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Use of fever detection in combination with thoracic ultrasonography to identify respiratory disease, and compare treatments of antimicrobials and NSAID: a randomised study in dairy calves

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ABSTRACT

Background This study explored the combined use of fever detection and thoracic ultrasonography to identify calves with early onset bovine respiratory disease (BRD). Thoracic ultrasonography was then used to assess the efficacy of antimicrobial and non-steroidal anti-inflammatory drug (NSAID) treatment for early onset BRD through a randomised study design.

Methods Calves were recruited from a single dairy farm in the UK, and fitted with a TempVerified FeverTag, which was activated when a calf developed fever (a temperature of 39.7°C for six hours). On identification of fever, a Wisconsin calf score was used to provide a diagnosis of BRD by exclusion of other causes. Calves were randomly assigned to experimental groups; group 1 (NSAID) received flunixin meglumine, group 2 (antimicrobial) received florfenicol, group 3 (both) received both drugs. A thoracic ultrasound was conducted within 48 hours of fever detection, and again 14 days later to assess lung pathology.

Results A total of 152 calves were recruited, with a relative BRD prevalence of 49 per cent (74/152). Thirty-two calves required a secondary treatment (due to continued fever), causing exclusion from statistical analysis of the change in ultrasound score and resulting in the study being underpowered for detecting statistical significance. Initial thoracic ultrasound scores were very low, with 70/74 calves scoring either 0 or 1, indicating few comet tails and no lung consolidation was seen and potential overdiagnosis of BRD. For assessment of therapy efficacy, no effect of experimental group was detected on average daily growth rates (mean 0.85 kg/day, P=0.89). Calves also displayed very few clinical signs at the time of fever detection. These factors combined suggest a high rate of false positive identification (low specificity) for BRD through fever detection alone. Calves given the NSAID only were more likely to require repeat treatments due to fever recurrence (OR=3.10 (95 per cent CI 0.86 to 11.15), P=0.083). Also calves affected by their first case of fever at an older age (21 v 28 days old) were less likely to go on to have further fever episodes (OR=0.95 (95 per cent CI 0.90 to 0.99), P=0.026).

Conclusion This study demonstrated calves given only an NSAID at occurrence of fever due to BRD may be more likely to require repeat treatments throughout the preweaning period. The use of fever detection alone for BRD indicated a low specificity for definitive diagnosis as shown by the low thoracic ultrasound scores and lack of clinical signs. The study was underpowered to assess the ultrasonic effects of the different treatment protocols on lung pathology.

INTRODUCTION

Thoracic ultrasonography has been a key diagnostic component in research and referral hospitalisation cases for a number of years, with an increasing utilisation in first opinion practice. Most vets now carry 7.5 MHz linear rectal probes, and their shape allows good diversification for use between the ribs for thoracic ultrasound. This technique provides a non-invasive method to identify the area and depth of affected lung tissue in both clinical and subclinical bovine respiratory disease (BRD) cases[1] with a reported 89 per cent sensitivity and 95 per cent specificity.[2] However, it is not able to identify lung lesions located deep to the pleura,[3] so limiting the identification of some lung lesions.

Detection of BRD is still challenging for calf rearers, despite high reported prevalences on UK farms of up to 61.9 per cent.[4] The insidious onset of the disease[5] and the variable success of pre-existing screening strategies such as calf scoring for clinical signs,[6] combined with poor sensitivity of 56 per cent for farmers' ability to detect BRD[7] have meant this disease remains an important and costly problem to the industry.

There is now an improved understanding of the need for early identification of calves infected with respiratory pathogens before the development of clinical signs, with calves experiencing subclinical BRD demonstrating

reduced daily weight gain[8] and an increased likelihood of going on to develop more severe clinical signs. There are also long-term implications for subclinical BRD such as decreased milk production and reduced reproductive performances.[9 10] This is due to physiological changes in the lungs that can be visualised by ultrasound, with influx of cellular infiltrates and debris creating areas of consolidated lung.[11] In addition to detection of these subclinically affected cattle, application of adequate treatment is necessary, but that requires specific and accurate identification to prevent overuse of antimicrobial treatments on false positive cases.

Provision of non-steroidal anti-inflammatory drugs (NSAID) has been advocated as an ancillary therapy for respiratory disease[12] due to their ability to reduce the pathological effects of respiratory inflammation.[13] Use of flunixin meglumine has demonstrated a benefit for treatment of older calves with moderate respiratory illness and clinical signs such as dyspnoea, resulting in a reduction in lung consolidation on post mortem.[14] Although NSAID usage in combination with antimicrobials have demonstrated some efficacy,[15 16] the pressure to reduce antimicrobial usage has led some practitioners to use NSAID as a standalone treatment. Previous studies that used NSAID alone indicated they may lead to increased odds of requiring additional or repeat treatments for respiratory disease.[17]

A way of identifying calves subclinically affected by BRD is through detection of fever, which is a key indicator of inflammatory and infectious processes, but lacks specificity due to its incitement by infectious processes other than BRD. An undifferentiated fever has previously been described as an indicator for BRD treatments,[18] with this premise used for previous work to investigate the effects of initiating therapeutic treatment early in the BRD disease course. These studies suggested that fever provides a sensitive method for early BRD detection, but it was difficult to robustly define the cause of the fever as being from BRD due to a lack of clinical signs.

This study aimed to explore the use of fever detection in combination with thoracic ultrasonography to identify calves with early onset BRD in a randomised clinical trial. The secondary objective was to assess the efficacy of antimicrobial compared with NSAID treatment for the undifferentiated fever, which was thought to be caused by BRD through a diagnosis of exclusion. The efficacy of the treatments was explored by both assessment of the resolution of fever, and any changes in inflammatory processes in the lungs identified via thoracic ultrasound.

MATERIALS AND METHODS

Animals

Calves were recruited from a single commercial Holstein-Friesian dairy herd in the South of England between February and August 2019. Calves were moved from a group calving pen to a large barn containing group pens within 24 hours of birth. Calves were initially housed in pens of five for a two-week period, and fed twice a day using a 26 per cent whey protein milk replacer, fed a total of 900 g/day at 150 g/l. After 2 weeks of age, the calves were moved onto an automatic milk machine in group pens of 20 calves, where they could consume milk replacer ad libitum for 4 weeks, and were then step weaned down over 4 weeks to be off-milk by 10 weeks of age. All calves had access to straw roughage and ad libitum concentrates. Calves were weighed at birth and within one week of weaning using a mechanical calf weighing crate (Bateman, UK), and this was used to estimate the average daily growth rate over the preweaning period. The weigh crate was calibrated monthly throughout the trial.

Fever detection

Each calf had a TempVerified FeverTag (Amarillo, Texas, USA) fitted into its left ear between one and three days of age. The FeverTag used an external ear canal temperature probe as a proxy for core body temperature, with the body of the tag clipping onto the ear. The purpose of the tag was to detect fever caused by BRD as described in previous studies.[4 17] The FeverTag was programmed to detect a six-hour sustained ear canal temperature of greater than or equal to 39.7°C, which then triggered a flashing LED light on the body of the tag—this was the method used for identifying a calf positive for fever. The calves were observed five times throughout the day for identification of activated FeverTags. The FeverTags had undergone quality-control testing as part of their manufacture, and had a temperature accuracy of ±0.1°F.

Treatment allocation and protocol

All calves born during the recruitment period (both heifer and bull calves) were randomly allocated at birth into one of three treatment groups. This was done by extraction of a numbered token from a bag by the researcher. This was carried out at birth to ensure that the farmer would be able to treat the calf immediately on enrolment without having to wait for the researcher to be present. Calves were eligible for enrolment into the trial until 10 weeks of age (when they were weaned). On detection of fever, a Wisconsin calf score (table 1) was conducted by the farmer (who received training from the researcher before the start of the study) to record any clinical signs and rule out other neonatal diseases that may be responsible for the fever (navel ill, joint ill, diarrhoea), therefore giving a diagnosis of BRD through exclusion. The scoring was done by the farmer before checking which treatment group the calf was in to provide blinding. Drugs were then administered by the farmer according to experimental group; calves in group 1 (NSAID) received 3.33 mg/kg flunixin meglumine topically (Finadyne Transdermal, MSD), group 2 (antimicrobial) received 40 mg/kg florfenicol subcutaneously (Nuflor Minidose, MSD), group 3 (both) received both 3.33 mg/kg flunixin meglumine and 40 mg/kg florfenicol. The calves remained in their groups for the whole study. Only a single dose of

Table 1 A description of the modified calf scoring point allocation system for assessing calf health

Points and description				
Clinical parameter	**0**	**1**	**2**	**3**
Nasal discharge	Normal, serous discharge	Small amount of unilateral, cloudy discharge	Bilateral, cloudy or excessive mucus	Copious, bilateral mucopurulent nasal discharge
Ocular discharge	Normal	Mild ocular discharge	Moderate bilateral ocular discharge	Heavy ocular discharge
Mental demeanour	Normal—bright, alert, responsive	Dull but responds to stimulation	Depressed, slow to stand or reluctant to lie down	Unresponsive to stimulation
Cough score	No cough	Induce single cough	Induce repeated coughs or occasional spontaneous cough	Repeated spontaneous coughing
Faecal score	Normal	Semi-formed, pasty	Loose, but stays on top of bedding	Watery, sifts through bedding
Naval score	Normal	Slightly enlarged, not warm or painful	Slightly enlarged with slight pain or moisture	Enlarged with pain, heat or malordorous discharge
Joint score	Normal	Slight swelling, not warm or painful	Swelling with pain or heat, slight lameness	Swelling with severe pain, heat and lameness

Adapted from the University of Wisconsin-Madison Calf Health Scoring system.[19]

flunixin meglumine (Finadyne Transdermal, MSD) was used as this was the licensed usage frequency for the product. A second Wisconsin calf score was conducted by the researcher at 14 days postfever detection for all calves in the study. The researcher was blind to the treatment group when carrying out the scoring.

Following provision of the initial drug, each calf was continuously monitored for the recurrence of fever by the FeverTags, as well as monitoring for development of acute or severe clinical signs by the farmer (the farmer was given training on identifying clinical signs before the start of the trial, and had a copy of the Wisconsin calf score available for reference). A repeat occurrence of BRD was classified as a case of fever detected greater than or equal to 14 days from the last treatment date. However, if the calf either had fever or developed clinical signs of respiratory disease within this 14-day period, the calf was given an additional secondary treatment which consisted of combined NSAID and antimicrobial treatment.

Thoracic ultrasonography was conducted on each calf by the researcher within 48 hours of enrolment into the study (fever detection using FeverTags). This time period was used due to logistical reasons related to restricted access to the ultrasound machine. The calves were then ultrasound scored again 14 days later.

In addition to ultrasound of the calves with BRD, a random sample of 35 healthy calves with no history of BRD also underwent thoracic ultrasonography to act as negative controls. These calves were randomly selected on a single day from enrolled calves present that had not yet experienced an episode of fever. Their ages ranged from 15 to 55 days, with an average age of 38 days.

A 7.5 MHz linear transducer was used to examine the lung areas. Briefly, calves were not shaved, but 70 per cent isopropyl alcohol applied to the thorax. The thoracic pathology was recorded in a categorical scoring system,[11] where the score 0 indicated normal aerated lung with no consolidation and none to few comet-tail (B-line) artefacts. Score 1 indicated diffuse comet tails but without consolidation. Score 2 indicates lobular or patchy pneumonia. Score 3 indicated lobar pneumonia affecting only one lobe. Score 4 indicated lobar pneumonia affecting two lobes. Score 5 indicated lobar pneumonia affecting three or more lobes.

Pathogen testing

A convenience sample of five nine-month-old calves were selected for serology to identify respiratory pathogen exposure. The calves had not received any vaccinations before testing. Three calves that had been affected by BRD and received treatment on the trial were sampled, and two calves that did not have a case of BRD were sampled for comparison. A tail vein blood sample was collected into a plain 7 ml blood vacutainer, and sent to a commercial laboratory (SAC Commercial) for serology against Infectious Bovine Rhinotracheitis (IBR), Parainfluenza 3 virus (PI3), Respiratory Syncytial Virus (RSV), Bovine Viral Diarrhoea Virus (BVDV), *Mycoplasma bovis* and *Histophilus somni*. It was not possible to test for exposure to *Mannheimia* or *Pasteurella* species.

Statistical analysis of results

A sample size calculation demonstrated that with a type I error rate of 0.05 and type II error of 0.2, 35 calves need to be recruited into each group in order to demonstrate a 30 per cent difference in the proportion of calves requiring repeat treatments for continued fever.

Data were analysed using SPSS (V.21, Lead Technologies, Chicago, USA). Associations between the treatment group, sex and daily liveweight gain, along with the effect on the change in thoracic ultrasound score was tested using analysis of variance (ANOVA). Calves were

Table 2 Description of calf distributions between the different experimental groups

Experimental group	Number of calves in group	Mean age of onset (days)	Ratio of bull:heifers	Number of calves requiring secondary treatments (therefore excluded from analysis)	Number of calves that died
Group 1 (NSAID)	24	22	11:13	11	1
Group 2 (antimicrobial)	23	25	11:12	12	0
Group 3 (NSAID and antimicrobial)	27	22	14:13	9	1

NSAID, non-steroidal anti-inflammatory drug.

excluded from the data analysis for the effect on the change in ultrasound score if they received a secondary treatment within 14 days of the initial fever detection. This was due to the confounding effect of the different timings of the application of the secondary treatment to each calf caused by the different timings of the recurrence of fever or clinical signs. Kaplan-Meier survival analysis was used to assess the age at which fever due to BRD was first detected. The requirement for additional treatments (both secondary and repeat treatments) for BRD in each treatment group was assessed using multivariable binary logistic regression, with backwards elimination for non-significant variable was used to produce the final model.

RESULTS

One hundred and fifty-two calves were recruited, with 74 calves (49 per cent) developing fever as identified by the FeverTags. There were 24 in experimental group 1 (NSAID), 23 in group 2 (antimicrobial) and 27 in group 3 (NSAID and antimicrobial). There was no significant difference in the number of heifer and bull calves between experimental groups (table 2).

Thirty-two calves met the requirements for a secondary treatment (a recurrence of fever or development of clinical signs, regardless of experimental group), meaning that they were excluded from the thoracic ultrasound analysis (but included in the rest of the analysis). A mortality rate of 1.7 per cent (two calves) was observed throughout the study (table 2). The mean age of onset of pneumonia as detected by the FeverTag was 24 days, with no difference found between the three experimental groups (LogRank 0.69, P=0.611).

The univariate ANOVA indicated no difference in daily liveweight gain between the experimental groups ($F(2,69)=0.12$, P=0.89), or between male and female calves ($F(1,70)=0.056$, P=0.81), with an average growth rate of 0.85 kg/day between birth and weaning (table 3).

Thoracic ultrasound scores at the first examination indicated 70/74 calves had a result of either score 0 or 1, reducing to 53/74 calves at the second examination two weeks later (16 calves had a score of 2, and one calf had a score of 5). There was no difference in the initial thoracic lung scores between the experimental groups ($F(2,71)=0.41$, P=0.67), or in the change of thoracic ultrasound scores between the first scan at the time of fever detection compared with the score two weeks later ($F(2,71)=1.13$, P=0.33) (33/74 scores remained the same, and only 9–13 of the calves had an increase in the lung score depending on the experimental group). The negative control calves who did not experience a case of BRD had ultrasound scores of 0 either 1, with these scores not being significantly different from those found in calves affected by fever caused by BRD.

A multivariable logistic regression model was produced to assess the requirement for additional treatments (both NSAID and antimicrobial) due to the recurrence of fever or development of clinical signs at any point up to weaning. The initial model contained the variables of treatment group, age at first occurrence of fever and change of ultrasound score. The change in ultrasound score was found to be not significant, so was removed from the final model (table 4). The Hosmer and Lemeshow goodness-of-fit test gave a p value of 0.18, indicating the model had appropriate fit to the data. Results indicated that experimental group 1 (NSAID) had a higher odds of requiring a repeat treatment (OR=3.10 (95 per cent CI 0.86 to 11.14), P=0.083) compared with the other two groups. However, the age at first occurrence of fever thought to be caused by BRD was significantly associated with the need for a repeat treatment (OR=0.95 (95 per cent CI 0.90 to 0.99), P=0.026). The mean age of calves when they first became ill that went on to require a repeat treatment was 21 days, compared with 28 days for calves that did not require a repeat treatment (figure 1). The average time of occurrence of a repeat case of BRD was 21 days later (minimum 14 days, maximum 44 days).

Each calf that was detected as having fever was subject to a clinical calf score. Overall, the number of calves

Table 3 Average daily liveweight gain of calves in different experimental groups within the trial

Group	Average daily liveweight gain, kg (sd)
Group 1 (NSAID)	0.85 (0.12)
Group 2 (antimicrobial)	0.84 (0.14)
Group 3 (NSAID and antimicrobial)	0.86 (0.12)
Male	0.85 (0.14)
Female	0.85 (0.12)

NSAID, non-steroidal anti-inflammatory drug.

Table 4 The OR and p values from the multivariable binary logistic regression for associations with the requirement for an additional treatments for BRD

Variable	B (se)	OR (95% CI)	P value
Experimental group 1	1.13 (0.65)	3.10 (0.86 to 11.14)	0.083
Experimental group 2	0.49 (0.63)	1.63 (0.48 to 5.54)	0.44
Age at BRD onset	−0.057 (0.025)	0.95 (0.90 to 0.99)	0.026

The experimental groups were group 1 (NSAID), group 2 (antimicrobial), group 3 (both). Experimental group 3 was used as the reference group.
BRD, bovine respiratory disease; NSAID, non-steroidal anti-inflammatory drug.

that had clinical scores was low (between 70 per cent–85 per cent of calves had score 0 for the different parameters at the first exam and 80 per cent–100 per cent had score 0 at the second exam), with the majority of calves having the same score at both evaluations (table 5). An improvement in mental demeanour was the most prevalent clinical change detected, but there was no significant difference between the experimental groups.

The serology results indicated that four out of five calves had been exposed to PI3 (including both of the calves that did not experience fever caused by BRD), and four out of five calves had been exposed to IBR (including both of the calves that did not experience fever caused by BRD). All of the calves were negative for *H. somni*, *M. bovis*, BVD and RSV.

DISCUSSION

This study aimed to explore the use of fever identification and thoracic ultrasonography to identify calves with early onset respiratory disease, and to assess the effectiveness of different treatment protocols. Fever identification (39.7°C for a sustained period of six hours as detected by the FeverTags) has been suggested as a suitable indication for treatment initiation for calf BRD.[4 18] The use of FeverTags for detecting this fever ensured consistency in the time of enrolment into the study, however the ultrasound scores at the time of initial BRD identification were very low, with 70/74 calves having a score of either 0 or 1 out of a 6-point scoring system.[11] The low number of calves with ultrasonographic lesions would suggest that fever detection alone has a low specificity for early identification of respiratory disease in calves. In addition to this, a lack of major clinical signs displayed by the calves in this study (table 5), and no effect on the average daily growth rates of calves between the three experimental groups (P=0.89) suggest a high rate of false positive identifications of respiratory disease, resulting in over application of treatments to calves.

However, this study did demonstrate that calves in the NSAID-only experimental group (group 1) had a higher odds of experiencing repeated cases of fever during the preweaning period (OR=3.04 (95 per cent CI 0.96 to 11.14), P=0.083). This study sample size may have been underpowered to identify this finding as statistically significant, but this could be addressed in future study designs. The reason for this association is unclear

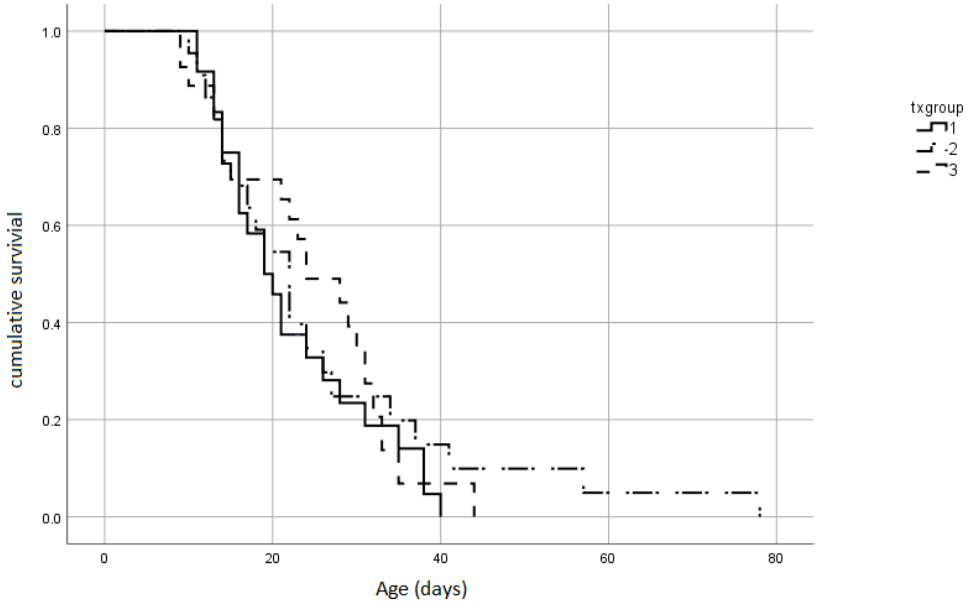

Figure 1 A survival curve demonstrating the age at which calves first developed fever due to bovine respiratory disease (BRD) within the different treatment groups. The treatment groups were group 1 (non-steroidal anti-inflammatory drug (NSAID)), group 2 (antimicrobial), group 3 (both).

Table 5 The number of calves that were recorded as having their clinical scores either improve, remain the same or become worse over a two-week period, along with the range of scores for the two time periods

Clinical calf score	Declined	Remained the same	Improved	Range at first score	Range at second score
Cough	12	52	10	0–2	0–2
Nasal discharge	10	63	1	0–1	0–1
Mental demeanour	5	47	22	0–3	0–2
Ocular discharge	10	60	4	0–1	0–2

given the apparent lack of ultrasonographic changes and therefore lack of surface pathology within the lungs, but it does support previous work that NSAID usage may not be appropriate as an isolated therapy for undifferentiated fever thought to be caused by respiratory disease.[4 16 17] In human research, NSAID usage for viral respiratory disease indicated it only had analgesic effects of reducing headaches, ear pain and general malaise, but no other clinical signs.[19] This may be why NSAID-only usage did not improve ultrasound scores, but including a NSAID treatment could be beneficial for improving the demeanour and therefore feed intake of the calf, which is important to ensure calorie intake to provide energy for the immune system to function effectively. Some respiratory pathogens are temperature sensitive, so body temperatures above the normal physiological range (fever) may be beneficial to reduce pathogen replication abilities.[20] In addition, fever appears to be linked with an upregulation of lymphocyte proliferation and increased cytokine production, both of which are important for a successful immune response to infection.[21] This would therefore indicate that an NSAID may interfere with an effective immune response when not combined with an antimicrobial therapy. While most of this work is based in non-bovine species, some of these physiological principles are likely to play a role in calf respiratory disease.

Another reason for the apparent lack of ultrasonographic changes at the time of fever detection could be the time lag between identification of the fever and ultrasound of the lungs (up to 48 hours in some calves). Lung consolidation may appear quickly within 24 hours in calves affected by the bacteria *Mannheimia haemolytica*.[22] The application of therapeutic treatments up to 48 hours before scanning may mean that there had been some resolution of lung pathology within this short time period, explaining why so many calves were negative for lung consolidation. This indicates that future studies will require thoracic ultrasound at the immediate point of fever detection (ideally before treatment) to avoid missing acute lung pathology. Use of a combination of additional diagnostic criteria may also be beneficial to try and improve the specificity of early detection methods for BRD, and may include detection of changes in behaviour such as reduced feed consumption and increased lying times.

Existing literature indicates that a binary cut-off of more than 1 cm depth of consolidation in the lungs (equivalent to an ultrasound score 2 or greater in this study) was required to have a significant clinical effect on average daily growth rates,[23] with other studies suggesting a depth of more than 3 cm of consolidation just in the cranial lung lobes provided the best sensitivity and specificity for BRD detection.[2] Future studies should combine these diagnostic methods for BRD identification in calves, with requirement for both fever identification and lung consolidation to ensure a true positive diagnosis. This would allow for a more efficacious investigation into the effects of the different treatment protocols under study as the second objective of this trial.

Within the limitations of this study on experimental drug effect, there was no significant difference in the change of thoracic ultrasound score between the three experimental groups (P=0.33). This may have been exacerbated by the relatively small sample size created by exclusion of calves through requirement for a secondary treatment due to continuation of fever or development of clinical signs within 14 days of the initial treatment. This should be taken account of in future sample size calculations.

Serology of a sample of the study calves indicated that they had been exposed to both PI3 and IBR respiratory pathogens, although the time of sampling does not allow accurate conclusions to be drawn about the pathogens responsible for the fever during the study. It may be more appropriate to use paired serology at the time of fever identification in future studies, with a rising titre helping to support the diagnosis of respiratory disease in these cases.

The average age of fever onset in this study cohort was 24 days, which is earlier than previous studies have reported at 29 days[4] and 4–5 weeks for BRD.[24] There was a statistically significant effect of the age at which calves developed fever and their requirement for a repeat treatment (P=0.026), with younger calves (mean 21 v 28 days of age) suffering their first episode of fever being more likely to have further episodes. This may be influenced by the fact that calves who developed their first case of BRD at an older age had less time to be eligible for another case of respiratory disease before the end of the study (at 70 days of age). However the mean time to a repeat case was 22 days, indicating the majority of repeat cases would have occurred before the end of the study. This finding may also be influenced by the still developing nature of the immune system of the calf, with a decline in maternally derived antibodies beginning at around 13 days old,[25] and a slow increase in endogenous antibodies

in response to pathogen exposure. This also highlights that calves are most vulnerable to developing long-term consequences of disease that develops at an earlier age, which may influence the choice of treatment regimens employed by farms if developing standard operating procedures (SOPs).

CONCLUSION

This study has demonstrated that calves in the experimental group receiving NSAID only at the occurrence of fever (thought to be caused by respiratory disease) may be more likely to require repeat treatments throughout the preweaning period. While the physiological reasons for this are still unclear, it would suggest that NSAID-only therapy may not be suitable for early onset of calf BRD. The use of fever detection to indicate respiratory disease demonstrated a low specificity for definitive diagnosis as shown by the low thoracic ultrasound scores and lack of clinical signs, but does not exclude the presence of subclinical respiratory disease. Although the combination of fever detection and ultrasound may be beneficial for case definitions, it may be cost prohibitive for use on every calf in a commercial setting, but may provide valuable additional information for future studies on lung health. The study was underpowered to assess the ultrasonic effects of the different experimental protocols on lung pathology.

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Competing interests None declared.

Ethics approval The study was approved by the University of Surrey's ethical review board (NASPA-2018-002).

Provenance and peer review Not commissioned; externally peer reviewed.

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