from the analysis. Two data practices were related to data collection: routine data collection and observation. These data collection practices led to two other data practices: data administration, and data use and interpretation.

Routine data collection

Routine data collection is defined as data that is collected for all (or most) calves on the farm. Some examples of routine data collection included weighing calves at regular intervals and testing colostrum quality after birth.

> "We have been weighing very frequently for quite some time now. With my calves, I weigh them every two weeks. And I find that what you get out of that is huge." (Beef Focus group (FG) 1, Respondent (RES) 3)

When farmers collected data, they tended to be thinking about the future of their farm.

> "We all want to do our best, [rear] calves as good as we possibly can because we all know that that's your future." (Dairy FG4, RES3)

Some data collection was assisted by technologies. For example, farmers would use apps on their smartphones or electronic identification readers to input data. These were seen as efficient ways of collecting data in the field. However, not all farmers or workers had the required technological competencies to use these technologies. When they did not have these skills, farmers would use paper-based data recording methods.

> "People in the parlour aren't always good at putting it on the phone so it all gets written in a paper diary - births, services and treatments, and then they get transferred to a database." (Dairy FG2, RES4)

Farmers also could not carry out routine data collection with technologies because they did not have the required infrastructure or money to invest in technology.

> "If I had all the money in the world yes, I'd straight away get a herd [monitoring] system. Because it's so nice, you can be there on your phone, you've tagged an animal and you can just input and then it puts it straight onto CTS [Cattle Tracing System] like that'll be lovely but it's just too much money I think for us on our [small] scale." (Beef FG2, RES2)

Observation

Observation refers to farmers looking over their animals constantly to assess their health and welfare. “Knowing your herd” was a symbol of being a good farmer.

> “Good farmers are proactive, and you know your land, you know your stock, you know your herd.” (Beef FG2, RES1)

Farmers used their observational skills to identify youngstock who were unwell. They did this by relying on their experiential knowledge. They also used their senses of sight, touch, hearing and smell to understand their animals.

> “You can just tell [by] looking at them, “She’s not right.” It’s just something, I don’t know, maybe I’ve, we’ve all grown up with it and we’ve just been able to, it’s something we’re able to do…” (Dairy FG3, RES1)

The practice of observation tended to happen at the same time as other practices on the farm (e.g. feeding animals). Cameras were a technology that allowed farmers to observe their animals whilst away from the herd.

> “My guys absolutely love them [cameras] because they can be anywhere and they will have two or three in the calving shed and they can be three fields over, plant some grass or do some silage, they've had a ping on their phone, there's a calving alert from the collars, they will just go on the camera…” (Dairy FG2, RES1)

Data administration

Data administration is the process of converting recorded data into a format that can be used and interpreted. This practice was required for two main reasons. First, many data were collected on paper and it was not possible to analyse this because of the number of animals or scale of analysis required. Therefore, paper-based data needed to be digitised by entering the data into a spreadsheet or herd management software.

> “The majority of it is always initially taken in by hand - it’s always pen and paper. We then have Excel sheets for each individual cow which we have tick boxes for all the things that need to be done from kind of TB [Tuberculosis] testing to which injections have gone in and so on.” (Dairy FG1, RES3)

Second, data may be collected via several different technologies. Often the outputs of these technologies do not work well together. Therefore, farmers had to merge datasets from different sources.

> “I’d like a bit more integration and Cow Manager’s [software] got the breeding information on it but not any yield information so it would be nice to have it all integrated.” (Dairy FG3, RES1)

Many of the farmers did not enjoy this practice as it felt like a waste of time. The practice was often tied to the office space. This took time away from animal-based practices.

> “I think I prefer the time with the cows rather than the time at the computer, to be honest.” (Dairy FG4, RES6)

Data use and interpretation

Data use and interpretation practice refers to transforming data into actionable insights which farmers can make decisions from.

> “Again, it's trying to work out what gains you've made, what's profitable, is there a breed cross that works better? Are you able to shave off finishing time?” (Beef FG4, RES1)

However, some farmers suggested that they lacked skills to transform data into meaningful information.

> “Where I often failed as well is wanting to record something but to actually take that data and turn it into something meaningful to use on your farm to improve your lot is another exercise altogether and that was often where I fell down.” (Dairy FG2, RES5)

One barrier towards data use and interpretation was a lack of standardised outputs in cattle farming. Standardised outputs would allow farmers to measure their progress and benchmark against other farms.

> “Like I see how many times a day they clear the corn trough, but I am not measuring that I am just keeping an eye on it. Whereas if I could officially record that and compare it to other farms and see if I was on track or not, it would probably encourage me to find the time to do more recording.” (Beef FG1, RES2)

Sometimes it was the farmers’ veterinarians who would carry out the data use and interpretation practice. This was more common for dairy farms where they had routine veterinary visits. However, not all farmers had access to a veterinarian who would make use of their data. There were therefore inequalities in farmers’ access to appropriate social structures for data use and interpretation.

> “My vets here don’t, they don’t really seem to believe in prevention and data recording and stuff, unfortunately. They are more just throw the antibiotics into them and that’s it… Yes I would love if they would actually work on a health programme rather than like a fire brigade programme.” (Beef FG1, RES3*)*

DISCUSSION

This study draws on social practice theory to understand UK dairy and beef farmers’ data use practices. The social practice lens has provided new insights into the data and digital divides which are evident in agriculture.

Data divide

The analysis showed that there can be a disconnect between farmers' data collection and data use practices. This is because data administration practice is often required before farmers can perform the data use and interpretation practice. However, farmers associated data administration with negative meanings such as time-wasting and therefore the practice was not always completed. Technology can help to remove the requirement for data administration by facilitating the connection between data collection and data use. To do so, technologies need to be compatible with each other.

The connection between data collection to data use can also be broken at the data use stage where farmers do not have the skills to transform the data into meaningful information. Previous studies have also shown that farmers find it difficult to interpret generated data (Lunner-Kolstrup et al., 2018; Marshall et al., 2022). Learning data use and interpretation skills may require social and participatory styles of learning. Some examples include exchanging knowledge through demonstration projects and peer-to-peer discussions (Sahakian and Wilhite, 2014; Adamsone-Fiskovica and Grivins, 2021; Sutherland and Marchand, 2021).

Digital divide

The "digital divide" is an issue in agriculture where some farmers do not have access to, or engage with, technologies in the way other farmers do (Hennessy et al., 2016). Although many of the farmers saw technologies as the optimum way to collect and analyse their data, some did not use such technologies. One of the barriers towards technology use was that some farmers or their workers did not have the skills needed to use technologies in their data practices. It can take time for farmers and their animals to transition to using a new technology as it requires the accumulation of new skills (Tse et al., 2018). Members of the farming community who have already acquired the relevant skills (e.g., early adopters, younger generation or people who have worked with multiple farm systems) can help to develop these skills in others.

Another barrier was that there were inequalities in access to social structures, such as farming groups and veterinarians, which would allow farmers to benchmark against other similar farms. For many of the cattle farmers in this study, there appeared to be no normalisation of what data should be collected or what data should be analysed. It may be useful to develop a set of standardised concepts which are named and described so that farmers can follow these to enable them to compare themselves against other similar farms.

Farmers with smaller dairy herds and beef herds may also avoid adopting technologies because they were usually associated with large scale dairy herds. However, technologies such as automatic milking systems may be more suited to small and medium farms (Martin et al., 2022). This suggests that technologies should consider marketing towards small and medium farms, so that farmers believe that technology can fit with their farming system.

Another obstacle for the adoption of technologies was appropriate infrastructure. For example, lack of Wi-Fi, mobile signal, or electricity can restrict methods of data collection in barns or fields and restrict data use and interpretation in the office. The UK government provides grants for purchasing new technologies such as automatic weighing equipment but this is only useful if farmers already have the necessary infrastructure. Focusing on grants to improve the farming infrastructure first may help to bridge the gap between this digital divide.

Conclusion

We suggest that instead of focusing on individual behaviours, data use on farms can be improved through transformation of practices (Shove, 2010). This can be done by attempting to alter the elements (meanings, materials, competencies) that form practices and the connections between them.

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USE OF A NOVEL GRAPHICAL USER INTERFACE TO EXPLORE PSYCHOSOCIAL FACTORS ASSOCIATED WITH FARMER BEHAVIOUR IN A DISEASE EPIDEMIC

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SUMMARY

A novel graphical user interface (GUI) was used to dynamically illustrate the spread of an epidemic disease of cattle in Great Britain and investigate when farmers would undertake vaccination during a simulated outbreak using the GUI in online interviews. Farmers also completed an online survey to investigate a range of psychosocial and behavioural change characteristics. The association between the time the disease epidemic had elapsed prior to vaccination and farmer psychosocial factors were analysed using multinomial logistic regression. Farmers who had high trust in Governmental judgements about infectious disease control and low trust in other farmers to control disease were more likely to vaccinate early than mid epidemic. Farmers who rated advice from the veterinary profession as high quality were more likely to vaccinate mid-epidemic than late in the epidemic. Finally, farmers with high physical opportunity and fewer cattle were more likely to vaccinate early in the epidemic.

INTRODUCTION

The actions of farmers are fundamental to disease control in their livestock, and the disease control behaviours they do in their own herds contribute to the success of disease control nationally. For example, (i) engaging with bovine viral diarrhoea testing is voluntary in England and Wales, however, it is necessary for all farmers to engage with these practices to achieve the goal of bovine viral diarrhoea eradication by 2031 (Armstrong and Gow, 2021; Ruminant Health & Welfare, 2021), (ii) risky cattle purchasing behaviour by individual farmers is associated with new bovine tuberculosis breakdowns in herds with implications for both regional and national bovine tuberculosis control (Vial et al., 2015), and (iii) willingness of farmers to report the presence of disease on their farm is important for the control of disease epidemics (Hernández-Jover et al., 2016). Mathematical models can give useful insights into disease control; however, they traditionally treat farmers as passive bystanders and ignore heterogeneity in disease control behaviours. There have been recent calls to incorporate psychosocial factors and behavioural heterogeneity into disease transmission models (Bedson et al., 2021), which will allow improved model predictions for successful disease control.

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Although there is increasing evidence for the role of psychosocial factors in human health behaviour (Sheeran et al., 2017), there is little research into how these are associated with livestock infectious disease control by farmers. Trust is one psychosocial factor that is commonly investigated in livestock disease control. Trust is a key component underlying cooperation (Kuipers, 2022), with cooperation a key component underlying successful vaccination behaviour (Betsch et al., 2013; Betsch et al., 2017). Indeed, trust in other farmers improves willingness to join disease control schemes (Heffernan et al., 2016; Shortall et al., 2016) and is important in farmer decision-making regarding who to buy cattle from (Hernández-Jover et al., 2016), however it is also associated with farmers not controlling bovine viral diarrhoea (Prosser et al., 2022). Trust in sources of information is also important, with farmers preferring to follow advice from veterinarians rather than Government (Brennan and Christley, 2013; Fisher, 2013; Bard et al., 2019). Related to trust is psychological proximity, which is how close someone feels to someone else. Psychological proximity encompasses trust, but also includes feeling close, behaving close, connection with the other, independence from the other and similarities with the other (Aron et al., 1992). Psychological proximity with others is important in human health behaviour (Haskins et al., 2019; Tu et al., 2021) but has received little attention in livestock disease control by farmers. One study found that high psychological proximity to the veterinarian is associated with proactive bovine viral diarrhoea control by farmers (Prosser et al., 2022).

Behaviour is also influenced by capability, opportunity and motivation, as theorised within the COM-B behaviour change framework (Michie et al., 2011). Capability incorporates having the physical ability to do the behaviour (physical capability) and the knowledge and understanding required (psychological capability). Opportunity includes having enough time and money to do a behaviour (physical opportunity) and the support from other people and organisations (social opportunity). Finally, motivation comprises of both decision-making and goals (reflective motivation) and habits and emotions (automatic motivation). Factors that make up this framework have often been investigated in isolation in the context of disease control and use of the entire framework in livestock disease is rare. The COM-B framework has been used to investigate farmer approaches to bovine viral diarrhoea control, where it was found that automatic and reflective motivation, psychological capability and physical opportunity were all associated with proactive bovine viral diarrhoea control (Prosser et al., 2022).

Disease epidemics in the UK are rare but can have catastrophic consequences, an example being the 2001 foot-and-mouth disease epidemic. It is difficult to elicit behaviour for a future event; however, this is crucial to improve our understanding of the way people may respond to approaches to control a disease epidemic in cases where individual behaviour has important implications for disease transmission. Scenarios and games can be used to elicit such behaviour (Maye et al., 2017; Sok et al., 2018; Enticott and Little, 2022). These have the advantage of being able to control variability between farmers, presenting the farmers with a common experience to put them in the same situation. For scenarios to work well, they need to be plausible (van der Heijden, 2005). The use of scenarios and games to understand farmer behaviour in the face of disease risk is uncommon, however they have been used to investigate farmer decision rules for selling cattle (Utomo et al., 2021), factors that are important in buying cattle (Enticott and Little, 2022), people and organisations of influence to farmers in different disease control scenarios (Maye et al., 2017) and influences on biosecurity behaviours (Koliba et al., 2022).

Farmer behaviour in a disease outbreak scenario was investigated using a novel graphical user interface (GUI) to dynamically show the progress of the epidemic and elicit when farmers would use a vaccine that was available to them. Multiple validated measures were used to investigate how trust, psychological proximity and COM-B factors were associated with heterogeneity in farmer vaccination behaviour in the face of the disease outbreak.

MATERIALS AND METHODS

Farmer recruitment and reimbursement

Cattle farmers from Great Britain (GB) were recruited from two sources: (i) a pool of farmers who had taken part in previous research (Prosser et al., 2022) and confirmed that they were interested in taking part in further research, and (ii) via advertisement through veterinary practices and cattle interest organisations. The interviews took place online using Microsoft Teams, took up to one hour and all farmers were reimbursed with a £40 voucher for their time.

Graphical user interface design

To investigate how GB cattle farmers would behave in a disease epidemic, a novel graphical user interface (GUI) was created to dynamically illustrate the spread of a hypothetical disease. The GUI showed the progress of the disease epidemic by plotting the locations of infected herds on a map week by week. The disease outbreak initiated in southern-central France (epidemic stage 1) before spreading to GB, with the exact location of the infected herds dependent on the county of the interviewee to create a common outbreak experience at each stage of the epidemic in terms of distance to the nearest infected herd. The GUI also gave a summary of the total number of herds that had been infected and the distance to the nearest infected herd from the interviewee's farm for each week. The progress of the epidemic in terms of the number of infected herds and the distance between the interviewee's herd and the nearest infected herd are described in Table 1 and the GUI can be found at https://feed.warwick.ac.uk/map.html.

Table 1. The number of infected herds and the distance of the nearest infected herd from the interviewee's herd for each week during the disease epidemic scenario

Stage of epidemic	Time since previous stage (weeks)	Number of infected herds (in GB)	Distance to nearest infected herd (km)
1	2	0	France
2	2	2	322
3	1	10	322
4	1	40	161
5	1	100	161
6	1	150	48
7	1	450	16
8	1	600	5

Interview design and application

The interview commenced with a series of questions about the farmer and their herd. The farmers were then given a detailed description of a hypothetical disease that had just been detected in southern France and only infects cattle. Cattle were infected with the disease by inhaling or ingesting droplets of virus, and transmission could be direct or indirect (with the virus surviving in biological material from cattle for up to two weeks and on a fomite for up to three days), with airborne transmission of up to 48km. All infected cattle became infectious and showed clinical signs after 5 days since infection and infected herds were culled. The farmers were offered two effective prevention measures: a 100% protective vaccine that took 5 days to take effect, cost £50 per animal and had to be given to the entire herd including youngstock on the same day, and housing which would reduce their risk of infection by about 50%. The farmers were given the opportunity to ask questions to ensure that they understood the disease, the implications of infection and the control measures available to them.

The GUI was then used to show how the disease epidemic was progressing geographically and paused at weekly intervals to ask the farmers if they would vaccinate, house, or do any other preventative measures. Throughout the epidemic, there was no Government involvement in disease control except for mandatory culling of infected herds.

After the interview all farmers were given a link to an online survey that included questions on trust, psychological proximity and the COM-B behaviour change factors. Trust in others was measured using Likert-scale statements (Ferguson et al., 2022; Prosser et al., 2022), psychological proximity to others was measured using the Inclusion of Other in the Self (IOS) scale (Aron et al., 1992; Mashek et al., 2007) and the COM-B factors were investigated using the questions based on the published guide (Michie et al., 2011; Michie et al., 2014). The survey website generated an individual code for each respondent, which was recorded and used to anonymously link the responses in the online survey to the responses in the disease scenario once all interviews were completed.

The GUI, interview and survey questions were pilot tested on three dairy farmers from three counties and two countries of GB.

Association of psychosocial and behaviour change factors with vaccination uptake

All data analysis was conducted in R statistical software v4.2.1 (R Core Team, 2022). Farmers were categorised into three groups by their vaccination strategy. Early vaccinators vaccinated when the disease was still restricted to France or was first detected in GB (epidemic stages 1 and 2, Table 1). Mid-epidemic vaccinators vaccinated over the three weeks when the outbreak was spreading in GB but was at least 100 miles away (epidemic stages 3 – 5, Table 1). Finally, late vaccinators vaccinated at some point when the closest infected herd was within 48km away or closer (epidemic stages 6 – 8, Table 1) or never vaccinated.

Association between the time when a farmer decided to vaccinate, and farmer psychosocial factors were evaluated using a multinomial logistic regression model, shown in Eq.(1).

$$\begin{aligned} logit(\pi_{1k}/p_{i0k}) &= \beta_{0k} + \sum \beta_0 \, \mathrm{X} + e_k \\ logit(\pi_{2k}/p_{i0k}) &= \beta_{1k} + \sum \beta_1 \, \mathrm{X} + e_k \end{aligned} \quad (1)$$

$logit(\pi_{1k}/p_{i0k})$ and $logit(\pi_{2k}/p_{i0k})$ are the probabilities of vaccinating mid versus early and late versus early epidemic respectively, β_{0k} and β_{1k} are constants for vaccinating mid and late epidemic, $\beta_0 X$ and $\beta_1 X$ are coefficients for demographic and psychosocial covariates X for vaccinating mid and late epidemic, and e_k are the binomially distributed residual random errors.

The model was built using bidirectional covariate selection, with selection based on p-value (threshold of 0.05) and starting with the null model. Each covariate considered for inclusion in the model was tested in the model, with the covariate with the lowest p-value retained. Any covariates that were no longer significant were removed. This process was repeated until no remaining covariate had a p-value below 0.05 when included in the model. Model fit was assessed by fitting the multinomial logistic regression model on the full dataset and comparing the observed and expected data using a Hosmer-Lemeshow goodness-of-fit test and decile plots (Fagerland and Hosmer, 2012), and also by comparing predicted vaccination class from the full and 10 x 10-fold cross validated models.

To counteract the problem of overfitting in wide datasets, the stability of the covariates considered for inclusion in the model were calculated (Lima et al., 2021). To achieve this, the dataset was bootstrapped 500 times and a multinomial logistic regression model built on each dataset. The stability of each covariate was then calculated as the proportion of the 500 models where the covariate was selected (Lima et al., 2021). Stability thresholds for different probabilities of a variable being a true positive was calculated using the following method. The response variable was shuffled 10 times to create 10 randomly permuted datasets. Each permuted dataset was bootstrapped 20 times, a multinomial logistic regression model was built on each bootstrapped dataset and the stability of each covariate calculated. The distribution of stability values for all covariates was defined using an empirical cumulative distribution function and thresholds were taken for a probability value. The mean was then calculated of the thresholds from all permuted datasets for a probability value, which was taken as the stability threshold. To obtain the odds ratios of the stable covariates, the multinomial logistic regression models were fit for each of the bootstrapped datasets, limiting the candidate covariates to the covariates above the stability threshold, and the odds ratio calculated from the mean coefficient.

RESULTS

Participating farmers

Sixty farmers (39 beef and 21 dairy) completed the interview. Farmers were from all nations of GB, with 73% (44) from England, 15% (9) from Scotland and 12% (7) from Wales. The median dairy herd size was 155 cows (range = 30 – 330) from 20 herds with dairy cows (one herd only reared heifers). The median number of cows in beef herds was 35 (range = 5 – 200) for the suckler herds (one herd fattened cattle only). English farmers were slightly overrepresented and the herd sizes slightly larger than the national averages (AHDB, 2019).

Vaccination behaviour

The farmers showed a wide variety of approaches to preventive vaccination with 96.7% (58) using vaccination at some point during the scenario: 13.3% vaccinated at the first opportunity (a localised outbreak restricted to southern France), 26.7% vaccinated as soon as there were cases in GB and 56.7% vaccinated at some point during the GB epidemic (Fig.1).

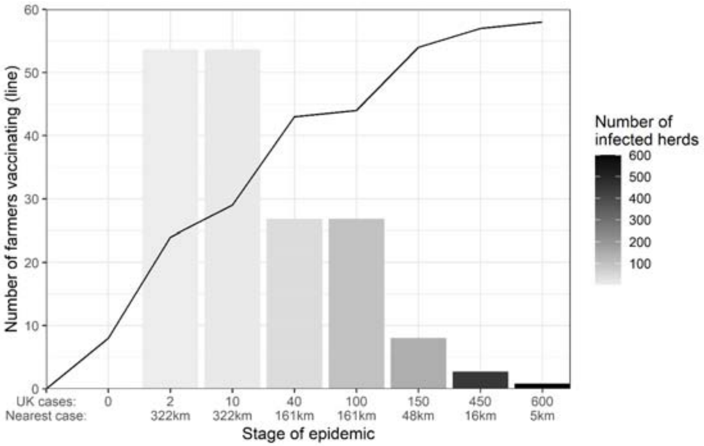

Figure 1. The cumulative number of farmers vaccinating at each stage of the epidemic (line) with the distance to the nearest infected herd (bar height) and the cumulative number of herds that have been infected (bar colour)

Association between farmer behaviour and psychosocial factors

Four covariates were selected by the multinomial logistic regression model built on the full dataset. No covariate had a stability above a stability threshold where it would be expected that all covariates were true positives (0.45) (Table 2). Two covariates were retained when the stability threshold was relaxed to an expected false positive rate of 10% (0.24), which were trust in governmental judgements about how to control infectious diseases in cattle and physical opportunity (Table 2). A further three covariates were retained when the stability threshold was relaxed to allow an expected false positive rate of 15% (0.20), which were high quality advice from the veterinary profession, trust in other farmers nationally to control infectious diseases and herd size at time of disease outbreak. Three of the covariates selected by the multinomial model also had a stability above the 0.20 threshold, which were trust in governmental judgements about infectious disease control, trust in other farmers nationally to control infectious diseases and herd size at time of outbreak.

Table 2. The stability and median odds ratio (OR) of the covariates above the stability threshold for an expected 15% false positive rate (0.20)

Covariate	Stability	Mean OR Epidemic stage 3 – 5	Mean OR Epidemic stage 6 – never
Trust in governmental judgements for infectious disease control	0.28	0.29	0.66
Physical opportunity	0.26	0.85	0.19
High quality veterinary advice from the veterinary profession	0.22	1.82	0.14
Trust in other farmers nationally to control infectious diseases	0.20	6.18	1.25
Herd size at time of disease outbreak	0.20	1.01	1.01

DISCUSSION

A novel GUI was successfully designed and applied to elicit farmer behaviour in a disease outbreak scenario and the heterogeneity in the time it took for the farmers to vaccinate their cattle was associated with psychosocial and behaviour change factors.

The GUI was effective in eliciting farmer behaviour and successfully separated farmers out behaviourally. Scenarios and games are occasionally used to elicit farmer behaviour (Maye et al., 2017; Utomo et al., 2021; Enticott and Little, 2022), however their use has focussed on routine decision-making and the control of endemic diseases. Sok et al. (2018) used a choice experiment to investigate farmer preferences between possible government strategies for controlling a bluetongue epidemic in the Netherlands, and in a similar way described a hypothetical disease outbreak, however this did not investigate how farmers would behave voluntarily during an epidemic as was done here.

The farmers behaved heterogeneously in their vaccine use, showing different levels of risk aversion and cooperation, which could be described as mutually cooperative, parasitic or free-riding (Bshary and Bergmueller, 2008). The farmers who vaccinated early show behaviour consistent with being mutually cooperative, vaccinating quickly to produce the maximum immediate benefit to others and themselves and avoid any risk of infection. Those who vaccinated mid-epidemic can be described as behaving in a form of behavioural parasitism, waiting to see how the infection spreads and benefiting from what they observe happening to others. The behaviour of late vaccinators is consistent with free-riding as they are risk-taking and only act if they need to, relying on the protection from other farmers vaccinating. The behavioural heterogeneity of the farmers can be incorporated into disease transmission models to investigate both how the epidemic would develop accounting for farmer behaviour and to test how modifications to behaviour, for example an incentive to shorten the time to vaccination use by the farmers, would affect the course of the epidemic.

Psychosocial and behavioural factors were associated with the heterogeneity in farmer behaviour. Farmers with high trust in Governmental judgements about how to control infectious disease were most likely to vaccinate early and least likely to vaccinate mid-epidemic. This is consistent with the positive link between trust and cooperation which would be expected if the early epidemic vaccinators were mutually cooperative. Also, some farmers are more likely to look to and trust Government advice in uncertain situations (Maye et al., 2017). A novel disease epidemic with severe consequences is a highly uncertain situation, which may be why high trust in Governmental judgements for infectious disease control is important for prompt vaccination here, especially in those with a preference toward cooperation. This association could also be vaccination specific, with other research having found that farmers would expect greater Government involvement in provision of information about vaccination if it became part of bovine tuberculosis control versus other forms of bovine tuberculosis control (Maye et al., 2017); therefore, farmers that trusted Government decisions may be more receptive to a vaccination intervention, even without Government promotion or advice. Further research will be needed to investigate this.

Farmers who had high physical opportunity and fewer cattle to vaccinate were most likely to vaccinate early and least likely to vaccinate late. Vaccination was a costly intervention (£50 per animal); therefore, it is not unexpected that farmers who feel they have enough money are more prompt in vaccine uptake. High vaccination cost decreases the likelihood of farmers vaccinating in a bluetongue outbreak (Sok et al., 2018). High physical opportunity is also associated with uptake of disease control measures for bovine viral diarrhoea (Prosser et al., 2022). Subsidising an intervention measure is a tool that could change farmer behaviour for earlier intervention use (AHDB, 2018), which could have implications for the progress of a disease epidemic. Cost is a barrier to uptake of disease control and farmers are more likely to use disease control measures if they are affordable (Jones et al., 2015; Mingolla et al., 2021). However, subsidisation is unlikely to change farmer behaviour if it is impractical (Bennett and Cooke, 2005), and a large level of subsidisation was required to increase the preference for bluetongue vaccination in the Netherlands (Sok et al., 2018).

Farmers who felt that they received high quality advice from the veterinary profession were most likely to vaccinate mid-epidemic and least likely to vaccinate late epidemic. By the time the infection is within the bounds of airborne spread, farmers have little choice but to vaccinate because infection appears imminent, whereas there is still a lot of uncertainty of risk of infection mid-epidemic. It is also possible that the farmers who had high trust in veterinary advice would have vaccinated earlier if they had had access to veterinary advice earlier in the epidemic that encouraged them to vaccinate, or that this is the point where they would seek that advice out, and in its absence have resorted to vaccination. Veterinary advice is generally trusted by farmers (Brennan and Christley, 2013; Bard et al., 2019), therefore this could be a route to promoting interventions to achieve prompt uptake and better epidemic control.

Finally, farmers with high trust in other farmers nationally to control disease were most likely to vaccinate mid-epidemic and least likely to vaccinate early in the epidemic. These farmers may not be vaccinating during the early weeks of the epidemic because they trust other farmers to vaccinate which would limit the epidemic, and then vaccinate once it is evident that the disease is spreading into new regions of the country quickly and that their herd is at risk. This behaviour is consistent with the behavioural label of parasitism (Bshary and Bergmueller, 2008), waiting to see what happens to other farmers before deciding to act themselves. Other research has identified that high trust in farmers to control disease can reduce disease prevention behaviours farmers use in their own herd because they perceive their risk of disease from other farms to be low (Oliveira et al., 2018; Prosser et al., 2022).

A limitation of this study is that there was a small sample size and no covariate had a stability over a stringent threshold that would avoid false positives. However, the threshold used is expected to lead to the selection of fewer false positive covariates than by a model built on the full dataset without bootstrapping (Lima et al., 2021), giving more confidence that the covariates identified are associated with the vaccination behaviour. Also, although the scenario was carefully controlled to investigate vaccination, there are other practices that farmers would have used to lower their risk, which could have different associations with psychosocial factors, and further research will be needed to investigate these.

In conclusion, the novel GUI successfully identified heterogeneity in farmer behaviour in a disease epidemic scenario and this analysis identifies new psychosocial and demographic factors that are associated with the timing of farmers vaccinating their herd in response to an outbreak of a fast-spreading livestock pathogen. High trust in Governmental judgements about disease control, high physical opportunity, low trust in other farmers nationally to control disease and having few cattle to vaccinate were all associated with farmers vaccinating their herd early in this disease scenario.

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IMPROVING THE COMMUNICATION BETWEEN FARMERS AND VETERINARIANS TO ENHANCE THE ACCEPTABILITY OF ANIMAL TUBERCULOSIS ERADICATION PROGRAMMES

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SUMMARY

France and Spain have been fighting against bovine tuberculosis (bTB) for years, even though new outbreaks continue to appear, generating social distrust in the eradication programme and competent authorities. Effective communication can ensure trust and stakeholder engagement and increase the acceptability of the eradication programme. This study characterises the communication on bTB in the trans-Pyrenees region and provides recommendations to improve it. Results highlight the existence of a controversial debate on bTB and a heterogeneous understanding between stakeholders. Communication mainly focuses on bTB detection and control, and wildlife reservoirs, while other aspects are left in the background. Main proposals to improve the communication include: (i) create participatory meeting spaces to share opinions and information; (ii) develop clear and written protocols; (iii) increase the stakeholders' participation in the design of protocols; (iv) establish a local 'Crisis Committee' with representatives of farmers and veterinarians to manage specific bTB cases.

INTRODUCTION

The application of control programmes and preventive measures requires changes in people´s behaviour and habits, and the maintenance of such changes over time (Moda, 2006; Pfeiffer, 2006; Ellis-Iversen et al., 2010, Hidano et al., 2018). The willingness to adopt changes is influenced, among other factors, by prior knowledge and the perception about the disease risk (Calba et al., 2016; Ritter et al., 2017; Hidano et al., 2018). Moreover, trust in competent authorities and institutions in charge of managing the risk, and confidence between stakeholders are other important factors that affect attitudes related to the implementation of preventive and control measures (Enticott et al., 2014). Behaviour changes are difficult to induce and maintain, even in situations where recommendations, measures, or guidelines are evidence-based, practical, and affordable (Moda, 2006; Pfeiffer, 2006; Ellis-Iversen et al., 2010). Therefore, stakeholders' engagement and commitment are key factors for the successful implementation of preventive and control strategies (Moda, 2006; Pfeiffer, 2006). Guaranteeing commitment requires providing support and advice and acknowledging aspects

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that can critically affect it, such as social networks, sources of advice, relationships between farmers and advisors and the trust between them.

Animal tuberculosis (bTB) constitutes a major concern both to human and veterinary public health sectors, due to the zoonotic aspects of this disease and the important economic and sociological problems that it implies. France and Spain have been fighting against bTB for years, although new outbreaks continue to appear on farms of both sides of the border. France is officially free of bTB since 2001, however in the south-western areas the bTB incidences are increasing, putting the free status of the country in jeopardy. In Spain, the eradication of the disease has not yet been achieved; the herd prevalence is very heterogeneous at the regional level, being below 1% in the northern regions and above 5% in the south-western regions (MAPA, 2022). The prolonged failure of control programmes has led to a serious social distrust in the usefulness of the official health programmes and the possibility of eradicating bTB (Moda, 2006; Pfeiffer, 2006). This was linked to a perceived lack of reliability of diagnostic tests, and lack of control on the wild reservoirs which are considered responsible for the maintenance of the disease in the territory (Ciaravino et al., 2017; Ciaravino et al., 2020). In this context, the communication between stakeholders is of utmost importance as it may affect how the disease is perceived, thus the acceptability and the effectiveness of the bTB eradication programme.

Language is not neutral, and different ways of framing risks in communication may lead to different perceptions (Freudenstein et al., 2020). Appropriate communication helps to ensure that all stakeholders are informed of the nature and level of risk (i.e., improved understanding), and what behaviours are desirable to minimise it (EFSA, 2021), supporting informed decision making and behavioural changes. Moreover, it can contribute to increased trust in authorities and the degree of confidence between stakeholders. Understanding how farmers and veterinarians conceptualise and frame bTB (i.e., the way in which the risk is understood) is crucial to achieve effective communication and increase the probability of success in eradicating the disease (Pfeiffer, 2006; Ellis-Iversen et al., 2010; Ritter et al., 2017). Therefore, the objective of this study was to characterise the communication on bTB between people involved in the implementation of the eradication programme, and to develop recommendations to improve the communication strategies in place.

MATERIALS AND METHODS

The research was carried out in Catalonia (Spain) and Pyrénées-Atlantiques (France) as part of the INNOTUB project (https://innotub.eu/) aimed at improving control and surveillance of tuberculosis in livestock and wildlife in the trans-Pyrenees region. Digital press analysis and in-depth interviews with farmers and private veterinarians were employed to characterise the communication about animal tuberculosis (i.e., process, discourses, and outcomes), and to identify the sociological factors that might affect it. The development of recommendations to improve the communication between stakeholders was accomplished through a pilot participatory intervention which involved farmers, private veterinarians, and the official veterinary services.

Digital press analysis

The sampling frame were digital texts (i.e., press releases, and other communication materials) available online in Spanish, Catalan, or French. The keywords used for the online searching were “Bovine tuberculosis”. The criteria applied for the screening and selection of the sample (set of full texts to be analysed) were: i) the geographical area of reference: national level, and Catalonia or Pyrénées Atlantiques (other regions were excluded); ii) the year of publication: only texts published between 2018 and 2020 were included; iii) the diversity of sources: institutional, scientific, and sector-specific sources (i.e., webpages of public institutions, research institutes, associations and unions, and newspapers and magazines from the fields of agriculture and animal health); iii) the level of diffusion of the source. The number of publications to select from each source was established under the criteria of "repetition". The selected sample was analysed both quantitively and qualitatively. Content Analysis (CA) was applied to identify the main themes covered (i.e., communication's contents), and to elaborate a map of main actors involved in the debate on bTB and the voice / role they play (communication's processes). Public discourses on bTB and the language used by the farmers, private veterinarians, official veterinary services, and researchers/experts were investigated by using the Critical Metaphor Analysis (CMA) proposed by Charteris-Black (2004), focusing on metaphors as cultural and linguistic tools for conceptualising disease. The identified metaphorical expressions were classified according to what metaphor was used, its source domain (i.e., the conceptual or semantic area from which the metaphorical expressions are drawn), and the target domain to which it refers (i.e., the domain that is understood through its use).

In-depth interviews

In each area, six farmers and four private veterinarians were interviewed in-depth to gather information about how the communication on bTB is perceived, and the most trusted sources of information (i.e., processes and outcomes). A convenience sampling strategy was used to ensure heterogeneity of the sample. The size of farms and the level of experience were considered for the sample's composition of farmers and veterinarians, respectively. Interviews were based on the following thematic guide:

- Profile's characterization: gender, working routine, and social networks.
- Previous experience with bovine tuberculosis.
- Channels, Sources and Content of the received information (formal / informal).
- How knowledge is generated and with whom it is shared.
- Solving problems process (in case of doubts on the disease and its control).
- Perceptions on the role and activities of associations and unions.
- Weaknesses / Strengths of the existing communication, and suggestions to improve it.

Participants were interviewed individually in their native language. Before starting the interview, participants were informed about the aims and content of the project and signed a letter of informed consent. The interviews were audio-recorded, upon participants' consent, and transcribed verbatim. Transcripts were examined under the qualitative thematic analysis based on an iterative comparative method (inductive approach).

Participatory intervention

The purpose of the pilot participatory intervention was to generate, among all participants (i.e., farmers, private veterinarians, and official veterinarian services), recommendations to improve the communication on bTB, and to reassure and enhance the dialogue between the stakeholders. An approach inspired by the STAVE (Systematic Tool for Behavioural Assumption Validation and Exploration) method (Espluga et al., 2016) was applied to guide the study design which included sequential meetings with the farmers, private veterinarians, and official veterinary services, and a final workshop. Participants were recruited through a purposive sampling strategy to seek diversity of viewpoints within each group and provide the most comprehensive understanding of the factors at play.

The pilot intervention consisted of a first round of group sessions with farmers and private veterinarians, separately (up to eight people per group). Farmers and private veterinarians who had already taken part in the in-depth interviews were also invited to participate. Preliminary findings from the groups were presented and discussed with representatives of the regional veterinarian services. The received feedback was delivered to the participants during a second group session joining farmers and private veterinarians together (i.e., deliberative focus group). Selected results from the individual in-depth interviews (i.e., key outcomes) were used for opening the discussion during the first round of focus groups. These key outcomes were presented visually on slides as verbatim extracts from the interviews. Thereafter, the card clusters technique was used to gather proposals and ensure the contribution of each participant. Participants were invited to think individually and write on sticky notes their proposals/ideas to improve the relations between actors and communications on bTB ('silent generation of ideas'). Written ideas were shared and discussed within the group and categorised by similar themes. During the second group session (i.e., deliberative group meeting), a collective presentation was held to all the people involved in the previous phases. Participants were able to consider both the results produced during their first meeting and the feedback received from the official veterinary services. The validity, the relevance and the suitability of the identified themes and the proposals was discussed within the group. Then, participants were allowed to adjust and refine their own findings (i.e., previously developed proposals), accordingly. The focus groups were audio-recorded with the permission of participants and detailed notes on the discussions were taken by the researchers. Finally, a deliberative workshop (i.e., dialogue meeting) was organised to find a consensus on the developed proposals. The workshop involved key persons (up to five people per category) who were identified during the previous activities.

RESULTS

The obtained results highlighted a heterogeneous understanding on the disease between people involved in the bTB eradication programme, which is reflected by the difference between the topics and the language used by the different actors. The participatory activities carried out with the farmers, private veterinarians, and official veterinary services raised a series of improvements in communication about tuberculosis.

Digital press analysis

A sample of 153 Spanish and 66 French digital texts (i.e., corpus) were analysed to investigate topics, metaphors, and actors of the communication on bTB. The sources and the number of texts (i.e., units of analysis) extracted from each source is presented in Table 1.

Table 1. Selected sample of digital text by type of source and geographical area

Type of sources	Coverage Level	Spanish Units (N=153)	French units (N=66)
Institutional	National/Regional	5	23
Scientific	National/Regional	9	14
Sector-specific	Veterinarians	64	11
	Farmers / Hunters	75	18

The thematic structure of the analysed units was common to both countries. The main themes covered were related to the detection and control of the disease and the role of wildlife and domestic reservoirs other than cattle, which together represented the 82% and 71% of the Spanish and French sample, respectively. Whereas topics related to training and communication/outreach or the proposals to change the bTB eradication programme were little covered in both samples. The major difference between the two samples was observed on themes related to the risks of bTB and the benefits of being disease free, which appears in 13.6% and 1.3% of the French and Spanish texts, respectively (Table 2).

Table 2. Themes covered by the selected sample of French and Spanish texts

Main covered themes	Spain (N=153)	France (N=66)
Social and economic aspects	4.6%	0.0%
bTB detection and control	57.5%	45.5%
Training and communication/outreach	3.9%	9.1%
Proposals to change the bTB eradication programme	7.8%	6.0%
Wildlife and domestic reservoirs other than cattle	24.8%	25.8%
bTB risks and benefits of being bTB-free	1.3%	13.6%

The distribution of the selected texts (i.e., units of analysis) according to the targeted audience was the following: 36% and 24% of the Spanish and French texts, respectively, targeted farmers; veterinarians were targeted in 46% and 24%; the general public, experts, or a not specified audience was the target of 8% and 52% of the Spanish and French texts, respectively. The relationship between themes and targeted audience observed in Spain and France is shown in Fig. 1 and 2, respectively. It is worth mentioning that topics related to training and communication/outreach do not appear in the Spanish communication to farmers, and that social and economic aspects were topics of concern in the communication to farmers and veterinarians, but not to other audiences (Fig.1).

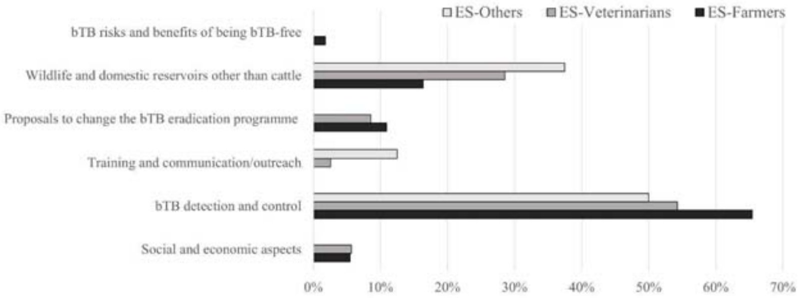

Figure 1. Relationship between themes and targeted audience in the Spanish (ES) sample

On the other hand, in the French sample, the proposals to change the bTB eradication programme had certain relevance in the communication to the farmers, while social and economic aspects were not addressed independently to the targeted audience (Fig.2).

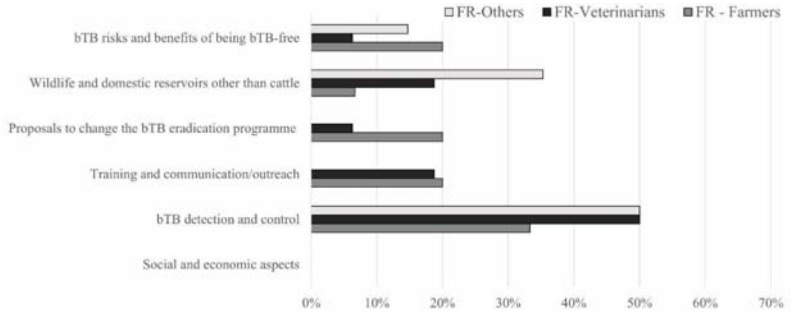

Figure 2. Relationship between themes and targeted audience in the French (FR) sample

There were 349 and 246 metaphorical expressions detected in the Spanish and French sample, respectively. Overall, the most frequently used metaphorical lines or frames referred to: "war" (n=282; 47%), "religion" (n=33; 6%), "container" (n=101; 17%) and "motion" (n=76; 13%), which together represented 83% of the used metaphorical expressions.

Few metaphorical expressions were identified in both the Spanish and French institutional communication (18 and 38, respectively), while the metaphors detected through the scientific communication were 44 and 125 in the Spanish and French sample, respectively. In both countries, the institutional and scientific communication made use of metaphors mainly to refer to the disease (i.e., target domain). The source domain of "war" (i.e., military metaphors) was the metaphorical expression most frequently used (e.g., "*Necesidad de luchar en diferentes frentes contra la enfermedad*"; "*lutte contre cette infection [...] des outils pour la combattre*"). It is worth noting that, in the Spanish sample, 23% of metaphorical expressions identified in the scientific communication focus on the role of science and researchers, making use of the frame of "motion", indicating their movement forward and advances in science (e.g., "*Los investigadores hemos dado un paso más*") to refer to this target domain. The communication among farmers was more diverse than the institutional and scientific communication both in Spain and France. Its variety was reflected by the wide range of target and source domains that were presented in their communication. In addition to the disease, farmers communicated about themselves and their herds, about wild reservoirs, and also about protocols, laws, and regulations, science, and about their relations with the official veterinary services. Out of 233 and 77 metaphorical expressions detected, 85% and 77% of metaphors referred to five target domains in the Spanish and French samples, respectively. Beside the metaphor of "war", the domains of "motion" and "container" are largely used in both samples. As a peculiarity, the communication between Spanish farmers differed in that it included the usage of religious metaphors to refer to the farmer/livestock sector (i.e., target domains "farmers and herds") (e.g., "*Consecuencias sangrantes para el sector*"; "*No al castigo al ganadero por unos protocolos injustos*"). Whereas the specificity of the French communication was the use of military metaphors to refer to the relationship between farmers and the official veterinary services. Differences in the communication of veterinarians were observed. In the Spanish sample (92 metaphorical expressions), the conceptual structure was close to that of the farmers in terms of the diversity of target domains and source domains. In the French sample (30 metaphorical expressions) the conceptual structure followed that observed in the institutional and scientific communication, with 80% of metaphorical expressions referring to the disease (i.e., target domain "bovine tuberculosis").

In-depth interviews and participatory intervention

In-depth interviews with a qualitative sample of farmers and veterinarians were carried out in the two study areas between May and September 2021. Only beef cattle farmers were interviewed in both studied areas since this production system is the most representative, and the most affected by bTB outbreaks. The profile and composition of people interviewed in each area is shown in Table 3.

Table 3. Descriptive summary of the sample composition for the in-depth interviews

	Pyrenees-Atlantiques (FR)	Catalonia (ES)
Farmers (N=6)	83% Men 50% aged < 45 years 33% experienced bTB cases 50% raised more species Farms' Size: • < 50 heads: 2 farms • 50-100 heads: 3 farms • > 200 heads: 1 farm	Sex ratio 1:1 67% aged < 45 years 50% experienced bTB cases 17% raised more species Farms' Size: • < 50 heads: 1 farm • 50-100 heads: 3 farms • > 200 heads: 2 farms
Veterinarians (N=4)	75% Women 75% aged between 35-40 years 50% had experience with bTB cases	Sex ratio 1:1 75% aged < 35 years 50% had experience with bTB cases

Among all the topics that emerged during the interviews, the qualitative thematic analysis focuses on two major areas: the inter-relationships between actors (i.e., farmer-to-farmer, farmer-to-private veterinarians, farmer-to-official veterinary services, private veterinarians-to-official veterinary services) and the communication/outreach processes (i.e., sources of information, formal and informal communication channels). Participants' viewpoints and main opinions that emerged from both Spanish and French interviews were similar.

Regarding the inter-relationships between actors, the farmers reported that relations with their private veterinarians are frequent and usually good. Private veterinarians are the first person of contact in case of concerns (about bTB or anything else) or problems on the farm. They are perceived as easily accessible, trusted, and respected by farmers. However, a certain distrust is expressed when dealing with a bTB-related issue/outbreak, since it is felt that different interests are represented by the two parties. On the other hand, farmers' relationships with the official veterinary services are more complex and ambiguous, especially in areas where bTB outbreaks have occurred. In general, official veterinarians are perceived as distant to farmers, having little to no empathy, and mainly committed to monitoring farmers rather than supporting them. Farmers from the same territory generally maintain mutual relationships, however it is observed that there exists a combination of companionship and mutual distrust. On one hand, they maintain relationships of friendship in the productive and leisure sphere, on the other, the relationships are much more complicated and individualised when dealing with infectious diseases, and especially bTB, since it generates a feeling of social stigma. The interviewed veterinarians perceive the relationships with farmers as generally good, even though relations may easily become much more tense when there is a bTB problem. In such situations, it becomes difficult to communicate with farmers, give them the appropriate support, and manage their feelings of uncertainty. It is also mentioned that veterinarians can rarely impose anything on farmers, due to their commercial relationship. This makes it difficult for them to play the controlling role ("of police inspection") that the official veterinary services attribute to them. A certain lack of cohesion between farmers was reported by the Spanish veterinarians, which pointed out that the different livestock sectors (cattle, sheep, poultry, etc.) maintain tense relations between them, and this makes the work of veterinarians more challenging. Relationships between private veterinarians and the official veterinary services are described as formal and basically one-way. Official veterinarians are perceived as a control body, which plays mainly an inspection role, rather than as support for private veterinarians. In this way, private veterinarians perceive themselves closer to the farmers than to the official veterinary services.

Regarding the training and the communication/outreach processes, both farmers and veterinarians considered that the official information provided is not sufficient and they perceive that some relevant information on bTB risks is not accessible, for example, data on positive cases detected in the territory, in slaughterhouses, or in wildlife. Veterinarians reported that they often search for bTB information online and that the main sources of information are official veterinary services or local veterinarian groups. They acknowledge they play a passive role in the communication about bTB, citing a (perceived) scientific uncertainty on the disease as the reason for their poor communication with farmers. Despite veterinarians recognising that the training on bTB is useful, they highlighted that the knowledge is mostly theoretical and delivered with no interactions through a top-bottom approach. Moreover, veterinarians claim that the training content focuses almost exclusively on how to carry out skin test screening, but not on how to communicate to the farmer on bTB-related issues. Farmers receive information from institutional channels or sector-specific newspapers and magazines. The existing information is highly valued, although farmers tend to consider that it is incomplete and contains too many uncertainties. The information that farmers receive mostly comes from informal channels, among which social networks have a relevant role.

The participatory focus groups were conducted between November 2021 and March 2022. Farmers and private veterinarians agreed on the need for sharing information on the epidemiological situation in the region. They asked for regular feedback and updates on the number and location of bTB outbreaks, positive wildlife reservoirs, and the protocols to follow in the case of positive test results. During the meetings, it was highlighted that were was a need to create participatory spaces to communicate doubts, or to make joint reflections and share reliable information between farmers and veterinarians (e.g., thematic conferences). Farmers especially requested protocols that can be adapted to specific cases, without generating comparative grievances ("protocolised flexibility"), and the production of concise (and written) documents which clarify the rules and explain step by step the protocols to follow in the case of an inconclusive or positive bTB case. Both farmers and private veterinarians asked for having more voice (greater participation) in the design protocols and for the establishment of a 'Crisis Committee' to support decisions on specific cases or bTB outbreaks. Moreover, they suggested to carry out pedagogical activities among the general population to raise awareness about the rural sector and its contributions to the society, giving value to their work. On the other hand, private veterinarians don't feel that their work is valued or relied upon by the official veterinary services, and they would like to receive constructive advice and not to be just supervised or criticized.

The last workshop was conducted in April 2022 with representatives of farmers, private veterinarians, and regional veterinary services. The previously generated proposals were discussed to find a consensus among all participants. All participants were aware of the need for improving the communication process. Farmers and private veterinarians also recognised that (to realise their proposals) they should first strengthen their organisation and engagement and generate an internal debate to identify the priority issues to be solved together with the official veterinary services. It was acknowledged that private veterinarians from the livestock health defence groups should play a role in such organisational processes and contribute to fill the communication gap between farmers and official veterinary services. At the end of the workshop, participants agreed on the following actions:

- Organise meetings which could also be used for discussing doubts and simplifying procedures, or for detecting administrative dysfunctions (i.e., working groups).
- Improve the accessibility of the information already available in the territory: simpler and more transparent mechanisms than those currently in place (e.g., updating websites or sharing databases).
- Produce visual material (infographics, short videos, fact sheets, etc.) with contextual information about the disease (impact, risks, diagnostic procedures, etc.).
- Redesign the training courses to make them less unidirectional (for example, give space for sharing experiences and knowledge from the field), and to widen the range of topics besides the more technical already included (e.g., content related to social, economic, pedagogical, and administrative aspects).

DISCUSSION

In the trans-Pyrenees region, the bTB eradication programmes are carried out in a social context marked by a certain distrust between the various actors, which makes it difficult to reach a shared assessment of the bTB related risk and reduce the acceptability of the eradication programme in place. Results pointed out that the sociocultural and political-institutional dimensions of the bTB risks prevail over the economic and health dimensions, and highlighted the importance of improving the level of information on prevention and control measures and the trust between farmers, private veterinarians, and official veterinary services.

To explore the dimensions of bTB in the public debate, digital press releases and other communication materials were analysed under the postulates of the agenda setting theory and the theory of framing. In the first place, the theory of the agenda setting revealed how issues related to bTB are addressed by the different actors and their relevance to public opinion. Secondly, the framing theory indicated how the disease is understood and the rhetorical strategies used by the different actors to express and support their own views and ideas. This approach allowed us to address, from an evidence-based perspective, the concerns and viewpoints of people involved in the implementation of the bTB eradication programme. The institutional and scientific communication focused almost exclusively on the detection and control of the disease, while other social and economic aspects were left in the background. Conversely, farmers extended their communication to a greater variety of themes and in their communication referred to a large variety of target domains, indicating their concern for different aspects related to bTB and not only for the disease itself. Thus, it is recommended to broaden the themes covered by the institutional/scientific communication, addressing issues that directly affect and/or concern farmers, such as bTB risks and benefits, economic and social aspects, or topics related to training/outreach. The framing of bTB strongly differs among actors, highlighting the existence of a controversial debate about bTB in which each party defends different positions: the official veterinary services and researchers “fight” against bTB and “progress” towards its eradication, farmers place themselves in a framework of sacrifice and, particularly in Spain, they play a passive role. Military metaphors have been widely used to refer to infectious diseases, being one of the standard metaphor systems for animal and human diseases (Nerlich, 2004; Ribeiro et al., 2018; Wicke and Bolognesi, 2020). In the Spanish context, the “war” frame does not take farmers into account; they do not appear in the developed narrative and, only in a few cases, experts or authorities mention that farmers should be considered allies. In the French context, it seems that farmers play a more active role, and they perceive themselves to be part of the “fight” against bovine tuberculosis. However, the frequent use of the “war” frame as conceptual metaphors to refer to the official veterinary services, suggests the existence of tense relations between the two parties. A common understanding on bTB is needed as well as the searching for common and broader metaphorical frameworks, since using the same metaphors means assuming the same view on the issue. It is also important to empower farmers through communication: make them visible as fundamental actors, give them a voice, and turn them into active subjects of the measures.

The active participation of farmers and veterinarians in the development of recommendations and proposals for a better communication on bTB contributed to promote their commitment and empowerment. Main proposals developed by farmers and veterinarians to improve the current communication on bTB included: (i) create participatory meeting spaces to share opinions, information and to make joint reflections; (ii) develop clear and written protocols that can be adapted to specific cases; (iii) increase the participation of stakeholders in the design of protocols; (iv) establish a local ‘Crisis Committee’ with representatives of farmers, veterinarians, and veterinary services to support decisions on specific bTB cases. The use of the STAVE approach enables dialogue between regional veterinary services, farmers, and private veterinarians (i.e., people in charge of the implementation of animal health policies and people targeted by such policies). This method has been shown to be successful in reducing the mismatch between what people say they do and what they actually do, facilitating the engagement process, and promoting exchange of knowledge and views between different groups (i.e., citizens and policymakers) (Espluga et al., 2016). Results highlighted that both farmers and private veterinarians should carry out an internal debate to prioritize obstacles that make their daily work difficult and identify needs and concerns. This should allow farmers and veterinarians to play a more active role in the dialogue with the official veterinary services. As it was said above, private veterinarians from the livestock health defence groups could be key players in this articulation, although it would be necessary to carry out preliminary informative and pedagogical work to make them feel more involved and be better prepared to participate in decision-making processes. In light of these results, it can be concluded that to enhance the communication strategy it is crucial to increase the motivation of farmers and veterinarians, boost the trust between actors, avoid fatalistic attitudes towards the disease and create a common understanding about bTB. The participatory activities conducted in this study identified a series of proposals to improve the communication on bTB. However, their effective implementation would require a more structured organisation of both the farmers' sector and the private veterinarians' group, and a higher commitment to participate in decision-making processes.

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SURVEILLANCE

MOVING TOWARDS ONE HEALTH SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN FRANCE: KEY FINDINGS OF THE SURV1HEALTH PROJECT

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SUMMARY

In France, the 2016 interministerial roadmap for the control of antibiotic resistance (ABR) set an impulsion for a One Health approach against ABR. However, an integrated ABR surveillance system is still lacking. As a first step in this direction, the Surv1Health project (2020-2023) aimed to i) map the French system for surveillance of ABR, antimicrobial use and residues in humans, animals, food and the environment, ii) assess to which extent the surveillance programmes collaborate together, and iii) identify the main drivers for collaboration. We present here the key findings of this project. Overall, France has a rich yet complex and fragmented surveillance system, with limited integration between sectors and hazards. Twelve recommendations were shared with risk managers to improve the One Health-ness of surveillance and feed future control strategies. Part of these should be addressed via two meta-networks launched in 2021, showing the surveillance system has an ever-evolving picture.

INTRODUCTION

Antibiotic resistance (ABR) is a threat to modern health care and is recognised as one of the major public health issues (Interministerial Committee on Health, 2016; Murray et al., 2022). Since antibiotic-resistant microorganisms and genes circulate within and between ecosystems, prevention and control of ABR is a complex issue, which requires the development of integrated actions at the human-animal-environment interface. Already in 2015, the World Health Organization (WHO) Global Action Plan on Antimicrobial resistance (World Health Organization, 2015), jointly adopted by the World Organisation for Animal Health (WOAH, founded as OIE) and the Food and Agriculture Organization of the United Nations (FAO), underscored the need for surveillance using a One Health approach. In the European Union (EU), the 2017 EU One Health Antimicrobial Resistance Action Plan (European Commission, 2017) also argued for a more integrated surveillance system of antibiotic resistance, including closely related topics, namely antibiotic use (ABU) and antibiotic residues in ecosystems.

In France, the 2016 interministerial roadmap for controlling antimicrobial resistance (Interministerial Committee on Health, 2016) has set an impulsion towards a One Health approach to surveillance, emphasising the need to rationalise surveillance data across sectors

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and to promote cross-sectoral collaborations, in addition to sectorial national action plans. However, an integrated ABR surveillance system is still lacking at this stage. As a first step in this direction, the nationally funded Surv1Health project (2020-2023) aimed to i) comprehensively map the French system for surveillance of ABR, ABU and antibiotic residues in humans, animals, food and the environment, ii) assess to which extent the identified programmes collaborate together for surveillance activities, and iii) identify the main drivers for collaboration between surveillance programmes.

MATERIALS AND METHODS

Identification of surveillance programmes

We retained in our study only those initiatives corresponding to the following definition of a surveillance programme: "a structured group of actors and/or institutions in charge of collecting, centralising, analysing and communicating quantitative data on a regular and long-term basis" (Hoinville et al., 2013). Both local/regional and national surveillance programmes were included. Exclusion criteria were unrepeated research studies, inactive programmes at the time of the literature review, clinical research programmes, as well as programmes assessing appropriateness of antibiotic use. The focus was on antibiotics only, excluding other categories of antimicrobials.

A literature review was conducted in January-February 2021 in both the scientific and grey literatures in English and French languages to identify all potential French programmes for surveillance of ABR, ABU and antibiotic residues in human, animal, food and the environment. Primary literature sources were official websites of ministries, public health agencies, and other public and private institutions involved in ABR-related surveillance. To screen the scientific literature, the following search string was used in PubMed®, including articles published since 2005 only: (antimicrobial*[Title/Abstract] OR antibiotic* [Title/Abstract]) AND (surveillance[Title/Abstract] OR monitoring)[Title/Abstract] AND France[Title/Abstract]). After listing all potential programmes identified, the coordinator of each programme was contacted by email to check if the programme matched the inclusion criteria. Lastly, the list of identified programmes was submitted to a group of 20 French experts with long-term expertise in ABR surveillance or policy-making in the human, animal, food and environmental sectors (i.e., the Surv1Health scientific advisory board), in order to identify any potential missing programmes and validate the final list.

Mapping and characterisation of the surveillance system

Each surveillance programme was characterised using a standardised grid adapted from the ECoSur data collection file developed by Bordier et al. (Bordier et al., 2019). The grid included 62 variables of interest covering aspects related to organisation (e.g., regulatory status, ownership, steering and coordination activities), methods and operations (e.g., target population, coverage, sampling strategy, data collection and analysis, indicators used, dissemination of the results), as well as collaborations with other surveillance programmes (e.g., collaborative strategy and activities, programme strengths and weaknesses influencing collaboration). Contribution to supra-national surveillance programmes was also recorded.

For each surveillance programme, the descriptive grid was pre-completed using information available from the literature collected by the research team, made of two scientists from the human sector and two from the animal/food sector. In addition, 51 interviews with programme coordinators (n=36) and key informants with core expertise in ABR-related surveillance in humans, animals/food and the environment (n=15) were conducted by the research team to complete and validate the grid. In order to ensure the comparability of the information collected, one of the interviewers (LR) was present in all interviews and was assisted by one or two other interviewers (other co-authors). We defined a subsystem as a group of at least three surveillance programmes that share a component or an activity.

Evaluation of the level of collaboration between programmes

Following guidance from the CoEval-AMR network (The CoEvalAMR consortium, 2022), the ECoSur semi-quantitative evaluation tool (Bordier et al., 2019) was used to evaluate the level of organisation, implementation and functionality of collaborations within the French surveillance system. Using data collected as part of the characterisation step described above, the research team scored the 75 criteria of the ECoSur evaluation matrix. Of note, to better fit the complexity of the ABR surveillance system, we adapted the grid: each criterion was initially split and scored at three levels, i.e., collaborations i) within the overall system, ii) within subsystems and iii) between two programmes (i.e., bilateral collaborations). The three scores were later grouped into an average score for each criterion, hence facilitating the scoring of the multiple observed collaborations.

Results were displayed in the form of three output charts, describing 23 organisational attributes related to both governance and operational aspects (output 1), three organisational indexes (output 2) and nine functional attributes (output 3). Scores were validated during a one-day workshop where detailed results of the three outputs were discussed with the Surv1Health scientific advisory board. Minor edits to scores and justifications of the scores were implemented where needed.

Identification of the main drivers for collaboration

Building on the 51 interviews mentioned above, we carried out a qualitative study to investigate the panel of factors influencing the establishment of collaborations between surveillance programmes within the French ABR surveillance system. Semi-structured interviews were used to collect qualitative data through open-ended questions. In order to maximise both the quantity and quality of data collected, an interview guide was drafted ahead of the interviews, following the framework of the Theory of Planned Behaviour (Ajzen, 1991). The guide was pre-tested through an exploratory interview with one coordinator. Although the interviewers used interview guides, respondents were free to introduce any other information they felt was relevant. Data continued to be collected until saturation occurred. Interviews were performed between February and June 2021, using online video conferencing because of Covid-19 related travel restrictions. Interviews were recorded to facilitate subsequent data analysis. The protocol was approved by the department of legal affairs of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

The interview recordings were manually transcribed and compiled with the notes. At first, data analysis involved reading through all of the transcripts to get a sense of the dataset as a whole (Graneheim and Lundman, 2004). Then, the transcripts were subjected to thematic analysis (Beaud and Weber, 2003). The analysis was conducted inductively in a circular process and used a constant comparative method (Braun and Clarke, 2014): repetitions of forward and backward movements from transcripts, gathering of text fragments, attribution of codes and introduction of inferences (Mukamurera et al., 2006). Before making any inference, evidence to the contrary was sought. The data were examined in regard to the research questions, significant text fragments were identified, coded and grouped into categories, i.e., groups of content that share a common feature. Similarly, categories were organised around themes. The triangulation principle and iteration principle were strictly applied (De Sardan, 2008).

RESULTS

Description and mapping of the French surveillance system

From 79 surveillance initiatives initially identified, 48 were retained in further analysis; these targeted the human (n=35), the animal/food (n=14) and/or the environmental sector (n=1). Only two programmes covered both the human and animal/food sectors (Fig. 1). Monitoring programmes were either regulated/official (n=29) or voluntary (n=19). They primarily relied on passive surveillance (n=41). The majority were publicly funded (n=34), while nine were based on a mixed public-private funding and five on private funding only. Most programmes had national coverage (n=43) and among them, 31 included at least one overseas territory. In the human sector, targeted populations included hospitals (n=30), the community (n=23) and/or long-term care facilities (n=20). In the animal sector, these included diseased food-producing animals (n=10), diseased companion animals (n=2) and/or healthy food-producing animals (n=2). Three programmes from the animal/food sector also included meat and meat-borne products. The only programme retained in the environmental sector targeted surface and underground water.

The majority of surveillance programmes targeted ABR (n=35), while 14 programmes targeted ABU. Three monitoring programmes targeted both ABU and ABR in the human sector (Fig. 1). Only two monitoring programmes targeted residues of antimicrobials. Among the 35 ABR monitoring programmes, 23 had access to bacterial isolates and were able to perform molecular characterisation in addition to conventional antimicrobial susceptibility testing. ABU monitoring was based on various data sources including administration (n=6), deliveries or dispensing (n=5), reimbursements (n=3), sales or prescriptions (n=1) of antimicrobials. Indicators for ABU were highly variable both within and between sectors, while ABR indicators appeared relatively harmonised. However, different standards were used to determine resistance profiles in humans and animals.

We identified four sub-systems with established and formalised collaborations (Fig. 1). These varied in size (from two to 14 surveillance programmes involved) and in types of collaborative activities. Notably, the French monitoring programmes also contributed to 12 established supra-national programmes for monitoring of ABR, AMU or antimicrobial residues (Fig. 1), and to one programme under construction for ABR monitoring in clinical pathogens of animals in Europe (EARS-Vet) (Mader et al., 2021).

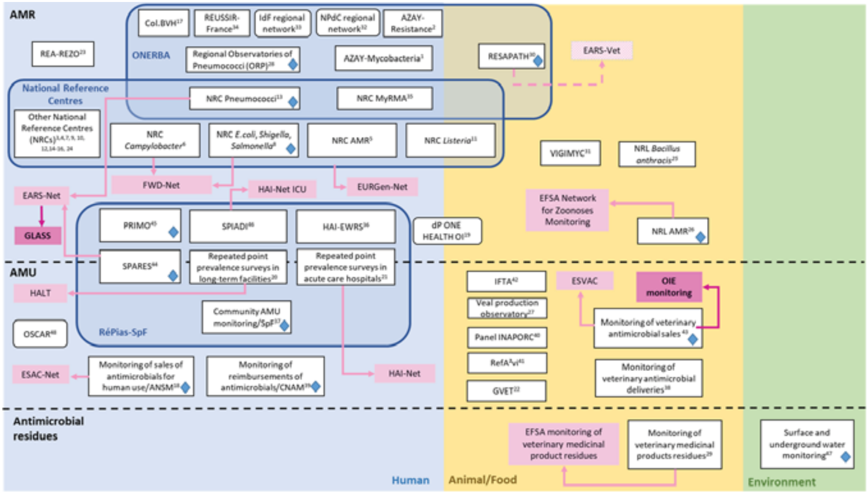

Figure 1. Mapping of the existing surveillance programmes for antibiotic resistance (ABR), antibiotic use (ABU) and antibiotic residues in humans, animals/food and the environment in France in 2021

Legend: White boxes: French surveillance programmes (straights corners = national; rounded corners = regional). Light grey boxes: European surveillance programmes (with EARS-Vet under construction). Dark grey boxes: international surveillance programmes. Diamonds: programmes contributing to the annual joint One Health Antibiotic Resistance brochure coordinated by Santé publique France

Evaluation of the level of collaboration

The three outputs charts of the application of EcoSur to the French ABR surveillance system are displayed in Fig. 2. With regards to governance of ABR surveillance (including aspects related to steering, coordination and scientific support activities), the evaluation demonstrated that the national collaborative strategy, as described in the interministerial roadmap and the national action plans, was well formalised and relevant within the broader context, including the political, socio-economical and epidemiological situation, as well as the European and international recommendations. However, a cross-sectoral coordination body that would facilitate the implementation of the national collaborative strategy was lacking. While stakeholders appeared fully engaged into surveillance roles attributed to them as part of various national working groups, some sectors (e.g., the environmental sector) and disciplines (e.g., social sciences) appeared under-represented. Other gaps included the lack of training in One Health surveillance of ABR, as well as regular evaluations of the level of integration or collaboration within the surveillance system (this study being the first of this kind).

In terms of operations, collaborations existed for surveillance activities located downstream the surveillance process, such as external communication and dissemination of the results to decision makers. One concrete example in this area was the publication of a One Health Antibiotic Resistance brochure coordinated by Santé Publique France, summarising the key results from the major national surveillance programmes into a single document and released annually at the occasion of the World Antimicrobial Awareness Week. Conversely, very few collaborations existed for upstream surveillance activities such as protocol writing, data sharing or data analysis, where collaboration primarily occurred via time-limited research projects. While joint data analysis was partly conducted at a European level under the Joint Inter-Agency Antimicrobial Consumption and Resistance Analysis (ECDC et al., 2021), no similar initiative was in place in 2021 at national level.

Main drivers influencing collaboration

Our qualitative study demonstrated that the implementation of collaborations between sectors and programmes was multifactorial; we identified 42 factors grouped into six categories, including i) characteristics of the overall ABR surveillance system (e.g., structure, clarity and legibility), ii) features of the collaborating programme (e.g., visibility, technical skills, access to strains or metadata, resources), iii) profile of the actors involved (e.g., willingness to share data or expertise, to open up to transdisciplinary approaches, perception of the One Health approach), iv) characteristics of the collaboration itself (e.g., level of formalisation, perceived impacts, resources available for collaboration), v) broader context (e.g., One Health as a priority for coordinators and/or funders, national and international incentives, One Health training) and vi) ABR research activities (e.g., research call encouraging collaboration and providing resources to kick start collaborations).

In general, collaborations were mainly fostered by good interpersonal relationship between actors, their interest in transdisciplinary approaches and the perceived benefits of collaboration on the involved programmes. Limited resources and the lack of visibility of the ABR surveillance system hindered collaboration. Paradoxically, coordinators generally did not perceive collaborations as a resource-pooling tool since they generally set them up only after consolidating their own programmes. Interestingly, there were no differences between the views of the respondents from the different sectors or the views of the coordinators being involved or not in collaborations.

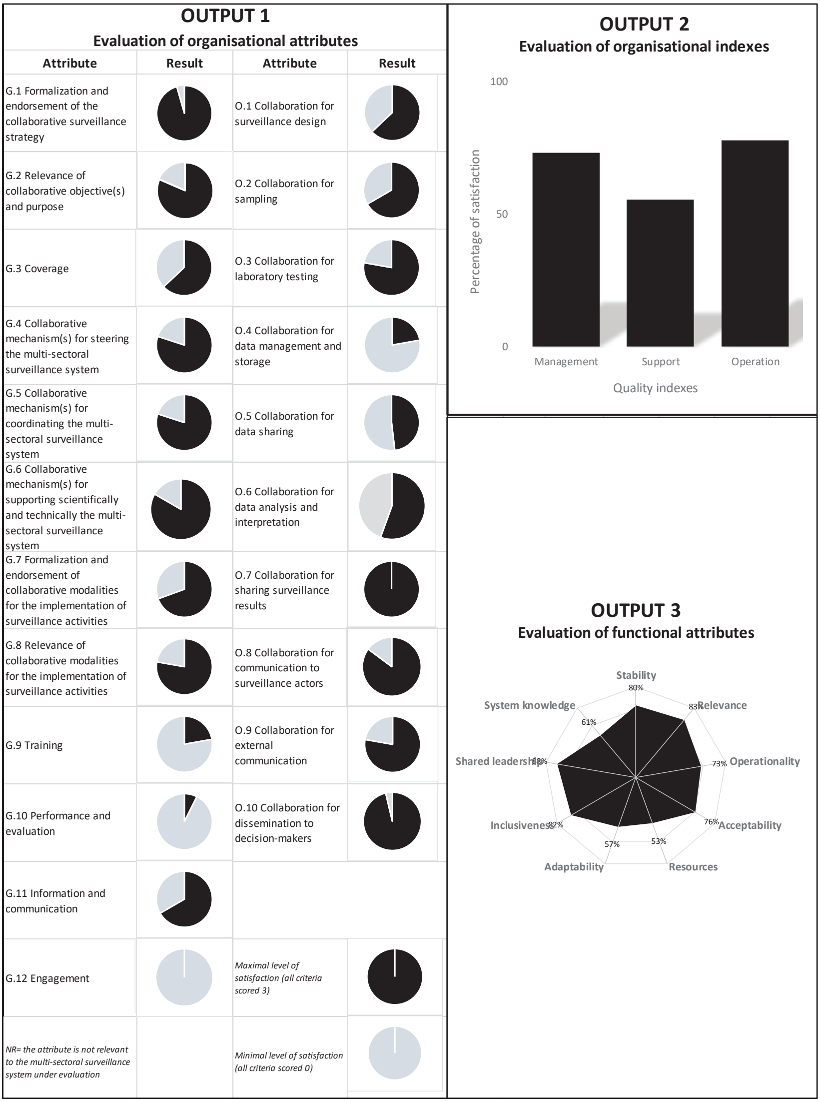

Figure 2. Output figures of the EcoSur semi-quantitative evaluation tool applied to the French system for surveillance of ABR, ABU and antimicrobial residues in 2021. a. Organisational attributes related to both governance and operational aspects (output 1); b: Organisational indexes (output 2); c: Functional attributes (output 3)

Recommendations for improvement of ABR integrated surveillance

Building from our findings, we formulated a list of 12 practical recommendations for improvement of integrated ABR surveillance in France; the top 5 are presented in Table 1. These recommendations were shared with risk managers to improve the One Health-ness of surveillance and feed future ABR control strategies.

Table 1. Top 5 recommendations for improvement of collaborations within the French ABR surveillance system

1	Create a One Health body for national coordination of surveillance grouping together the actors working at operational level and contributing to facilitate collaboration between programmes. Its role could be to improve data interoperability and harmonisation of surveillance protocols (e.g., data formats, standards and interpretation criteria for antimicrobial susceptibility testing), to facilitate joint communication of the results between sectors and ABU/ABR, and to work towards mutualisation of surveillance resources.
2	Reinforce surveillance in the environment, with full-scale implementation of surveillance in the environmental sector, beyond surface and ground water. Surveillance could be expanded to community and hospital wastewater, costal seas and farm environments. In addition to the impact on human and animal health, the impact of environmental ABR on ecosystems should also be considered.
3	Create a national cross-sectoral working group dedicated to *(i)* the definition and interpretation of common indicators across sectors and programmes, and *(ii)* the implementation of integrated data analysis across sectors and programmes, inspired from the European joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) reports.
4	Improve the legibility of the French ABR surveillance system: 4.1. Clarify the role of each actor and programme; 4.2. Develop a unique and sustainable entry point / dashboard to access reports, websites and data from the various French surveillance programmes.
5	Strengthen joint One Health communication of surveillance data from the three sectors: 5.1. Reinforce the dissemination and impact of the One Health Antibiotic Resistance brochure coordinated by Santé Publique France and further precise its target audience; 5.2. Envisage co-coordination of the One Health Antibiotic Resistance brochure across sectors; 5.3. Where needed, develop other joint communication material to better respond to the needs of the various actors.

DISCUSSION

To our knowledge, this work represents a first attempt to map, characterise and evaluate the level of collaboration within the ABR surveillance system in France, as well as better understand the drivers for collaboration. Our mapping study demonstrated that France currently has a rich and extensive, yet complex and fragmented surveillance system, made of 48 surveillance programmes. This large number of programmes partly related to several characteristics: i) in several instances, epidemiological and molecular ABR data were collected through separate surveillance programmes, ii) national reference centres (in humans) and national reference laboratories (in animals) were split by bacterial species, iii) ABU surveillance programmes were built by separate animal species in the animal sector and iv) for historical reasons, several older programmes at local or national levels persisted and partly overlapped with new national programmes launched only recently in 2018. There is a need to improve the visibility of the system and to facilitate synergies, hence improving the overall surveillance efficiency.

Despite their large number, the French programmes complemented each other by targeting different populations and providing evidence to support and evaluate national and supra-national actions. In the human and animal sectors, coverage of relevant target populations generally appeared satisfactory. In the animal sector, both healthy and diseased animals were covered by national ABR surveillance programmes, a situation still uncommon in Europe (Mader et al., 2022b). Additionally, several farm-level ABU surveillance programmes dedicated to selected livestock species complemented the overall surveillance of sales data. Yet, an important gap was a dedicated ABU-surveillance programme in companion animals. However, the upcoming implementation of the EU Regulation 2019/6 on veterinary medicinal products (European Commission, 2018) should address this gap within a few years (by 2027 for horses and 2030 for dogs and cats). Overseas territories were also poorly represented in the majority of national programmes. Additionally, antimicrobial susceptibility testing in diseased animals was limited to antimicrobials authorised in veterinary medicine, hence limiting the assessment of the zoonotic exposure to ABR of public health relevance (e.g., resistance to carbapenems). The EARS-Vet network recently proposed a panel of antibiotics of primary interest to both animal and human health, and could be considered for surveillance purposes (Mader et al., 2022a).

A major gap in the French system coverage was ABR surveillance in the environment, with only one programme complying with our definition of a surveillance programme. Other initiatives existed but were not sustainable at this stage. Structured national surveillance of antibiotic residues was limited to surface water and animal-derived food. No residue surveillance programme was identified in other important areas such as farm environments or wastewater treatment plants, although various research studies explored this issue. This was not surprising since worldwide efforts towards environmental surveillance of ABR and antibiotic residues have only recently started. There is a need to enlarge and strengthen the structuration of ABR and antibiotic residue surveillance in the environment, and to harmonise surveillance indicators being used in this sector.

Overall, the French surveillance system appeared fragmented, as the large majority of surveillance programmes were addressing a single sector, and focused on either ABR or ABU. Four subsystems partly counterbalanced the apparent lack of integration, by facilitating collaborations between programmes. Several governance activities were in place to facilitate collaboration, but national coordination between surveillance programmes was generally lacking. Collaboration for operational activities primarily focused on external communication of the results, but collaborative activities upstream of the surveillance process, e.g., the design of surveillance protocols, were lacking. Such activities would certainly contribute to improve the harmonisation and inter-operability of surveillance data.

Our work demonstrated that actor-related factors played a decisive role in the willingness to collaborate. Current collaborations were based more on the network of actors and good interpersonal relationships, than on lead institutions or a national or supranational demand for collaboration. All the contextual elements (i.e., conferences, workshops, education and training) that encouraged actors from different sectors or disciplines to better know each other, to exchange and to learn from other disciplines, ultimately facilitated collaborations. Therefore, in order to move towards the concrete application of a One Heath approach, all initiatives aimed at bringing coordinators together should be supported. In terms of barriers to collaboration, the lack of human, financial and/or technical resources dedicated to collaboration, the siloed surveillance system, and the sectoral priority of programmes, appeared as challenges difficult to overcome. Moreover, the poor legibility of the surveillance system led to a lack of knowledge of the existing programmes by the coordinators. We believe our mapping will contribute to increase the visibility of the surveillance system and support future collaborations.

A major strength of this study was the comprehensive approach we used, addressing ABR from a broad perspective including ABR, ABU and antibiotic residues in humans, animals/food and the environment, since these are closely connected. To our knowledge, no such overview is available elsewhere in the literature. By direct exchange with the coordinators of each programme, we are confident our data are accurate and validated. Nonetheless, this study also had some limitations. While we collected detailed description of data and information being generated by each programme, getting access to the actual programme databases, e.g., to look at data formats, or thesaurus, was beyond the scope of this study. Hence, we were unable to evaluate the inter-operability of existing data. This partly related to the choice of the EcoSur tool, which primarily focuses on collaboration, while other aspects of integration, e.g., interoperability, are not well covered (Sandberg et al., 2021). Still, we believe this study will be of interest to policy makers, as well as surveillance stakeholders.

Our mapping only provided a snapshot of the surveillance system in 2021 and did not capture changes over time. Yet, the French ABR-related surveillance system appeared as an ever-evolving system. As an example, two large national meta-networks funded through the French Priority Research Programme on ABR were launched in November 2021: (i) the meta-network PROMISE (PROMISE, 2022) aims to build a One-Health community of actors on ABR, to develop a joint data warehouse for ABR surveillance and to set up a national network for environmental surveillance of ABR, and (ii) the meta-network ABRomics-PF (IFB, 2022) aims to build a platform for ABR multi-omics One Health data sharing. These two meta-networks appear to be excellent opportunities to further facilitate integration of surveillance programmes, and address some of the gaps identified in this study.

To conclude, we believe that the whole approach of mapping the national surveillance system to identify gaps and overlaps, evaluate collaborations between programmes and explore drivers for collaboration, is an added value to the ABR surveillance landscape and will inspire other countries willing to progress step by step towards One Health surveillance of ABR.

ACKNOWLEDGEMENTS

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EVALUATION OF AN ACTIVE SURVEILLANCE PROGRAM ON CORVIDS FOR THE EARLY DETECTION OF WEST NILE VIRUS

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SUMMARY

The West Nile virus (WNV) cycle involves mainly birds and mosquitoes, but WNV may spill over to humans. In the Emilia-Romagna region, Italy, a WNV integrated surveillance program is carried out. We assessed the ability of the component related to the active testing of corvids to detect WNV before the notification of the first human case of disease. In the period 2013-2021, 17,709 corvids were tested by PCR for WNV, with 529 (3.0%) testing positive for infection. In the same period there were 312 notifications of human cases. West Nile Virus was detected in 62 out of the 81 seasons evaluated. West Nile Virus was notified in birds 58 times (93.5%), and 44 times (71.0%) in humans. West Nile Virus was notified first in birds in 48 seasons (77.4%). Testing at least 5 birds per 100 km^2 appears sufficient to give good sensitivity to the system, but for early detection birds must be collected between mid-June and mid-August.

INTRODUCTION

West Nile virus (WNV) is a neurotropic mosquito-borne flavivirus belonging to the Japanese encephalitis serocomplex. It is regarded as the most widespread arbovirus in the world and has circulated in Europe for decades, where it has significantly expanded in recent years. The natural infection cycle involves mosquitoes, primarily *Culex* spp. and birds, while horses and humans are considered dead-end hosts. Most human cases remain asymptomatic, however 20-40% of infected people show clinical symptoms ranging from flu syndrome to encephalitis (Kramer et al., 2007). Asymptomatic infected donors represent a risk for the safety of blood transfusions and solid organ transplantations because WNV can be transmitted by these medical procedures (Iwamoto et al., 2003; Montgomery et al., 2006; Capobianchi et al., 2010; Pupella and Pisani, 2013). The timely detection of WNV circulation is therefore essential for the effective implementation of measures such as safety procedures for blood collected for donations, vector control and communication to the relevant Animal and Public Health authorities as well as to the general public (Gossner et al., 2017).

In Europe, where WNV seems to have limited or no pathogenicity for birds (Calistri et al., 2010), it is recommended to combine the passive surveillance in wild birds with some sort of active surveillance (Rizzoli et al., 2015). The use of sentinel birds has been proposed as an effective strategy for the early detection of WNV circulation and for the identification of

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affected areas (Komar, 2001; Gossner et al., 2017). Passeriformes, and in particular the *Corvidae* family, are particularly susceptible to WNV infection (Komar et al., 2003; Lim et al., 2015; Jiménez de Oya et al., 2018), hence Eurasian magpies (*Pica pica*) have been effectively used for the detection of WNV circulation in endemic areas in France (Jourdain et al., 2008), Greece (Valiakos et al., 2012), and Spain (Napp et al., 2019). Several factors make this species, and the Hooded crow (*Corvus cornix*), good sentinels (Jourdain et al., 2008; Napp et al., 2019): they are territorial and abundant; they have a broad distribution near houses; and they also have a scavenging behaviour that favours infection with WNV by the oral route. Moreover since magpies, jays and crows prey on eggs and chicks of songbirds and gamebirds, and eat berries or other fruits, they are considered a harmful bird species and are frequently subject to population control in Europe (Díaz-Ruiz et al., 2015), a kind of action that may be useful for WNV surveillance, as in our case.

The first detection of WNV in the Emilia-Romagna region, Northern Italy, occurred in 2008 (Macini et al., 2008), and since 2009 an integrated surveillance system is in place in order to detect early the circulation of WNV in the environment (mosquitoes and birds), and mitigate the risk of virus transmission through blood donations. Active surveillance of WNV is conducted in mosquitoes, birds, horses and humans with neurological disease symptoms (Angelini et al., 2010; Bellini et al., 2014). Over time, the system has proved economically sustainable and capable of detecting the virus in the environment before the onset of human cases of disease (Bellini et al., 2014; Paternoster et al., 2017).

In this paper we report the results of the surveillance system component regarding the active surveillance on corvids, focusing on its capability to detect the virus circulation before the notification of WNV infection cases in humans.

MATERIALS AND METHODS

Survey area

The survey was carried out in the Emilia-Romagna region (lat. 44°30′38″N; long. 10°57′25″E). This territory covers 22,509 square kilometers of which about half is lowland including the Southern part of the Po river valley. This region has a population of about 4.5 million people and is administratively divided into nine provinces (from West to East: Piacenza (PC), Parma (PR), Reggio Emilia (RE), Modena (MO), Bologna (BO), Ferrara (FE), Ravenna (RA), Forlì-Cesena (FC), Rimini (RN)). All these provinces are covered by the WNV integrated surveillance program, although sampling of birds are carried out only in the lowland (13,798 km2), where the WNV vector population (Culex pipiens mosquito) is most abundant.

Sampling and testing of corvids

The Italian integrated WNV surveillance program requires a yearly testing of at least 100 sentinel birds every 1200/1600 square kilometers, corresponding to 6.25 birds/100 km^2, and samples must be collected between April and November of each year (Rizzo et al., 2016). Between May and October of years 2013-2021, 12,163 European magpies (*Pica pica*), 3821 Hooded crows (*Corvus cornix*), and 1725 Eurasian jay (*Garrulus glandarius*) were collected during official pest bird control programs within the Emilia-Romagna region. In all the provinces of the region, birds were shot or captured using Larsen traps and killed by trained hunters by means of cervical dislocation according to the provisions set out by the national legislation on animal welfare (Council Regulation (EC) 1099/2009). Sampling was performed under the supervision of the official veterinary services, which provide a quick delivery of the birds to the laboratory in charge of the testing.

From each sampled bird, heart, brain, kidney, and spleen were pooled, mechanically homogenized, and tested by real time PCRs to detect WNV RNA (Tang et al., 2006; Eiden et al., 2010; Del Amo et al., 2013). Samples testing positive were further submitted to traditional PCRs to obtain amplicons for sequencing. All positive samples were submitted to a Pan-flavivirus protocol targeting the NS5 gene (Scaramozzino et al., 2001), and to a specific protocol directed to the gene E (Lanciotti et al., 2000). All tests were performed in the same laboratory. The following data were used for the statistical analysis: bird species, sampling date, sampling province, date of delivery to the laboratory, testing start date, test result, date of notification of positive result.

Data on human cases of West Nile disease

West Nile Virus infection is a notifiable disease in Italy since 2007 (Pupella and Pisani, 2013). Data on human cases of WNV infection were kindly supplied by the Service of Collective Prevention and Public Health of the Emilia-Romagna region in the framework of the regional WNV integrated surveillance system. Data provided were anonymised and only the following were used for this study: case code, date of notification, type of disease (neurological - WNND; fever - WNF), and the most probable province for the origin of infection.

Definition of threshold for early detection

Since the sanitary measures are determined at the provincial level, in the analysis we examined the data for each of the 9 years during the period (2013-2021) in each of the nine provinces of the region. We therefore evaluated 81 distinct epidemic seasons. For each season we calculated the notification dates of the first human case and of the first infected bird and counted whether the notification occurred first in birds or in humans. Maps were created in the R environment using the tmap package (Tennekes, 2018; R Core Team, 2020;). To calculate the best threshold (number of birds/100 square kilometres) for early detection of WNV in corvids we computed a ROC curve. This analysis was performed in the R environment using the pROC package (R Core Team, 2020; Robin et al., 2011).

RESULTS

WNV active surveillance on corvids

In the 9 year period covered by this study, from May to October 17,709 corvids were tested by PCR, and 529 (3.0%) of them tested positive for infection with WNV. The highest prevalence was registered in magpies (409/12,165; 3.3%, 95%CI 3.0%-3.7%), and hooded crows (111/3821; 2.9%, 95%CI 2.4%-3.5%), while jays (9/1726; 0.5%, 95%CI 0.3%-1.0%) showed a lower level of infection. Except in 2016 and 2017, when the first infected bird was notified in June (weeks 25-26), generally the WNV was first detected in July (weeks 27-31), while peaks were registered between August and September (weeks 34-39; Fig. 1). In the 81 seasons evaluated, WNV was detected in birds 58 times (93.5%, CI95% 84.3%-98.2%), of which 40 occurred together with notifications of human cases of disease due to WNV infection. West Nile Virus was only notified in corvids alone in 18 of the seasons (Table 1).

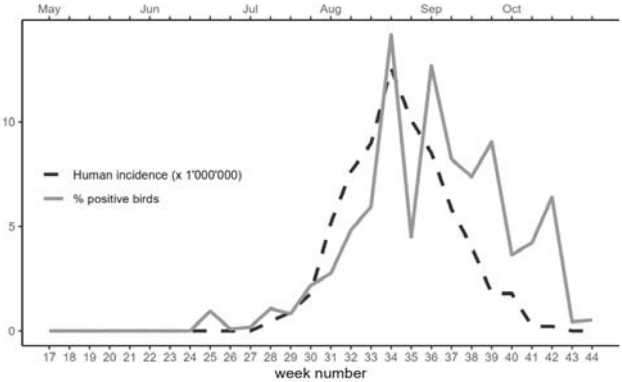

Figure 1. Cumulative incidence (per million inhabitants) of human cases of West Nile Disease and percent prevalence of West Nile virus infection in corvids, by week of notification. Emilia-Romagna region, 2013-2021

Human cases of West Nile disease

In the 9 year period considered, 312 human cases of disease due to WNV infection (111 cases of WNF, and 201 cases of WNND) were notified in the Emilia-Romagna region. In this study we did not count the cases of WNV infection in asymptomatic donors. The highest incidence was registered in 2018 (172 cases; 38.5 cases/100,000 inhabitants). Generally, the human cases were first notified in July (weeks 28-29), while the peak of incidence was registered in August (weeks 33-36; Fig. 1). In the 81 seasons evaluated, WNV was detected in humans during 44 seasons (71.0%, 95%CI 58.1%-81.8%), of which 10 occurred before notification of WNV infection in corvids. In four seasons human cases of disease were notified in the absence of virus detection in birds (Table 1).

Table 1. Results of West Nile virus active surveillance in humans and corvids. Emilia-Romagna region, 2013-2021

Number of epidemic seasons		Notification of human cases of disease due to WNV infection		
		Yes	No	Sum
WNV notification in corvids	Yes	40	18	58
	No	4	19	23
	Sum	44	37	81

In the 9 year period considered, in Emilia-Romagna region WNV was detected every year, although not in all the provinces (Fig. 2). Considering only the 40 seasons in which both human and bird cases occurred, WNV was first detected in birds 30 times, with an average of 24 days in advance (Table 2).

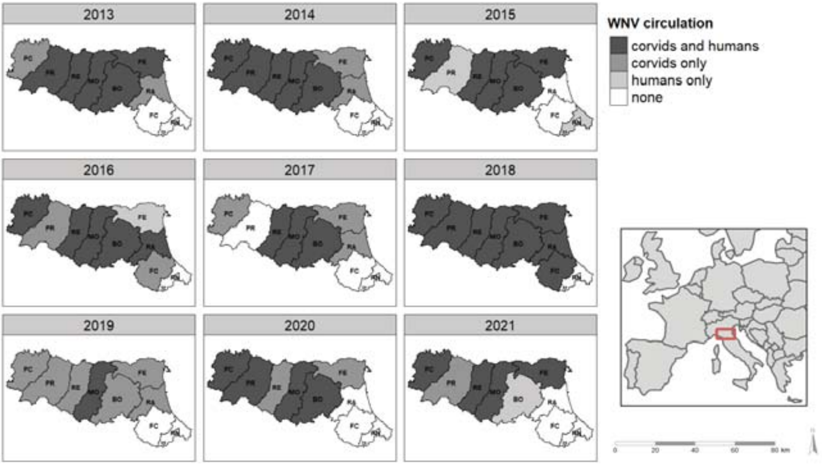

Figure 2. Detection of West Nile virus in humans and corvids, by province and year in Emilia-Romagna region, 2013-2021

Table 2. Number of days between notification of West Nile virus in humans and corvids. Emilia-Romagna region, 2013-2021

WNV notification	N. of seasons	Mean (±SD)	Median	Q90	Min.	Max.
First in corvids	30	24.3 (± 16.9)	22	44.6	1	62
First in humans	10	23.2 (± 13.2)	23.5	37.6	3	43

Definition of threshold for WNV early detection in corvids

In the 9 year period covered by this study, human cases of West Nile disease occurred in 44 epidemic seasons. Figure 3 reports the distribution of the number of corvids tested per 100 km2 before the notification of the first human case of West Nile disease. In the 30 seasons in which active bird surveillance has detected WNV before the notification of the first human case of disease, the number of corvids tested per 100 km2 was higher than in the 14 seasons in which the first WNV notification occurred in humans. Notably, in 70% of the seasons in which early detection occurred in corvids, the density of birds tested per 100 km2 was at least five. In the ROC curve the highest accuracy value corresponds to the threshold of 3.3 tested birds per 100 km2 (Table 3).

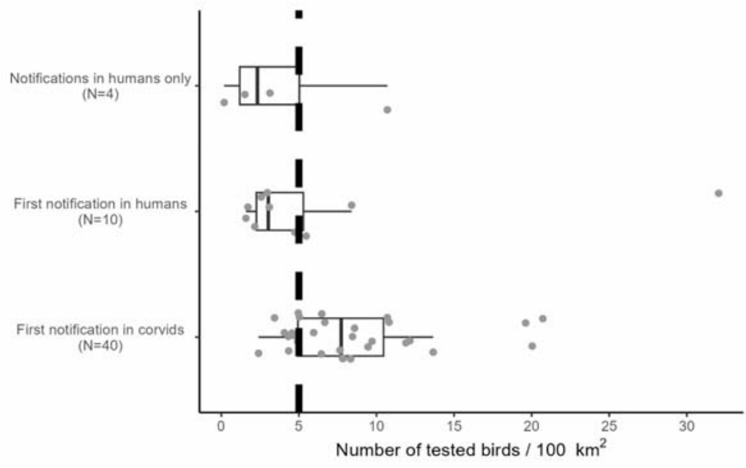

Figure 3. Distributions of the number of birds per 100 km^2 tested before the notification of the first human case of West Nile disease. Emilia-Romagna region, 2013-2021

Table 3. West Nile virus active surveillance in corvids. ROC curve output for selected thresholds. Emilia-Romagna region, 2013-2021

Threshold (birds/100 km^2)	Specificity	Sensitivity	Accuracy	TN	TP	FN	FP
2	28.6	100	77.3	4	30	0	10
3.3	64.3	96.7	86.4	9	29	1	5
5	71.4	70	70.4	10	21	9	4
6.25	78.6	63.3	68.2	11	19	11	3
8.5	85.7	36.7	52.3	12	11	19	2
11	92.9	20	43.2	13	6	24	1

Note: TN: late or no WNV detection in corvids. Number of tested birds was below the threshold; TP: WNV early detection in corvids. Number of tested birds was over the threshold; FN: WNV early detection in corvids. Number of tested birds was below the threshold; FP: late or no WNV detection in corvids. Number of tested birds was over the threshold.

DISCUSSION

Our results show that the active surveillance on corvids is more sensitive than a syndromic surveillance in human patients: in the 81 seasons evaluated, WNV was detected in 62 seasons, 58 times in birds (93.5%, CI95% 84.3%-98.2%), and 44 times in human patients (71.0%, CI95% 58.1%-81.8%).

Three parameters are requested for quantification of the sensitivity of an early detection surveillance system: population coverage, temporal coverage, and detection sensitivity (Cameron et al., 2020). It is impossible to put under surveillance a significant proportion of a wild animal population. However, our data show that testing at least 6.25 corvids per 100 km^2, as requested by the integrated Italian WNV surveillance program, results in a high probability (19/22; 86.4%, CI95% 66.7%-95.3%) of detecting the virus before the notification of human cases of disease when this threshold has been achieved during the early stages of the epidemic season.

In Emilia-Romagna region WNV circulation in birds and humans shows a clear seasonal trend, strictly related to the mosquito vectors activity. Early virus detection occurred in late June (weeks 25-26), with the peak of incidence around mid August (weeks 33-36), while only rarely were cases in birds notified in the second half of October (weeks 43-44).

Corvids, especially magpies, have been confirmed as a valid sentinel species for WNV, and have been used in many serological surveys (Jourdain et al., 2008; Napp et al., 2019). In our surveillance system we preferred to use PCR testing for several reasons, first of all its high specificity. Usutu virus (USUV), another flavivirus belonging to the Japanese encephalitis serocomplex, cross-reacts with West Nile virus (Calisher and Gould, 2003; Llorente et al., 2019), and it is endemic in Emilia-Romagna (Tamba et al., 2011; Calzolari et al., 2017). The circulation of different Flaviviruses, such as WNV, USUV or Bagaza virus, on the same territory requires confirmation by virus neutralization or plaque reduction test of positive sera in ELISA (Jourdain et al., 2008; Tamba et al., 2017; Llorente et al., 2019), but these tests require at least 3 days of virus incubation (Di Gennaro et al., 2014; World Organisation for Animal Health, 2022), while PCR can be done within one working day.

Corvids experimentally infected with WNV show detectable viral genome in organs up to 17 days post infection (Komar et al., 2003; Dridi et al., 2013; Lim et al., 2014, 2015; Jiménez de Oya et al., 2018). Therefore, since persistent infection with WNV is a rare event in passerines (Nemeth et al., 2009), a positive PCR generally suggests a recent infection, even in adult birds. On the other hand, seropositivity in an adult corvid could be due to a past infection which occurred in previous years (Wilcox et al., 2007; Jourdain et al., 2008), while we were only interested in detecting WNV circulation in the current season.

In conclusion, our data shows that active surveillance on corvids generally allows the detection of WNV before the onset of human cases, although not consistently. Failure of this surveillance component system occurred mainly in seasons where the number of tested birds was low. However, there are other components of the integrated surveillance system in Emilia-Romagna region, such as passive surveillance of birds or monitoring of mosquitoes, capable of compensating for any deficiencies in the active surveillance of corvids (Riccardo et al., 2018; Lauriano et al., 2021, 2021;). From our results, active testing of at least 5-6 corvids per 100 km^2 seems sufficient to give good sensitivity to this surveillance system component, but to achieve an early detection of the virus, birds must be collected mainly in the period between mid-June and mid-August.

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MACHINE LEARNING CLASSIFICATION METHODS INFORMING THE MANAGEMENT OF BOVINE TUBERCULOSIS INCIDENTS IN ENGLAND

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SUMMARY

Bovine tuberculosis (bTB) continues to be the most complex animal health problem in England. Improving diagnostic testing with the additional deployment of more sensitive tests, like the interferon (IFN)-gamma test, is one of the government's top priorities. We developed classification machine learning algorithms to evaluate the deployment of IFN-gamma testing in high-risk herds. The final model, with an area under the ROC curve (AUC) > 95, predicted eight percent (3,510 of 41,493) of eligible active herds in 2020 as at-risk of a bTB incident, with the majority of them (66% or 2,328 herds) experiencing at least one incident. Only 18% (330 of 1,819) of incidents in predicted high-risk herds had the IFN-gamma test applied in 2020. We therefore conclude that this methodology provides a better way of directing the application of the IFN-gamma test towards the high-risk subgroup of herds

INTRODUCTION

Despite intensive eradication efforts over decades, bTB continues to be a high-priority animal health problem in England (Defra, 2014), where a strategy aiming to eradicate bTB by 2038 is currently being deployed (Defra, 2014, 2020). Effective bTB control requires the early recognition and prompt removal of asymptomatically-infected (subclinical infection) animals to prevent transmission (Cousins, 2001; de la Rua-Domenech et al., 2006; Good and Duignan, 2011; Álvarez et al., 2012). The primary surveillance test in England is the Single Intradermal Comparative Cervical Test (SICCT) or tuberculin skin test. However, no current bTB diagnostic test provides a perfect separation of all infected and uninfected cattle (de la Rua-Domenech et al., 2006). In addition to this, as it is a comparative test, the SICCT can produce an inconclusive reactor (IR) result: i.e., a non-negative result below the threshold to be declared a reactor. Improving diagnostic testing to root out bTB more effectively, with the additional deployment of more sensitive tests, is one of the top priorities for the government, together with mitigating the risk IRs pose (Defra, 2020).

Residual infection arises from the imperfect sensitivity of current diagnostic tests, even if optimally applied: the sensitivity of the SICCT has been quoted as 75.0-95.5% (de la Rua-Domenech et al., 2006). To further reduce the risk of residual infection in incidents, supplementary diagnostic tests, such as the interferon (IFN)-gamma and antibody blood tests, can be used in parallel to the tuberculin skin test to increase the diagnostic sensitivity (TB Hub, 2021a). Although more sensitive, these supplementary testing regimes are less specific.

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Therefore, targeted strategic risk-based application, rather than blanket use of these tests, is recommended to reduce the risk of false positives, particularly in high-incidence areas (de la Rua-Domenech et al., 2006; Good et al., 2018).

Decision trees (James et al., 2014; Therneau and Atkinson, 2018) and random forest methodologies (Breiman, 2001; Liaw and Wiener, 2002) have been used to identify high-risk bTB surveillance tests that disclose IRs in absence of reactors, likely to result in an incident at the inconclusive reactor 60-day retest test (Romero et al., 2021). Using very similar data on risk factors and the same geographical and temporal limits (i.e., England, 2012-2020), here we aim to identify high-risk herds at significant risk of having reactors disclosed at their surveillance test. All the high-risk herds identified in England in 2020 could be subject to preventive measures, like intensified engagement with the Animal and Plant Health Agency (APHA) and/or dedicated visits by advisory bodies (TBAS, 2021). We used the model outputs to evaluate the deployment of higher sensitivity tests (IFN-gamma test) if an incident was detected in herds identified as high-risk, and compared it to its deployment as per existing policy requirements. The overall aim of the study is to deal with undetected infected cattle, one of the two big contributors to disease persistence (More, 2019) and a top priority in England's revised eradication strategy (Defra, 2020), to accelerate the progress towards eradication by 2038.

MATERIALS AND METHODS

Source datasets

Cattle bTB-testing data, and demographic and movement data on potential herd-level predictors for active herds in England from 2012 to 2020, held by the APHA, were extracted. An additional purpose-designed dataset comprising bTB incident information from 2012 to 2020 was populated by the APHA's Data Systems Group. This was used to identify the control measures used in incidents on the high-risk herds identified and to evaluate the extent of IFN-gamma test deployment. The initial dataset used for analysis was made up of the outcome variable and 94 explanatory variables. Herds with missing observations were removed (11,936 out of 380,955 or 3% of herds removed) (i.e., to enable complete-case analysis).

Statistical analyses were performed using the R statistical software (R Core Team, 2021), version 4.1.1.

Training and testing datasets

All eligible records from 2012 to 2019 were randomly split into a training dataset (80%) or a testing dataset (20%, Test 1). To evaluate the application of IFN-gamma test using 2020 policies, the 2020 dataset was used as a new testing dataset (Test 2 dataset) to identify high-risk herds.

Classification tree analysis

A classification tree model using the CART algorithm (Breiman et al., 1984; Therneau and Atkinson, 2018) was developed using the above mentioned training dataset and Test 1 dataset. The CART algorithm repeatedly allocated herds into the most homogeneous groups by outcome class (James et al., 2014; Bruce and Bruce, 2017), using the gini or purity index (G) as the splitting criteria, which is defined as in Eq. (1).

$$G = \sum_{k=1}^{K} \hat{p}_{mk}(1 - \hat{p}_{mk}) \quad (1)$$

Only the top 20 predictors in the variable importance list of the original classification tree analysis were included in the final classification tree model.

Random forest

The random forest model (Breiman, 2001) was implemented using the same training and testing datasets as the classification tree analysis. This was carried out for comparison purposes. The algorithms were tuned for the number of trees in the forest (500 initially) and the fixed number of input variables chosen at random before each split (eight initially) (Liaw and Wiener, 2002; Hastie et al., 2017). The mean decrease in Gini index was calculated to select the top 20 most important predictors, which were used to develop the final random forest prediction algorithm.

Model selection and evaluation of outputs

The final models' predictive performance was assessed on both testing datasets (Test 1 dataset, i.e., 20% of the 2012-2019 dataset not seen by the developed models, and Test 2 dataset from year 2020) (Kuhn, 2008; Khun et al., 2014). The parameters used were: accuracy (a property of classification models, based on the number of correctly classified observations in the confusion matrix); sensitivity; specificity; positive and negative predictive values; balanced accuracy (i.e., average between sensitivity and specificity), and area under the ROC curve (AUC) (Fei et al., 2017). The final model was chosen based on its predictive performance and ease of implementation. The 2020 real incident dataset was accessed, including the use of IFN-gamma tests, antibody tests, removal of cattle as dangerous contacts (DC), as well as the number of cattle tested and reactors disclosed. This allowed us to compare the extent of use of different disease control measures in real incidents in 2020 vs their use in incident herds identified as high-risk by the model.

RESULTS

Summary of data

There were 475,019 total cattle herds in England in the initial dataset (2012-2020). In total, 106,000 (22%) herds were excluded (government-approved finishing units, missing herd size value, not able to have an incident detected), to provide 369,019 eligible herds. Only 8% of eligible herds (30,946 of 369,019) disclosed an incident (i.e., an outcome variable result of "Yes") during the study period (2012-2020).

Data analysis

Classification tree analysis: The classification tree using the training dataset (random 80% of observations 2012-19), had 47 nodes; 24 of them terminal, with a depth of 11. The best classifier was *Time since the last incident was resolved (0-1 years ago).* The model had a 97% AUC and a balanced accuracy of 85%, with a higher specificity (97%) than sensitivity (73%).

Random forest: The model was tuned using 493 trees with eight variables tried at each split, resulting in an estimated out-of-bag (OOB) error rate of 5%. The most important variable in the model was *Time since the last incident was resolved*. The model demonstrated an AUC of

97%, a balanced accuracy of 82%, and a higher specificity (97%) compared to sensitivity (66%) in the Test 1 dataset.

Model selection: The classification tree model was the model of choice due to the similar predictive performance and better interpretability of the resulting tree (output not available in random forest analysis). This tree output can be used as a communication tool to facilitate adoption by operational staff as well as farmers.

Evaluation of model outputs against empirical disease control data: The predictive performance of the classification tree algorithm was very similar when the Test 2 dataset was used (2020 herds), with the same specificity and AUC and a slightly higher sensitivity (75%). Eight percent of herds were deemed to be high-risk by the chosen model and therefore selected for additional disease control measures in both testing datasets: 6,024 out of 65,504 herds in the Test 1 dataset and 3,510 out of 41,493 in the Test 2 dataset (Fig. 1).

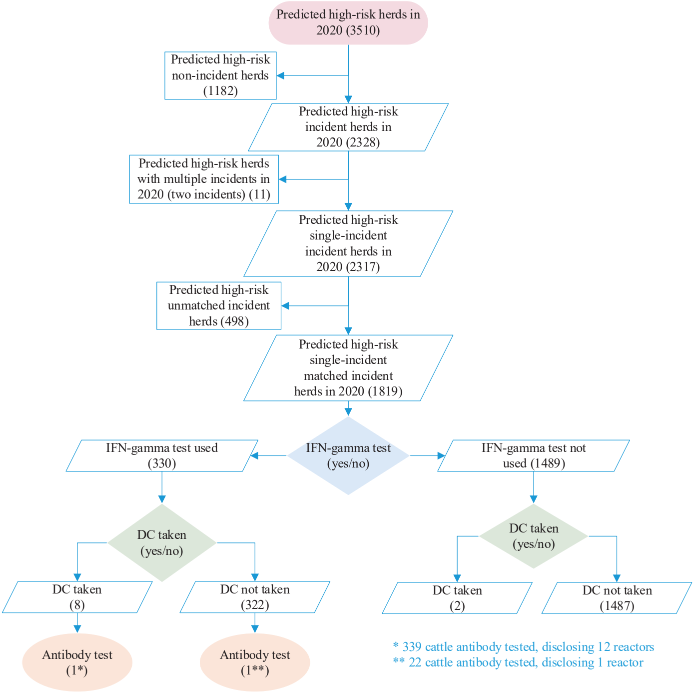

Figure 1. Disease control measures taken in high-risk herds predicted by the classification tree analysis model applied to the 2020 testing (Test 2) dataset

Out of the high-risk herds in 2020 that had an incident (66% or 2,328), 11 herds that had more than one (two) were removed. This left 2,317 single-incident herds used for further evaluation of model outputs.

The majority of the single-incident high-risk herds in 2020 were matched to incident data (79% or 1,819 out of 2,317). Less than one fifth (330 out of 1,819 or 18%) of the matched incidents used the IFN-gamma test in addition to the skin test. An even lower proportion had any cattle removed as a DC: 0.5% or 10 out of 1,819, the majority (8) in incidents where the IFN-gamma test had been used. Only two incidents had antibody testing, one had no DCs taken but IFN-gamma testing was used (22 cattle tested), whereas in the other one, both the removal of suspect cattle DCs as well as IFN-gamma testing took place (339 cattle tested).

Among the skin tested cattle in the matched high-risk incidents, there were two per 1,000 (0.21%) IR cattle, six per 1,000 (0.58%) skin test reactor cattle and 0.5 per 1,000 (0.05%) of cattle removed as DCs. Out of the cattle IFN-gamma and antibody tested, 44 per 1,000 (4.37%) cattle were reactors to the IFN-gamma test and 36 per 1,000 (3.6%) were reactors to the antibody test, respectively (Table 1). The 636 inconclusive reactors disclosed in high-risk incident herds could be removed as DCs, in addition to the 148 already taken, representing a 330% increase. Applying the IFN-gamma test to the 1,489 incidents that did not have one would have resulted in 196,452 cattle IFN-gamma tested (85% of 231,120) with 8,585 IFN-gamma reactors detected on average, an increase of 217% over the 2,710 IFN-gamma reactors already detected.

Table 1. a) High-risk incident herds in the Test 2 dataset (2,317 single incident herds out of 3,510 herds) matched to incidents (1,819) showing incident-related information: diagnostic test results to the Single Intradermal Comparative Cervical Test (SICCT) or skin test, the interferon (IFN)-gamma test, and the antibody test. Results to the skin test include the number of inconclusive reactors (IRs) disclosed. Reactors or positive cattle to more than one test are excluded; b) Same information presented for the low-risk incident herds in the Test 2 dataset (795 single incident herds out of 37,983 herds), matched to incidents in the incident dataset (600)

a

DC taken	IFN-gamma test	Antibody test	Total cattle	Total incident herds	Total incident skin tests	Total cattle skin tested	Total skin test reactors	Total IRs	Total DCs	Total cattle IFN-gamma tested	Total reactors IFN-gamma test	Total cattle antibody tested	Total reactors antibody test	Total slaughterhouse cases
FALSE	FALSE	FALSE	329672	1487	2028	230473	1145	456	0	0	0	0	0	121
FALSE	TRUE	FALSE	87193	321	541	70349	463	172	0	60240	2460	0	0	58
FALSE	TRUE	TRUE	447	1	2	438	4	0	0	372	20	22	1	1
TRUE	FALSE	FALSE	686	2	6	647	13	2	13	0	0	0	0	0
TRUE	TRUE	FALSE	1521	7	17	1501	57	6	43	991	113	0	0	3
TRUE	TRUE	TRUE	329	1	4	529	93	0	92	343	117	339	12	2
		Total	419848	1819	2598	303937	1775	636	148	61946	2710	361	13	185

b

DC taken	IFN-gamma test	Antibody test	Total cattle	Total incident herds	Total incident skin tests	Total cattle skin tested	Total skin test reactors	Total IRs	Total DCs	Total cattle IFN-gamma tested	Total reactors IFN-gamma test	Total cattle antibody tested	Total reactors antibody test	Total slaughterhouse cases
FALSE	FALSE	FALSE	126729	454	339	56913	506	142	0	0	0	0	0	84
FALSE	TRUE	FALSE	46255	141	245	43404	264	77	0	32524	1719	0	0	68
TRUE	FALSE	FALSE	268	1	2	275	7	0	1	0	0	0	0	0
TRUE	TRUE	FALSE	1646	4	10	1769	63	2	6	1427	119	0	0	2
		Total	174898	600	596	102361	840	221	7	33951	1838	0	0	154

DISCUSSION

For the most important livestock categories in Switzerland a method for assessing animal Machine learning classification algorithms were used to direct the targeted application of additional TB control measures to improve the detection of infected cattle. This approach, based on focusing on high-risk herds or areas is an effective design to purposely implement an action that can reduce the effect of a disease rapidly (Salman et al., 2003). This is underpinned by a solid understanding of what constitutes an at-risk herd (Stärk et al., 2006; Salvador et al., 2017).

Classification tree analysis produces explanatory outputs (a decision tree) that depict how different risk factors are interrelated, potentially showing complex interactions. Two of the top three variables for importance in the construction of the classification tree model (*Risk score* and the *Maximum number of reactors*) were present in the highest-risk pathway of the tree and were also shared with the random forest model.

The aim of a revised policy would be to increase the detection of infected cattle in an efficient way. The additional application of IFN-gamma test in parallel interpretation to the skin test is one way to achieve it. An alternative way of increasing the sensitivity of testing is to change the interpretation of the skin test. In standard interpretation, a reactor is declared if a positive bovine tuberculin reaction is greater than four millimetres compared to the avian reaction, whereas at severe interpretation the positive bovine reaction only needs to be greater than two millimetres over the avian reaction (Goodchild et al., 2015).

Severe (i.e. more sensitive) interpretation of the skin test was introduced to all incidents in the EA (Edge area: intermediate area in England for bTB incidence) from 2013 (Defra, 2013), and to all incidents in the HRA (High-risk area: worst affected area) from 2016 (Defra, 2016). However, in the LRA (Low-risk area: least affected area), the use of severe interpretation is restricted to confirmed incidents and certain unconfirmed incidents (which meet certain criteria) (Defra, 2016). An additional potential tool is the "ultrasevere" interpretation of the skin test, where all positive reactions to the bovine tuberculin injection that are bigger than the avian tuberculin reaction are considered positive. Although recommended by the authors of the 2018 (England) Strategy Review (Godfray et al., 2018), this was not considered here, but could be part of additional recommendations to increase sensitivity in certain incidents (e.g. additional application of antibody testing).

Removing IRs as DCs and the use of IFN-gamma tests would enhance the detection of infected cattle, contributing to reducing incident recurrence. The rollout of more frequent six-monthly default background testing in the HRA and EA (TB Hub, 2021b) is not likely to completely eliminate bTB, since the existing post-incident six-monthly test detected the same or a higher amount of incidents per 1,000 cattle tested than the default annual whole herd test (APHA, 2021). In addition, there are logistic and resource problems with rolling out blanket bTB control measures in the worst affected areas of England, particularly measures that increase sensitivity at the expense of specificity. Our recommendation to deploy additional control measures only in the subpopulation of high-risk scenarios is due, not only to efficiency (Salman, 2003) and logistical reasons, but also to minimise the proportion of false positive cattle by targeting a higher prevalence group. The methodology applied provides a mechanism to do this, with a 75% prevalence in the identified high-risk herds *vs* 8% in the general population of active herds.

The population targeted by the classification tree model seems to be different to the one currently eligible for the test since the majority of high-risk herds with incidents had not had the IFN-gamma applied. There is therefore scope to introduce refinements in the current policy to enhance the detection of infected cattle. However, tackling sources of reinfection in the herd would also be necessary to prevent recurrence (Conlan et al., 2012).

Classification tree models have been used as a guide to patient management (Scheetz et al., 2009; Afonso et al., 2012; Kawamura et al., 2012; Fei et al., 2017; Cheng et al., 2018) and risk identification (Staerk and Pfeiffer, 1999; Ortiz-Pelaez and Pfeiffer, 2008; Romero et al., 2020) following if-then scenarios, akin to setting criteria to designate herds as high-risk. The chosen model had >90% AUC without applying prior variable selection procedures (Romero et al., 2020, 2021). In addition, since the balance of sensitivity and specificity was adequate in this scenario, it was not necessary to manipulate the outputs when carrying out ROC analysis (Romero et al., 2021). Together, these make the model easier to adopt and deploy in an operational setting, directing the additional application of existing bTB control measures in a targeted way to increase the detection of infected cattle, a key priority to achieve bTB eradication in England by 2038 (Defra, 2020).

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DISEASE IMPACTS

EXPLORING THE IMPACT OF HEAT AND SEASON ON DAIRY COW HEALTH AND FERTILITY – A MIXED METHODS APPROACH

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SUMMARY

The biological cost of heat stress to cows is well known, yet the effect of summer heat waves on Swedish dairy herds remains unexplored. In this study, data collected monthly at cow and farm level between 2016-2019 as part of the Swedish milk and disease recording system were analysed. Seasonal trends, confirmed using generalised additive models, showed increased somatic cell counts (SCC) and reduced fertility measures during the summers. To understand variation between farms and farmer perceptions of the impact of season on udder health and fertility of Swedish dairy cows, in-depth interviews with 18 dairy farmers were undertaken. Farmers perceived and acted differently on problems related to SCC and fertility, suggesting that the lag between events and consequences affected farmer perception and actions. In addition, farms showing large deviations from the national average were observed, emphasising the need to consider each farm's unique circumstances.

INTRODUCTION

Extreme weather events are increasing globally because of climate change, especially droughts and heat spells (IPCC, 2021). This poses many challenges to animals and humans from different perspectives. One such challenge is maintaining a normal body temperature, i.e., avoiding heat stress, during these events (Fabris et al., 2019). In 2018, Sweden experienced the hottest summer recorded (since 1951), and the negative impact on dairy cows was highlighted in the media (SMHI, 2021).

There is a tremendous biological cost to heat stressed cows. They will increase their respiration rate and reduce their activity, as well as decrease their milk production (Polsky and von Keyserlingk, 2017). Heat stress also leads to alterations in physiological parameters, such as the immune response (Turk et al., 2015; Bagath et al., 2019), and an increased incidence of clinical mastitis has been observed during hot summers (Vitali et al., 2016). In addition, heat impacts fertility, for example through disrupted follicular development or embryonic losses, as well as indirectly by disrupting oestrus cycles and reducing the expression of oestrus behaviour (Sammad et al., 2020).

Many studies have used the temperature humidity index (THI), combining humidity and temperature, and have suggested that cows can experience heat stress from THI between 65-

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70 (Pinto et al., 2020). In Sweden the maximum average THI reaches well above 65 during "normal" summers and in the summer of 2018, it even reached 80 in many parts of the country (SMHI, 2021). A recent study has shown that temperatures from 20 degrees Celsius are associated with reduced milk production and increased economic costs to the Swedish dairy industry (Ahmed et al., 2022). While it is clear that heat can pose problems in dairy production in Sweden, the biological costs related to fertility and SCC have been less explored. An important difficulty in evaluating the connection between heat stress and biological costs in Swedish dairy herds are the changes in management that occur during the warmest months. Swedish legislation demands that dairy cows are provided with access to pasture during the time of the year with the warmest temperatures (i.e., spring/summer). This means that estimating the impact of heat stress by correlating the differences observed with THI, or comparing the summer and winter season, using for example summer to winter ratios (Flamenbaum and Ezra, 2007), risks being confounded by changes in management.

Moreover, little is known about how farmers perceive these events and the potential impact on their animals. Identification of a problem is the first step towards acting up on it (Janz and Becker, 1984). Thus, understanding how farmers perceive the biological costs related to season and heat stress is essential for developing advice that will lead to real impacts on farms. In this study we use a seasonal angle and a mixed methods approach to explore national trends and farmer perceptions of adverse impacts on udder health and fertility during summer.

MATERIALS AND METHODS

Our study follows an explanatory mixed methodology design (Creswell and Clark, 2017). This means that the analysis and results of the quantitative component (i.e., records from the cow and weather databases) were understood and validated in light of the qualitative component of the study (in-depth semi-structured interviews with Swedish dairy farmers). Applying a mixed methods design allows researchers to explore diverse perspectives and uncover relationships that exist in multifaceted research challenges. Here the qualitative component focused on deep and detailed descriptions of experiences, actions, practices, activities and interpersonal interactions from fieldwork, and was incorporated in the analysis because it was considered important for the interpretation of the meaning of a situation (i.e., extreme weather events) from the decision maker (i.e., farmer).

Overarching study population and measures for descriptive and quantitative analysis

This study includes data from the Swedish milk and disease recording scheme (SMDRS) and the Swedish Metrological and Hydrological Institute (SMHI) from 2016 to 2019. Details on data used can be found in Ahmed et al. (2022). In brief, the study includes 1465 farms participating in the SMDRS. Estimated bulk tank somatic cell counts (BMCC) were retrieved from monthly test-day milk records. To study seasonal deviations during the years, the monthly deviation in BMCC from the yearly herd average BMCC was calculated for each month.

The SMDRS also collects fertility parameters like inseminations and calvings. Based on this, a composite reproductive performance indicator was calculated: the pregnancy rate (PV30) within 30 days after the herd-specific voluntary waiting period (Löf, 2012). Thus, this included both the biological ability of the animal and the reproductive management on the farm. The herd specific voluntary waiting period (VWP) used in the calculations was estimated by identifying number of days after calving at which 10% of the animals had been inseminated.

The PV30 at the herd level was calculated for each calendar month, followed by yearly farm averages for PV30, and then the monthly deviation of each farm from this average was calculated. Successful pregnancies were identified as insemination periods followed by a calving or a confirmed pregnancy check. To allow for time to identify the following calving, the data from 2019 were used only to identify calvings following insemination, and were not included in the analysis of farm deviations from the PV30.

Descriptive and quantitative analysis was performed in R (R Core Team, 2018). Distribution of seasonal shifts in energy corrected milk production and BMCC were plotted using ggplot2 (Wickham, 2016). Seasonal trends in farm deviations from the yearly farm average in BMCC were calculated for each year (2016-2018). Significance of seasonal trends in deviation from farm average (%) were explored using generalised additive models (Wood, 2011). Month was modelled with a cubic cyclic spline. Interactions between month and year were explored and included when significant. Otherwise, year was included as a random effect. Herd was included as a random effect in all models.

Qualitative component - Recruitment of farms for in depth interviews

Farmers for in-depth interviews were purposely recruited to attain a theoretical maximal variation of experiences of the impact of yearly heat events on SCC and fertility in a dairy herd. Hence, participants that showed an increase in SCC or a decrease in fertility were actively recruited. Likewise farms that did not show such variation during summer months were also selected. Data from the overarching study population were used to estimate the impact of summer on SCC and fertility at the farm level. This was estimated by calculating the average summer deviation in SCC and fertility estimates (PV30) from the yearly farm average for 2016 to 2018. This allowed the generation of a list of 100 farms with the smallest and largest deviations in SCC as well as the 100 farms with the smallest and largest deviations in PV30. Farms from the list were purposively recruited via the leading dairy farm advisory company VÄXA Sverige, which has a well-established trust relationship with dairy farmers, to achieve a mixed sample of experiences and geographical representation (Fig. 1). Informed consent was gained from all participating farms prior to the interview process.

Interviews and qualitative analysis

Farm interviews were done in Swedish either on-farm face-to-face (n=11), via video conference (n=2) or over the phone (n=5) during spring 2021 by two of the researchers (LMT and GOA). Interviews were structured around the following topics: a) the general health situation of the farm, b) their definition/experiences of extreme weather, c) description of any on-farm challenges associated with weather events and d) animal challenges related to the summer season. Lastly, e) they described the current/future perspectives on how to cope with the challenges. All interviews were voice recorded and transcribed verbatim. Only representative phrases to illustrate the identified themes were translated into English. The transcriptions were open-coded by GOA and LMT using a Reflexive Thematic Analysis (Virginia Braun and Victoria Clarke, 2019; Byrne, 2022;), meaning coding was done around central themes arising from the data, curated emphasising the relevance to the research questions.

Upon revision with the legal department of SLU and according to the Swedish Ethical Authority, the study did not require a special provision or permit according to Swedish law (SFS-2003:460). The rationale being that no sensitive personal information was collected.

Nonetheless, all participants were informed of the objectives of the project and requested consent to take part in the interview process. The participant had the means and a point of contact to withdraw from the process at any time if they wished to do so.

Figure 1. Geographical location of the 18 farms participating in the in-depth interviews. Locations are an approximation so as to maintain the anonymity of participants

RESULTS

Of the several biological costs associated with the hot season, farmers expressed a clear link between hot spells and SCC. However, while all farmers recognised this impact, their perceptions of control differed, leading to either pro-active vs. reactive ways of managing the negative impact they identified on cows. Thus, on one hand we had farmers that expressed the situation as an "unpreventable" effect of summer:

"Yeah, It's inevitable…'it's ... summer cells [referring to SCC]'we've had that as our big dilemma" (F.111842)

Others discussed an active engagement in the challenge of keeping cell-counts down by naming the many reasons why this could happen as well as potential areas of action associated with varying degrees of success.

"Interviewer: You say'it's hard to keep low cells during the summer and feed hygiene was one reason. What else?
Farmer: There are a lot of small streams. We get a little less traffic in the summer, always have. Usually drop down there to 2.3-2.4 milk'ng's per day. And it goes without saying, the [milking] interval gets longer ...t'at's where you get the big problems [referring to SCC] or challenges with it" (F.115843)

At the national level the negative impact of summer described by farmers was observed as a shift in the density of farms with higher BMCC during the summer months (Fig. 2). However, the effect of summer was mainly observed as a shift in the population of farms with higher BMCC also in the winter. The distribution of farms with lower BMCC in the winter showed smaller differences throughout the year (Fig. 2). Yet, August 2018, which was unusually warm, appears to break this general pattern as the distribution was also seen among the farms with low BMCC shifts.

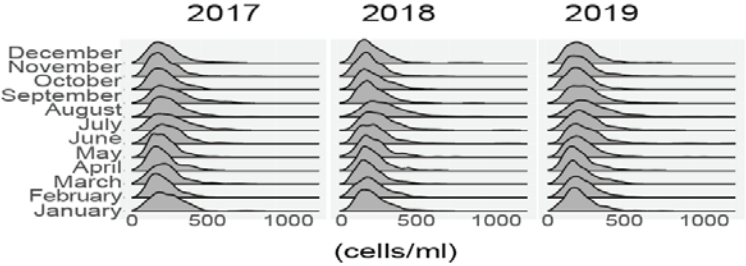

Figure 2. Monthly estimated somatic cell counts in bulk tank milk of the 1437 farms participating in the Swedish Milk and Disease Recording System between 2017-2019. (Data from 2016 has been omitted for visual reasons)

The estimated seasonal deviation of BMCC from farm averages is presented in Fig. 3. As suspected from the distribution of SCC, the deviation increased during the summer months with a peak in August. Interestingly, this deviation differed slighlty from the average THI during summer (which peaked in July).

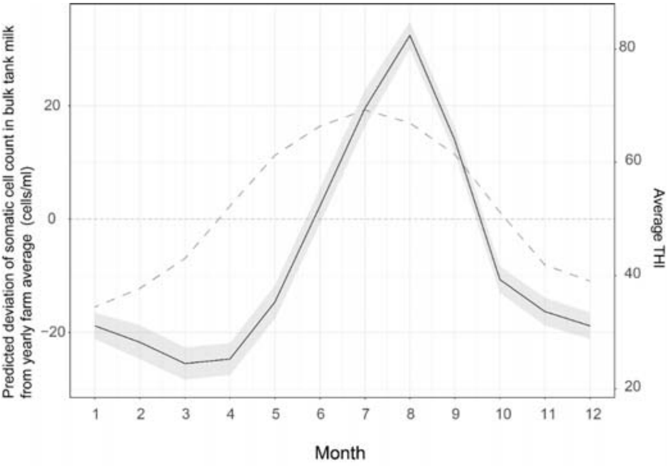

Figure 3. Predicted proportional deviation from farm yearly average of somatic cell counts in bulk tank milk according to generalized additive model by month (p<0.001). Shaded areas represent 95% confidence intervals and the dashed line represents average temperature humidity index in Sweden

While farmers easily connected increased SCC with heat and season, a negative impact on fertility was only acknowledged after thoroughly targeted elicitation. Here farmers described and confirmed problems associated with poor oestrus expression in cows, linked to difficulties in getting cows pregnant during the summer.

> *"The number of inseminations per pregnancy went up a lot [referring to summer of 2018]. Then we had... Well, specifically heifers that did not show any signs of heat at all. But we bought some new material, then. You want to avoid that, but that's what we did anyway." (F111509)*

> *"No, they don't show any heat [referring to summer]. And it is harder to get them pregnant when it is very hot." (F111223)*

A national pattern of fewer successful inseminations (leading to confirmed pregnancy or calving) during summer was supported by looking at farm deviation in the fertility indicator PV30 and showed a seasonal trend ($p<0.001$) in the pregnancy rate in dairy cows (excluding heifers) (Fig. 4). This trend suggested that farms are less successful in achieving pregnancies in animals calving from March to June (optimally inseminated from May to September). There was also a significant interaction between deviation and year, suggesting that the deviation was greater during the summer of 2018.

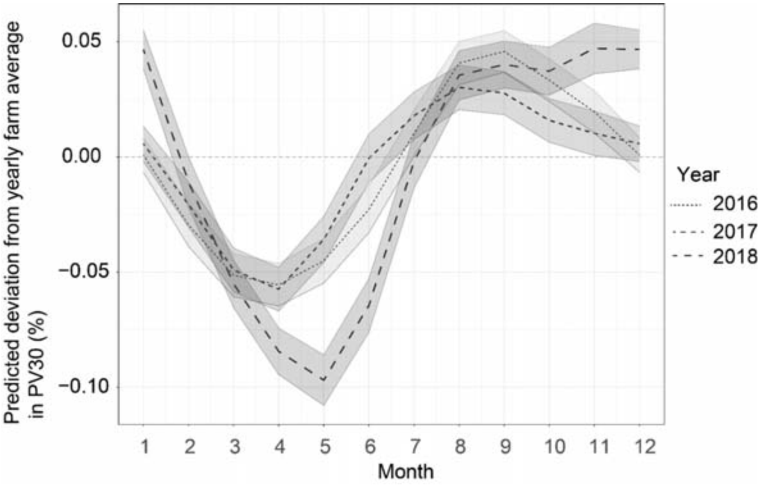

Figure 4. Predicted seasonal deviation (%) from the farm average pregnancy rate within 30 days after the voluntary waiting period (PV30) according to a generalised additive model by month ($p<0.001$). Shaded areas represent 95% confidence intervals

The calving distribution between 2016-2018 (Fig. 5) suggests a seasonal pattern where a higher number of cows and heifers are pregnant after inseminations performed from September to March (i.e., not during the summer). This shift has a direct effect on the work-flow and processes on the farms by causing unevenly distributed calvings. Farmers see these "unevenly distributed calvings" and describe them as a challenge that is identified too late to act upon, and thus it is solved reactively. However, as for immediate fertility issues, the problems with unevenly distributed calvings were not always explicitly formulated in relation to questions about fertility and seasons/heat, but instead was something mentioned when describing general farm challenges or particularly challenging periods. This reinforces the idea that fertility is not linked as a consequence of weather that needs to be acted upon.

"... you get out of that swing [referring to calving pattern], you might only have two or three calvings one month, and then the next month you might have 20. And that means we can't have a full stocking, we get disruption... works much better with the flow, with calves and weaning everything becomes much easier" (F.111509)

"No, I don't experience any [referring to fertility/health issues] as a problem, but a little uneven calving ... When there are 30-35 calvings in a month, and then there are only 10 the month after... That's a challenge. Last autumn and up until the turn of the year here now, we had such a huge peak with a lot of calvings. And then you get to a different infection pressure in calves..." (F.111223)

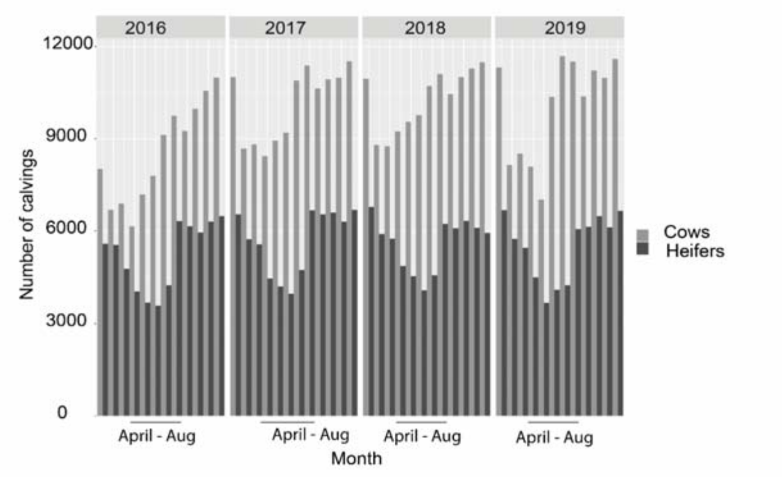

Figure 5. Number of calvings recorded in the Swedish milk and disease recording scheme between January 2016 to December 2019

While the farmers did not clearly connect heat with reduced fertility during the summer, they did reflect on seasonal patterns in calvings, and the particular difficulties with inseminating heifers at pasture during the summer were highlighted.

"You should have the same number of calvings every month all year round. We don't really have that... Well, it's better to have a few cows in the summer than in the winter. But the best thing would be to have full all year round. But then it has to do with this then that you are inseminating less ... Fewer heifers get pregnant from May to October or September " (F.115939)

In Sweden, heifers are let out to pasture in early spring, often on lands located some distance away from the farm which makes practical work with inseminations difficult. Observing the number of calvings at the national level (Fig. 5) shows a recurring seasonal trend, where the number of heifers calving starts to drop consistently from February or March to August every year.

DISCUSSION

The summer season was associated with a negative impact on SCC which is consistent with the patterns observed in other temperate regions, for example the Netherlands (Olde Riekerink et al., 2007). Similarly, patterns of seasonal variation in fertility (higher heat detection rates, conception rates and pregnancy rates during winter) have been observed in the USA, where the degree of impact varied between regions experiencing different THI-levels during the summer (Guinn et al., 2019). In this study no clear regional differences were observed but the distribution of heat impact on SCC varied between farms. The uneven impact on SCC indicates that there are farms that manage to avoid negative consequences, perhaps either by management strategies or by having more robust animals.

The farmers participating in the in-depth interviews mainly discussed management strategies related to feed hygiene and pasture. Farmers with automatic milking systems specifically talked about maintaining cow traffic (milking intervals and number of visits to the robot). Going into detail about the efficacy of different management routines is outside the scope of this study but would be very interesting to look into in the future, and to provide advice on how farmers may avoid negative consequences during the summer. However, considering that August 2018, which was an unusually hot summer month, was associated with an increased proportion of farms being impacted, suggests that some of the measures that are currently being successfully applied will not be enough. Thus, Swedish farmers may also need to be inspired by warmer countries and be open to new solutions that are currently not in use in Sweden.

It is also interesting to note that the peak in deviation to average BMCC comes later than the peak in average THI. This may suggest an accumulative effect of the warm period, or indicate that factors other than average THI play a role. For example, the nights in August may not cool down in the same way as they do in early summer. However, it could also indicate that the increased SCC during the Swedish summer is more closely affected by management, e.g., pasture or changes in hygiene practices during this time.

The Health Belief Model (HBM) is a model used to explain adoption of disease prevention strategies and has been suggested to be relevant when explaining adherence to advice on dairy herd health management, udder health and other disease control strategies in Sweden and other European countries (Jansen and Lam, 2012; Ritter et al., 2016; Svensson et al., 2019).

According to HBM, farmers perceptions of the threat and their belief in the effectiveness of preventive behaviour affects how they respond to the threat (Janz and Becker, 1984). The perception of the threat includes the susceptibility and severity of the threat. While all farmers were aware of the threats of summer on SCC, their idea of their susceptibility to changes in SCC varied. While some expressed that a negative impact was inevitable, others expressed ideas for possible reasons and ideas for how to avoid the consequences. Thus, it may be important for advisors to adapt their communication depending on which type of farmer they are discussing with.

While also being aware of the negative impact on fertility, our conversations with farmers suggested their perception of the seasonal impact was less clear than that for the SCC issue.

This is possibly due to the difference in time between these consequences. Whereas the increase in SCC is relatively immediate, the consequences on fertility do not materialise until long after the summer and may therefore be more difficult to perceive and link to the summer weather. An inability to see the consequences may impact the perceived benefits of acting to control a threat, which in combination with perceived barriers are an important part of how effectiveness of preventive measures are perceived (Janz and Becker, 1984; Svensson et al., 2019).

There were some differences in how farmers perceived barriers related to fertility in heifers and older cows. Part of the reason for heifers not being inseminated was practical difficulties related to them being on pasture, while the decrease in older dairy cows was mainly related to difficulties in observing heat or achieving pregnancy. This is a potential reason for the patterns in the national data on calvings where the calvings in heifers consistently followed the same pattern every summer (influenced by management) whereas the older dairy cows varied more between years (influenced by THI). The variation in perceived barriers may also affect what preventive measures farmers choose to focus on when trying to address the problems of unevenly distributed calvings.

Good reproductive performance does not only enhance management control but is also an important factor for herd profitability (Gröhn and Rajala-Schultz, 2000). Increasingly warm summers may pose even bigger challenges for maintaining dairy cow fertility. Awareness of seasonal trends on the farm and their long term consequences are important to highlight in order to prevent further escalation, as well as encourage preventive work to minimise the effects. Therefore, we propose increasing awareness of the role of uneven calving patterns, and looking into tools that visualise long-term effects on fertility as a result of heat stress to improve future on-farm resilience.

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DISEASE PRIORITISATION: MEETING THE NEEDS OF ANIMAL DISEASE DATA USERS

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SUMMARY

The Global Burden of Animal Diseases (GBADs) aims to provide information on animal diseases by species, production system, type of farmer and consumer, gender, geographical region and time period. A survey of disease information users was conducted to understand their current use of data and prioritisations, as well as their felt and unfelt needs for different, better information. It was found that most respondents used the data to present evidence for disease management, policy development and proposal writing. Few used it for prioritisation or resource allocation, and less than half were aware of the use of decision support tools (DSTs). Most respondents considered current disease metrics inadequate and animal health decision making non-transparent and unfair. The study concluded that improved disease data would lead to better evidence-based decisions and policies, and clients would need support (including DSTs) to optimally use disease information.

INTRODUCTION

Disease is a major constraint to animal production and health, and can have serious public health, economic and welfare impacts (Howe et al., 2013). Disease prioritisation is the hierarchical organisation of a list of pathologies based on their impacts, and is used for allocating resources and improving human, animal and ecosystem health. While human health disease burden has been extensively studied, information on the burden of animal disease is in its infancy. Data on mortality and morbidity of notifiable diseases is reported annually to the World Organisation of Animal Health (WOAH), but data are often inaccurate, especially from low- and middle-income countries (LMICs) (Grace et al., 2012). This has led to the development of a plethora of approaches to understand animal disease burden and prioritise diseases, mostly using multicriteria decision analysis, Delphi questionnaires and bibliometrics (Brookes et al., 2015).

Most disease prioritisations follow a generic process of identifying diseases, listing criteria on which to assess diseases, weighting criteria, scoring disease against criteria, and ranking diseases based on criteria scores. A recent systematic literature review identified more than 80 animal disease prioritisations studies since 2,000 (ENETWILD consortium, 2022). Multicriteria decision analysis was the most common approach (58% of prioritisations),

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followed by Delphi (24%), with questionnaires, bibliometrics, qualitative algorithms, multi-dimensional matrix used by several studies, and some using an unique framework.

While disease prioritisations often develop their own methodology, or adapt one from another study, a few frameworks have been more extensively used, such as the One Health Zoonotic Disease Prioritisation Tool, used mainly in Africa but also in China and Jordan (Kheirhallah et al., 2021; Wang et al., 2021), and the World Organisation of Animal Health (WOAH) Phylum tool used to prioritise transboundary animal diseases (Mpouam et al., 2021).

However, disease prioritisations are often limited by inconsistency of approaches, reliance on imperfect information, biases and limited information on validity and reliability (Perry and Grace, 2009; Brookes et al., 2015). To help address this, the Global Burden of Animal Diseases (GBADs) was launched in 2019 to develop a systematic process for measuring the impact of animal diseases. A global survey of leading animal disease data users was conducted to understand their current use of animal disease data and the felt and unfelt needs for more and better data on animal disease. Global Burden of Animal Diseases is expected to contribute to more useful and accurate prioritisation of animal diseases, and ultimately to improve human, animal and ecosystem health (Rushton et al., 2021).

MATERIALS AND METHODS

Identification of respondents

The views of various animal health and food safety experts involved in disease prioritisation and resource allocation were assessed using mixed methods (involving an online questionnaire survey and key-informant interviews). Respondents were selected from databases developed by the International Livestock Research Institute (ILRI). Selection criteria included expertise, geographical balance, sectoral balance, and likelihood of responding. Individuals were contacted by email and invited to participate.

Data collection

A questionnaire was developed and went through several rounds of refinement and pre-testing. The final instrument was formatted using the SurveyMonkey® online data collection platform. The questionnaire asked about the affiliations of respondents, awareness of animal different disease prioritisation processes (ADPPs), use of data, perception about different issues related to animal health decision making, and the budget allocation for animal health activities. The respondents were also asked regarding their level of trust (high, medium or low) in expert opinion for making decisions regarding animal health (e.g., estimating the burden of disease). The last part of the questionnaire contained the opinions of respondents about the existing decision-making process. The list of ADPPs was based on experience and through consulting various literature, and were presented as multiple choices in the online questionnaire. Tools were operationally defined as software, apps or online, or paper-based processes that can support a decision in resource allocation to animal health and related activities.

Data analysis

Descriptive statistics were calculated and presented in table or graph forms and statistical analysis conducted using chi squared or t-tests in Stata (StataCorp, 2022 version 17.0) or R (R Core Team, 2021 version 4.1.1.). The information was disaggregated depending on the whether the activities of the institutions for which the respondents work targeted LMICs or high-income countries (HICs) or both (irrespective of the country the participant lived in). For open-ended questions regarding the purposes of animal health data use, the responses were categorised into different categories (thematic areas) and the frequency tabulated accordingly.

First, second and third disease priorities were combined by assigning each a weight of one and summing them, and then by assigning a more realistic, but still arbitrary, weight of four for first priority, two for second priority and one for third priority and summing these. Animal diseases were next categorised as transboundary or endemic following the definitions of Clemmons et al. (2021), but excluding transboundary diseases that are zoonotic. Other animal diseases were considered endemic (excluding significant zoonoses). Zoonotic diseases were classified as emerging following the tripartite definition (Anonymous, 2004). Foodborne zoonoses were those considered as priority foodborne pathogens by the World Health Organization (WHO) (Havelaar et al., 2016). Other zoonoses were categorised as "neglected" and were cross-checked with WHO lists of neglected zoonoses and neglected zoonotic tropical diseases and literature on neglected zoonoses (Welburn et al., 2015). We classified diseases that were both an animal disease and a zoonoses as zoonoses, because the major economic and health impacts of zoonoses are due to their zoonotic character (World Bank, 2010).

First, second and third disease category priorities were combined as described for diseases. Next, we used rank ordered logistic regression in STATA to combine the first, second and third disease priorities of the respondents and to test for statistical difference between them. We conducted hierarchical cluster analysis using Ward's method in R to divide data users into groups based on feature similarities in order to provide insight into client segmentation in the market for GBADs data.

Ethical approval

Ethical approval was sought and granted by the Institutional Research Ethics Committee (IREC) of International Livestock Research Institute (ILRI) (Ref: IREC2021-48). The questionnaire was anonymous and no personal or country specific information was collected.

RESULTS

Response rate and respondent characteristics

E-mail invitations were sent out to 1485 potential respondents. A total of 791 (53%) e-mails were opened, 260 (33%) respondents replied and 185 (24%) completed all questions. Nearly two-thirds of respondents (65%) were affiliated to institutions working in low- and middle-income countries (LMICs), around a fifth affiliated (21%) to institutions working in high income countries (HICs) and the remainder (14%) to institutions which served LMICs and HICs. Experts were drawn from ten different disciplinary backgrounds, but just over two thirds of respondents were veterinarians. Human health disciplines constituted 14% of respondents, agricultural disciplines 12% and socio-economic disciplines 6%. Most respondents reported they worked in the public sector, followed by academia and only around 10% were in the private sector.

Disease priorities

Seventy-six individual diseases or groups of diseases were ranked as first, second or third priority by respondents. Among these, only 38 diseases were mentioned more than once (in any priority), and 16 diseases (22% of the total) accounted for 80% of all mentions. Of these top 16 diseases, six were transboundary animal diseases (TADs), six were zoonotic diseases (two each of neglected zoonotic diseases (NZD), foodborne diseases (FBD) and emerging zoonotic diseases (EZD)) and the remaining four were endemic livestock diseases (ELDs). Giving different weights to the different priorities (more to first priority disease, less to third priority disease) did not greatly influence the prioritisation. However, rabies and anthrax received relatively more placements in first position (Table 1).

Table 1. The top ten priority diseases across first, second and third choices weighted and unweighted by order of choice

	Unweighted	Weighted
1	Foot and Mouth Disease	Foot and Mouth Disease
2	Pest des Petits Ruminants	Pest des Petits Ruminants
3	Rabies	African Swine Fever
4	African Swine Fever	Rabies
5	Avian Influenza	Avian Influenza
6	Brucellosis	Brucellosis
7	Anthrax	Bovine (Tuberculosis)
8	Newcastle Disease	Newcastle Disease
9	Rift Valley Fever	Anthrax
10	Bovine (Tuberculosis)	Rift Valley Fever

In terms of disease categories, when all priorities were weighted equally TAD were considerably more important. Using weighted priorities did not much affect this, only instead of FBD having the same score as EZD it had a slightly higher score. Using rank ordered logistic regression allowed us to combine the first, second and third choices in a statistically more efficient way. This changed the order of categories with TAD over FBD over EZD over NZD over ELD. Only the difference between TAD and ELD was statistically significant.

Awareness of disease prioritisation processes

On average, participants were aware of 2.4 (range 0 to 8) Animal Disease Prioritisation Processes (ADPPs). The most widely recognised tool was the WOAH expert group ad hoc prioritisations, and just over half the participants were aware of the USA Centre for Disease Control (CDC) One Health Zoonotic Disease Prioritisation tool. Another 23 disease prioritisation tools were suggested of which three were mentioned twice.

Use of animal health and disease data

Respondents mentioned several purposes for animal health data. Top were: 1) for research, academic, publication, or official reports, 2) designing, implementation and surveillance of disease control, eradication, or prevention, 3) inputs for formulation of policy and/or strategy and its subsequent implementation, and 4) project proposal development (research, development, or business). Other uses included population estimation for vaccination, drug or vaccine development, and evaluation of global agricultural trade.

Satisfaction with current disease prioritisation processes

The survey indicated dissatisfaction with the current methods and processes of animal health decision making. Only 41% of the participants considered that animal health decision making was based on evidence, while less than a third felt the animal health decision making process was fair (31%) and available globally in a (27%) user friendly manner. Around four fifths (77%) felt the decision-making process was not transparent. Dissatisfaction was highest with animal health metrics: only 5% finding them sufficient.

Market segmentation for animal disease data users

The cluster dendrogram assorted users into three broad categories (Fig. 1). Cluster one was characterised by experts from LMICs who were more likely to work in the public sector, relied more on donor funding and were interested mostly in national data and less in regional or global data. Cluster two was characterised by participants with an affiliation to an institution with a global mandate or a high income country and were most likely to work in an international setting. The minority of respondents working in a private companies were clustered here. They were funded equally by donors and the public sector and were the cluster most interested in global data. The salient characteristic of the third group was that they were working in research or academia; their institutions mostly worked in LMICs with some work in HICs. They were the group with the most interest in sub-national data and the most reliance on donor funding.

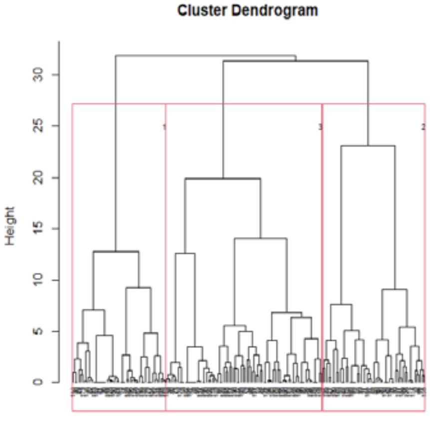

Figure 1. Cluster dendogram showing segmentation of animal disease data users

DISCUSSION

The viral diseases mentioned as a top priority by respondents are in line with many studies at global, regional or national levels being primarily TADs. Some of the TADs such as Newcastle disease, peste des petits ruminants, and African swine fever, highly pathogenic avian influenza and Rift Valley fever are emerging or re-emerging diseases (Myers, 2016; Torres-Velez et al., 2019).

Among the pre-listed prioritisation tools, a large proportion of the respondents (71.9%) were aware of the WOAH (formerly OIE) expert group ad hoc prioritisations for animal diseases. These are groups convened at the initiative of the Director General to provide expert advice. Several conduct disease prioritisation such as the two groups prioritising livestock diseases for which vaccines should be developed (WOAH, 2015). This is a straightforward process based on expert consensus of scores against criteria. The other disease prioritisation tool commonly known to the respondents was the CDC One Health Zoonotic Disease Prioritisation (OHZDP) tool, and this was mentioned by 55.7% of the respondents. The OHZDP is a semi-quantitative tool intended especially for the situation where quantitative data are scarce (Rist et al., 2014). The tool has been recently used in several countries and regional economic blocs for prioritisation of zoonotic diseases.

Various uses for animal health data were mentioned with relatively more use of data for research and publications, designing disease control and prevention programmes, and the formulation of generic policy and strategy. Only a few respondents mentioned explicitly the use of data for resource allocation and priority settings related to animal health. Less than half (42.5%) of the respondents were aware of DSTs in animal health. Although DSTs are increasingly used in animal health (Gibbens et al., 2016; Dewar et al., 2021) their use encounters challenges such as variability in data sources related to scale, completeness, timeliness and lack of end user preferences (Beard et al., 2018).

Most experts considered animal health information insufficiently available and not evidence-based, and most thought that animal health decision making was non-transparent and not fair. Satisfaction was lowest with metrics, reflecting the absence of a consensus metric that can be consistently used to measure the multiple burdens of animal disease. This is in contrast to human health where the existence of a widely accepted metric for measuring disease impact, the Disability Adjusted Life Year, the collection and availability of much more health information, and decades of investment in developing burden of disease estimates has resulted in the continuous improvement in accuracy, granularity and usefulness of information on disease impact, allowing better prioritisation and use of resources (Murray, 2022).

This survey gives baseline information about the opinions of experts working in the areas of animal health and related sciences. It will be used for an in-depth analysis of the process of disease prioritisation and animal health decision making in the development of decision support tools for disease prioritisation in the GBADs initiative.

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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	van Klink
2002	Cambridge	Wood & Newton
2003	Warwick	Green
2004	Martigny	Stärk
2005	Nairn	Gunn
2006	Exeter	Peeler
2007	Dipoli	Virtala & Alban
2008	Liverpool	Pinchbeck & Robinson
2009	London	Verheyen & Pfeiffer
2010	Nantes	Fourichon & Hoch
2011	Leipzig	Thulke & Lange
2012	Glasgow	Parkin & Others
2013	Madrid	Martínez-López & Vargas Alvarez
2014	Dublin	More & Collins
2015	Ghent	Mintiens & Dewulf
2016	Elsinore	Nielsen & Halasa
2017	Inverness	Gunn & Reeves
2018	Tallinn	Viltrop
2019	Utrecht	van Schaik
2020	Online virtual conference	Barrett
2021	Online virtual conference	Vergne
2022	Belfast	Menzies

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
2014-'15	K. Mintiens
2015-'16	H.H. Thulke
2016-'17	A. Lindberg
2017-'18	L.R. Nielsen
2018-'19	M.L. Brennan
2019-'21	K.M. McIntyre
2021-'22	G. van Schaik
2022-'23	P.A. Robinson

EXECUTIVE COMMITTEE 2022-2023

P. Robinson (President), G. van Schaik (Senior Vice-President), D. Brodbelt (Junior Vice-President), F. Dórea (Honorary Secretary), E. Fischer (Honorary Treasurer).

Honorary Auditors: K. Howe & K. Verheyen

LIFE MEMBERS

J.M. Booth (deceased), 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 (deceased), L.E. Green, K.S. Howe, M.E. Hugh-Jones, W. Martin, D. Mellor, F. Menzies, K. Morgan, A. Paterson, S.W.J. Reid, A.M. Russell, M.V. Thrusfield, J. Wilesmith,

PLENARY TALKS

Year	Gareth Davies Lecture	Conference Opening Plenary
2023	Francois Roger Contribution of epidemiology to the sustainable development of the Global South	Marius Gilbert Sciences at the policy-communication nexus during the COVID pandemic
2022	Julie Fitzpatrick Science based policy – Not *just* about animal disease!	Robert Huey The role of vets on the national stage
2021	Christine Fourichon Controlling infectious diseases: how does the interplay between field problems and epidemiological research lead to success?	John Edmunds Modelling to support policy in real time: insights from the COVID-19 pandemic
2020	Jonathan Rushton How GBADs will link to clinical practice and veterinary epidemiology	Matthew Stone The policy perspective and science in an evidence-based policy structure Sam Thevasagayam A funder’s perspective of disease studies
2019	Simon More Perspectives from the science-policy interface	Marion Koopmans To jump or not to jump: viruses at the human-animal interface
2018	Klaus Depner African swine fever: Lessons learned about the epidemiology, politics and practical implementation of control measures	Päivi Rajala-Schultz Veterinary epidemiology at the intersection of livestock disease, production and animal welfare
2017	Theresa Bernardo TRENDS: Technology, Research, Epidemiology, Networks, Data & Surveillance	Tine Hald Source attribution: Translating science into public health action
2016	Bernhard Url The foundation of science-based risk assessment for decision support on food safety and animal health in EU	Mirjam Nielen Evidence-based veterinary medicine needs clinical epidemiology
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

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Please enclose the membership fee (£60 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 Egil A.J. Fischer
Department of Population Health Sciences
Faculty of Veterinary Medicine
Utrecht University, Yalelaan 7, 3584 CL Utrecht
The Netherlands

TEL +31 30 253 1119
Email: treasurer@svepm.org.uk

Please turn over

INTEREST GROUPS

Please tick appropriate boxes to indicate your interests:

- ☐ Analytical Epidemiology (Observational Studies)
- ☐ Quantitative Epidemiology & Statistical Techniques (Incl. 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