An outbreak of Infectious Bovine Rhinotracheitis (IBR) in a herd vaccinated with a live glycoprotein E deleted (marker) Bovine Herpes Virus-1 (BoHV-1) vaccine: lessons to be learned

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TITLE OF CASE ***Do not include "a case report"***

An outbreak of Infectious Bovine Rhinotracheitis (IBR) in a herd vaccinated with a live glycoprotein E deleted (marker) Bovine Herpes Virus-1 (BoHV-1) vaccine: lessons to be learned.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

Keywords: Cattle, Respiratory, Vaccination, Infectious Bovine Rhinotracheitis (IBR), Bovine Herpes Virus (BoHV),

Vaccines are commonly used in the control of bovine respiratory disease (BRD), however the field performance of these vaccines is poorly understood. We describe an outbreak of Infectious Bovine Rhinotracheitis (IBR) in a 383 animal beef finishing unit in Scotland, four months after vaccination with a live glycoprotein E deleted (marker) Bovine Herpes Virus-1 (BoHV-1) vaccine. Seroconversion to the vaccine was confirmed in acute sera, and seroconversion to field virus confirmed in convalescent sera. BoHV-1 was also identified in broncho-alveolar lavage fluid and conjunctival swabs using PCR. This outbreak highlights the importance of the reporting of veterinary vaccine Suspected Lack of Expected Efficacy (SLEE) events, as well as the paucity of data available to practitioners relating to the field performance of veterinary vaccines.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Bovine respiratory disease (BRD) is a major cause of mortality, production loss, antimicrobial use and compromised animal welfare in cattle globally. On feedlots in the USA, production losses and treatment costs alone during a BRD outbreak (not accounting for time and labour) are estimated at approximately $14 per animal on the farm (Snowder, 2006) or between $23-54 in carcase losses per clinically affected animal (Schneider, 2009). In the UK, daily live weight gain of cattle with lung lobe consolidation is estimated to be reduced by 72-202 g/day depending on the degree of consolidation, compared to cattle without any evidence of gross lung pathology (Williams, 2007). Recent economic analysis of the costs of BRD in the UK is not available, however Andrews (2000) calculated an average loss per animal within an affected group of £43.26 for dairy and £82.10 for suckler calves. As BRD outbreaks are often complex and multifactorial, disease prevention can often be problematic (Edwards, 2010), however vaccination is a significant component of most prevention strategies in trying to reduce or mitigate economic losses and animal suffering caused by BRD.

Veterinary vaccines are typically developed and licenced using disease challenge models in small groups of animals under carefully controlled conditions. In the UK, field trials are required to demonstrate product safety, however due to difficulties with designing sufficiently powered studies, may not demonstrate efficacy. Licencing data is rarely made public, although a detailed scientific discussion based on submitted data is available for a minority of veterinary vaccines available in the UK through the European Medicines Agency. Combined with limited data relating to the field efficacy of vaccines targeting BRD (Taylor, 2010), practitioners predominantly rely on the Summary of Product Characteristics (SPC), pharmaceutical company representatives and their own experiences when making vaccination decisions (Richens, 2016). When investigating an SLEE event, it is often difficult for the practitioner to disentangle the performance of the product from the multitude of factors that may contribute to a BRD outbreak. Infectious Bovine Rhinotracheitis (IBR), caused by Bovine Herpes Virus-1 (BoHV-1) is a common pathogen involved in BRD in the UK (Graham, 2013). Awareness of disease is relatively high within the industry, illustrated by a recent survey of UK beef and dairy herds, where BoHV-1 vaccines were used in at least 45% and 60% of herds respectively (Cresswell, 2014). The widespread use of glycoprotein E (gE) deleted (marker) BoHV-1 vaccines that allow BoHV-1naïve, vaccinated and exposed animals to be differentiated, has facilitated the practitioner in determining whether BoHV-1 is the causative agent during a BRD outbreak (Ackermann, 2006). Here we describe the diagnosis of an outbreak of IBR in a herd vaccinated with a live gE deleted BoHV-1 vaccine.

CASE PRESENTATION ***Presenting features, clinical and environmental history***

A calf fattening unit in the central region of Scotland was populated with 383 weaned spring born calves of various breeds from 3 markets between the 3rd October 2014 and the 3rd November 2014. The cattle were sourced from 96 farms in the Highlands and Islands of Scotland (1-26 calves/farm). Upon arrival on farm in October, the calves were administered a live gE deleted BoHV-1 vaccine and an inactivated *Manheimia haemolytica* vaccine. Despite these products not being licenced to be administered concurrently, both vaccines were administered on the same day at different sites by intra-muscular injection.

The use of unlicensed vaccine combinations is common in veterinary medicine and in many systems is the only practical route by which animals can complete a vaccination course prior to the risk period for disease. Whilst work in veterinary species is limited, there is a strong body of

evidence within the human literature to support the simultaneous administration of vaccines and that there is no increase in either vaccine failure rates or adverse events when vaccines are administered concurrently (CDC 2016). The SPC for the live gE deleted BoHV-1 vaccine used states that "a decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis". This was done so in this herd, in conjunction with the market authorisation holder, and therefore the use of the vaccine as described in this case report is compliant with the SPC.

The animals also received a 10% fenbendazole oral drench at 7.5mg/kg. The animals were then housed for 5 days and fed a mix of *ad lib* silage and straw. The animals were then turned out on to grass/stubble, where they were trained to eat conserved forage with a gradual increased access to *ad lib* silage and straw, and trough fed concentrate mix at 2.5 kg/head. The homemade concentrate mix was approximately 80% barley, 20% brewer's grains and 150 g per head of a general purpose beef finisher mineral.

The animals were housed in December and continued on the same feeding regime. Three hundred animals were housed in a single airspace in 4 groups of 75 animals with two pens either side of a central feed trough. The remaining animals were in separate airspaces in groups no larger than 30. Upon housing, they all received a multivalent live intra-nasal parainfluenza virus 3 (PI3) and bovine respiratory syncytial virus (BRSV) vaccine. Two weeks later these animals had their backs clipped, pour-on ivermectin administered at 500 µg/kg, and a 10 mg/kg subcutaneous injection of nitroxynil.

INVESTIGATIONS *If relevant*

The Farm Animal Practice at the Royal (Dick) School of Veterinary Studies (R(D)SVS) was contacted in early February by the farmer due to a higher than expected incidence of pneumonia. Thirty individual animals in a separate airspace had been noted by the farmer to have poor feed intakes, hypersalivation and a moist cough with approximately 50% of the animals within the group being pyrexic. The farmer had undertaken metaphalaxis of the group with long acting oxytetracycline at 20 mg/kg and meloxicam at 0.5 mg/kg. He noted that clinical signs resolved within approximately 48 h, apart from a few animals with a persistent moist cough.

Approximately 1 week later the farmer reported a number of animals in a pen of 75 (in the shared airspace) presenting with similar clinical signs as seen previously. At this stage the farmer sought veterinary advice. The farmer provided a history of a similar disease outbreak the previous Christmas. However as the outbreak occurred over Christmas Eve and Christmas Day, a full investigation had not been undertaken and whole farm metaphylaxis had been implemented.

Upon examination, the calves in question appeared to be in good body condition and the housing was well ventilated. More than 50% of the animals in the affected group were pyrexic, with a rectal temperature greater than 40^{o}C. Several animals were observed to be hypersalivating, with a mild serous ocular discharge and light cough. A number of animals remained distant from the feed face and the farmer reported a lack of appetite and reduced feed intakes for the previous 48 hours. One calf examined was extremely dyspnoeic, exhibiting excessive upper respiratory tract noise and marked respiratory effort.

As the separate group of 30 animals on farm had already been successfully treated for

pneumonia by the farmer and over 50% of the animals examined were pyrexic, it was recommended that the affected group should be treated metaphalactically for primary/secondary bacterial pneumonia with 20 mg/kg long acting oxytetracycline by intra-muscular injection and 0.5 mg/kg meloxicam by subcutaneous injection, and that the farmer should be prepared to administer the same metaphalactic treatment to any subsequently affected groups if necessary. To minimise the risk of pathogen spread, no movement of stock was to occur between groups in the shared airspace or of at-risk animals from the affected airspace to other groups on the farm.

DIFFERENTIAL DIAGNOSIS ***If relevant***

Primary respiratory disease caused by:

- BoHV-1
- BRSV
- PI3
- *Pasteurella multocida*
- *Mycoplamsa bovis /dispar*

Respiratory disease secondary to concurrent immunosuppression due to:

- Bovine viral diarrhoea virus (BVDV)
- Fascioliasis
- Environmental, nutritional or husbandry stressors

TREATMENT *If relevant*

Further investigation and ancillary testing.

Broncho-alveolar lavage (BAL) was performed on 3 animals and submitted to the local veterinary diagnostic labs that day for viral PCR (BoHV-1, BRSV, PI3) and bacterial culture and sensitivity. Serum and faeces were collected from these 3 animals, as well as a further 3 calves. Animals selected for these samples were acutely affected, previously untreated, noticed as not feeding that morning, with a rectal temperature of greater than 40^{o}C and tachypnoea, but no nasal discharge.

Faecal worm egg counts and fluke sedimentation were negative when assessed that evening in the practice laboratory. Serum samples were stored in a freezer, for the assessment of paired serology 3 weeks later.

Four days after the initial reported outbreak, one animal from the original affected group died. A field post mortem revealed inflammation of the lungs, larynx and pleural surfaces. The trachea was filled with a necrotic diptheretic exudate containing caeseous suppurative material. Two conjunctival swabs were taken, one from the dead animal and another from an additional animal presented for clinical examination and submitted for respiratory virus PCR (BoHV-1, PI3 and RSV). No other samples were submitted from these two animals. During this visit, the farmer had remarked that the mild clinical signs seen in the initial outbreak had been observed in 3 of the 4 groups housed in the affected airspace, and metaphylactic treatment within these groups had been undertaken.

The results from the BAL were available 5 days after the initial outbreak. All animals were negative for BRSV and PI3. One animal was positive for BoHV-1 and *Pasteurella multocida* (sensitive to all antibiotics tested except tylosin) was cultured from another animal. The conjunctival swab from the live animal was also found to be positive for BoHV-1. The conjunctival swab from the dead animal was negative for BoHV-1. A presumptive diagnosis of primary IBR was made.

A live gE deleted BoHV-1 vaccine was administered intranasally to all animals on farm. In total, 280 animals were treated with oxytetracycline and meloxicam. The farmer reported that clinical signs were significantly reduced approximately 48 hours after treatment and that no new cases occurred. Eight animals developed chronic disease and were described as ‘persistent coughers’ by the farmer. Feed intakes returned to normal approximately 2 weeks after treatment. Overall one animal death was reported and 8 affected animals developed symptoms consistent with chronic suppurative pneumonia (ill thrift, suppurative nasal discharge, persistent cough with excessive abdominal effort and increased respiratory rate). These chronic cases were placed on a 4 week course of daily intramuscular procaine penicillin at 10 mg/kg. In total, 1.7 kg of oxytetracycline, 50 g of meloxicam and 600 g of procaine penicillin were used during the outbreak.

OUTCOME AND FOLLOW-UP

Definitive diagnosis

Paired serology was completed after obtaining a second serum sample 3 weeks after the initial outbreak. The results (Table 1) demonstrate that all of the animals were seropositive to BoHV-1

glycoprotein B (gB), whilst two of the animals were seropositive to BoHV-1 gE prior to the outbreak, hence indicating that four of the animals were naïve to field virus but had been vaccinated. Five of the six animals seroconverted to BoHV-1 gE during the outbreak, hence demonstrating an immune response to the field virus.

All of the animals were seronegative to Bovine Viral Diarrhoea Virus (BVD) and seropositive to PI3 and RSV prior to the outbreak, which is consistent with vaccination and/or natural exposure. No animals demonstrated a rising titre to BRSV, whilst only one animal demonstrated a rising titre to PI3. Two of the six animals seroconverted to *M. bovis* during the outbreak. Experimental studies have shown that BoHV can exacerbate respiratory disease due to *M. bovis* (Prysliak 2011). A diagnosis of a primary breakdown of IBR in a live gE deleted BoHV-1 vaccinated herd was made.

The farmer was advised to alter his vaccination regime in future years as follows: intranasal administration using a live gE deleted BoHV-1 vaccine upon arrival in October and a second intramuscular administration of the same vaccine at housing in December. This protocol is advised by the SPC for use of the vaccine in animals 'at immediate risk of IBR' and was implemented in 2015. No respiratory disease has since been observed or reported by the farmer, whilst total mortality in the 2015/16 housing period was 1%. It is worth noting that the single dose vaccination protocol used prior to the outbreak was in accordance with the SPC's advice on vaccine administration to calves over 3 months of age.

DISCUSSION *Include a very brief review of similar published cases*

A Suspected Adverse Reaction (SAR) to a veterinary pharmaceutical product is any observation in animals that is unfavourable and unintended and that occurs after any (label or off-label) use of a veterinary medicine. This includes SLEE events or reactions in humans (Anon 2007). Of the 399 Veterinary Medicines Directorate (VMD) recorded adverse events in UK cattle during 2014, 168 (42%) of these were SLEE events and 141 of these (84%) were related to vaccines (Anon 2016). Unfortunately, the VMD does not report the name of the products involved or the sales volumes of each product.

To the authors' knowledge, the annual pharmacovigilance review by the VMD (Anon 2016) is the only data describing vaccine SARs or SLEE events in the UK. This limited data is broken down by species and then by product groups only, with a brief description of predominant clinical signs and a few comments describing general trends. No details of suspected predisposing factors for SLEE events or confirmed case related data are available. The currently available data provides little guidance for a practitioner dealing with cases on their clients' farms. The data relating to these SARs must be recorded as it is reported to the competent authority (the VMD in the case of the UK) and the marketing authorization holder. Specific data related to SARs and SLEE events will also be held by product manufacturers obtained during field trials conducted when a product is licenced. Until this information is made publicly available for all products in the market, practitioners will not possess the necessary information to make informed decisions regarding the use of veterinary vaccines.

Due to the differences in veterinary vaccines used in the USA and the EU, case-based data relating to SSLE events from the USA are of limited relevance to practitioners within the EU. There has been some discussion in the literature regarding the appropriate investigation of SLEE

events related to BoHV-1 vaccination. Allcock and others (2010) have reported two SLEE events in dairy herds vaccinated using a live marker BoHV-1 vaccine. These cases were diagnosed on the basis of clinical signs, response to booster vaccination and fluorescent antibody testing (FAT) of conjunctival swabs. Penny (2013) noted that BoHV-1 FAT testing has a poor specificity and outlined the importance of investigating, diagnosing and reporting SLEE events correctly, specifically that confirmation of active BoHV-1 circulation requires serological testing for BoHV-1 gE and gB titres as well as the use of PCR from either BAL fluid, nasopharyngeal swabs or post-mortem samples. Due to epithelial destruction as the disease progresses, BoHV-1 is often not isolated from animals that have died during an IBR outbreak, with histopathology of the respiratory tract also often unrewarding. This highlights the importance of sampling animals early in the disease course and underpinned the rationale behind performing BALs on carefully selected animals in the acute stages of infection in this outbreak. To improve the chances of a satisfactory diagnosis, the authors would recommend that post mortem examinations are undertaken at a recognised veterinary investigation centre, however this was not feasible in this outbreak. A definitive aetiological diagnosis for the animal that died cannot therefore be made, however the gross post-mortem findings and testing of other animals within the same management group support a presumptive diagnosis of IBR. To our knowledge, this is the only published case report of an SLEE in a BoHV-1 vaccinated herd to use both PCR and serology to confirm circulating BoHV-1 as the primary pathogen related to the clinical signs seen. This highlights the need to increase the reporting of SLEE investigations using appropriate diagnostic tests. Only then can the predisposing factors leading to SLEE events be thoroughly investigated and the field performance of veterinary vaccines understood.

In this case, a presumptive diagnosis was achieved within 5 days by PCR following BAL and conjunctival swabs, which informed targeted herd management decisions. The BoHV-1 viral PCR used is unable to distinguish between field and vaccine virus (Fiona Howie, personal communication), hence the importance of serology in confirming the active cycling of field virus. More rapid diagnosis would have allowed these decisions to be made earlier and would have reduced the amount of antimicrobials used in this outbreak. This illustrates the need for rapid diagnostic tests to avoid inappropriate antimicrobial use. We also note that only one of the three BAL samples was BoHV-1 virus positive, hence highlighting the need to select an appropriate sample size and the importance of serological surveillance.

The use of a gE deleted vaccine allowed a more granular analysis of the serological data, by differentiating between vaccination and field virus exposure, hence confirming that field virus was actively cycling and infecting naïve animals. This highlights the necessity of using marker vaccines in the control and surveillance of BoHV-1 and that where vaccines are available that allow differentiation between infected and vaccinated (DIVA) individuals that these should be used preferentially.

Two of the six animals involved in the serological testing converted to *M. Bovis* during the outbreak. The role of *M. Bovis* as a primary or secondary pathogen in this outbreak warrants discussion. Prysliak and others (2011) described how 6-8 month old calves were more likely to develop clinical disease related to *M. bovis* after exposure to BoHV-1. Given that only two of the six animals tested seroconverted to *M. bovis* compared to five of the six seroconverting to BoHV-1, *M. bovis* is more likely to have been a secondary pathogen in this outbreak.

The SPC for the vaccine used prior to this outbreak notes that “After a single dose vaccination, a significant reduction of virus shedding duration has been demonstrated upon challenge for 6 months. After two doses of vaccine, the intensity and duration of clinical symptoms as well as the titre and duration of virus shedding are significantly reduced following infection”. This

outbreak occurred approximately 4 months after a single injection, therefore it could be argued that the vaccine was performing according to the expectations of the SPC by reducing viral shedding but not necessarily the intensity and duration of clinical symptoms. That said, the vaccine did not perform according to the client's and prescribing veterinary surgeon's expectations. This was reported to the market authorisation holder who supported the investigation of this outbreak, provided additional vaccine free of charge and reported the event to the VMD.

Immunosuppression either at the time of vaccination or the time of the outbreak could have been a contributory factor to this outbreak. Whilst the acute sera demonstrated seroconversion to the vaccine, only a small proportion of the herd were sampled, whilst serology gives no indication as to the avidity of the antibody response or magnitude of the T-cell response following vaccination. The possibility of a 'poor quality' response following initial vaccination due to concurrent disease or immunosuppression cannot therefore be excluded.

Investigations at the time of the outbreak failed to identify any other concurrent diseases or potential causes of immunosuppression. The growth rate and body condition score of the calves prior to the outbreak were appropriate as was the ration and minerals on offer. Furthermore, abattoir reports showed that active liver fluke was present in less than 2% of animals at slaughter, whilst faecal worm egg count and fluke sedimentation tests indicated that concurrent immunosuppression caused by parasitism was unlikely. Metabolic profiling was not undertaken and may have identified negative energy balance at the time of the outbreak, but given the lowered feed intakes due to respiratory disease, it would not have been possible to determine whether any negative energy balance was primary or secondary to the clinical outbreak.
The stocking density, air quality and ventilation were assessed and deemed to be satisfactory for the main shed housing 300 animals. Poor ventilation and air quality could have been a contributory factor to the disease observed in the separate airspace housing the remaining 83 animals. The farmer reported going on holiday prior to the outbreak starting and was concerned that a change in management and routine may have occurred during this period. Nothing unusual was reported by the farm staff and it is the authors' opinion that it is unlikely that this precipitated the outbreak.

The prevention of BoHV-1 circulation within a herd should ideally be achieved by appropriate biosecurity measures and protection of stock from pathogen exposure. Where possible, herds should be "closed" and bought in stock should be from a herd known to be negative for BoHV-1. Where the status of the herd of origin is unknown, bought in animals should be isolated and tested for BoHV-1 antibodies and then segregated depending on risk (Van Winden, 2005). With this in mind, vertical integration of farming systems may help to improve biosecurity and mitigate disease risk (Kahan, 2013). That said, the business model of the farm in this case report relies on purchasing calves from a large number of crofters in the North-West of Scotland. These units invariably do not know their disease status and there is a strong tradition of selling calves through markets, where they may be exposed to a variety of pathogens. Within this context, discussions relating to biosecurity have not been tractable and the use of vaccines have become the mainstay of BoHV-1 control.
The economic impact of this outbreak, excluding labour, is summarised in Table 2. The reduced live weight gain is calculated as a result of the overall reduced feed intakes for 383 animals over a two week period. As no animals were weighed during the outbreak and animals were only weighed at the start and end of the housing period (as is common practice) a conservative estimate reduction in daily liveweight gain of 0.5kg/day and the 2015 average market value of approximately £1.80 per kg of live weight have been used.

Had the revised vaccination programme been implemented before the outbreak in December 2014, the farm would have saved £13,662, assuming effective vaccine efficacy.

Conclusion

When investigating an SLEE event, it is often difficult for the practitioner to disentangle the performance of the product from the multitude of factors that may contribute to a BRD outbreak. Penny 2013 noted the importance of investigating, diagnosing and reporting SLEE events correctly. The currently available data provides little guidance for a practitioner dealing with cases on their clients' farms and limits decision making and appropriate herd health planning. This can ultimately impact animal welfare and farm profitability when such disease breakdowns do occur. This case report not only reviews the impact of one such breakdown, but also highlights the need for more data surrounding the subject to be made available to the general practitioner.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- The importance of appropriate investigation and reporting of veterinary vaccine Suspected Lack of Expected Efficacy (SLEE) events.
- There is a current paucity of data available to practitioners relating to the field performance of veterinary vaccines.
- The appropriate recording and usage of this data could help guide herd health planning and limit the impact of disease breakdowns on animal welfare and farm economics.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Table1: Paired serology results for six acutely affected animals

Pre = acute sera, Post = convalescent sera, IBR = Infectious Bovine Rhinotracheitis, g = glycoprotein, BVDV = Bovine Viral Diarrhoea, PI3 = Parainfluenza 3, BRSV = Bovine

Respiratory Syncytial Virus. The symbols + and ++ denote a positive or rising antibody titre.

Table 2. Approximate costs incurred during the disease outbreak.

OWNER'S PERSPECTIVE *Optional*

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Vaccines are commonly used in the control of bovine respiratory disease (BRD), however the field performance of these vaccines is poorly understood. We describe an outbreak of Infectious Bovine Rhinotracheitis (IBR) in a 383 animal beef finishing unit in Scotland, four months after vaccination with a live glycoprotein E deleted (marker) Bovine Herpes Virus-1 (BoHV-1) vaccine. Seroconversion to the vaccine was confirmed in acute sera, and seroconversion to field virus confirmed in convalescent sera. BoHV-1 was also identified in broncho-alveolar lavage fluid and conjunctival swabs using PCR. This outbreak highlights the importance of the reporting of veterinary vaccine Suspected Lack of Expected Efficacy (SLEE) events, as well as the paucity of data available to practitioners relating to the field performance of veterinary vaccines.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Bovine respiratory disease (BRD) is a major cause of mortality, production loss, antimicrobial use and compromised animal welfare in cattle globally. On feedlots in the USA, production losses and treatment costs alone during a BRD outbreak (not accounting for time and labour) are estimated at approximately $14 per animal on the farm (Snowder, 2006) or between $23-54 in carcase losses per clinically affected animal (Schneider, 2009). In the UK, daily live weight gain of cattle with lung lobe consolidation is estimated to be reduced by 72-202 g/day depending on the degree of consolidation, compared to cattle without any evidence of gross lung pathology (Williams, 2007). Recent economic analysis of the costs of BRD in the UK is not available, however Andrews (2000) calculated an average loss per animal within an affected group of £43.26 for dairy and £82.10 for suckler calves. As BRD outbreaks are often complex and multifactorial, disease prevention can often be problematic (Edwards, 2010), however vaccination is a significant component of most prevention strategies in trying to reduce or mitigate economic losses and animal suffering caused by BRD.

Veterinary vaccines are typically developed and licenced using disease challenge models in small groups of animals under carefully controlled conditions. In the UK, field trials are required to demonstrate product safety, however due to difficulties with designing sufficiently powered studies, may not demonstrate efficacy. Licencing data is rarely made public, although a detailed scientific discussion based on submitted data is available for a minority of veterinary vaccines available in the UK through the European Medicines Agency. Combined with limited data relating to the field efficacy of vaccines targeting BRD (Taylor, 2010), practitioners predominantly rely on the Summary of Product Characteristics (SPC), pharmaceutical company representatives and their own experiences when making vaccination decisions (Richens, 2016). When investigating an SLEE event, it is often difficult for the practitioner to disentangle the performance of the product from the multitude of factors that may contribute to a BRD outbreak. Infectious Bovine Rhinotracheitis (IBR), caused by Bovine Herpes Virus-1 (BoHV-1) is a common pathogen involved in BRD in the UK (Graham, 2013). Awareness of disease is relatively high within the industry, illustrated by a recent survey of UK beef and dairy herds, where BoHV-1 vaccines were used in at least 45% and 60% of herds respectively (Cresswell, 2014). The widespread use of glycoprotein E (gE) deleted (marker) BoHV-1 vaccines that allow BoHV-1naïve, vaccinated and exposed animals to be differentiated, has facilitated the practitioner in determining whether BoHV-1 is the causative agent during a BRD outbreak (Ackermann, 2006). Here we describe the diagnosis of an outbreak of IBR in a herd vaccinated with a live gE deleted BoHV-1 vaccine.

CASE PRESENTATION ***Presenting features, clinical and environmental history***

A calf fattening unit in the central region of Scotland was populated with 383 weaned spring born calves of various breeds from 3 markets between the 3rd October 2014 and the 3rd November 2014. The cattle were sourced from 96 farms in the Highlands and Islands of Scotland (1-26 calves/farm). Upon arrival on farm in October, the calves were administered a live gE deleted BoHV-1 vaccine and an inactivated *Manheimia haemolytica* vaccine. Despite these products not being licenced to be administered concurrently, both vaccines were administered on the same day at different sites by intra-muscular injection.

The use of unlicensed vaccine combinations is common in veterinary medicine and in many systems is the only practical route by which animals can complete a vaccination course prior to the risk period for disease. Whilst work in veterinary species is limited, there is a strong body of

evidence within the human literature to support the simultaneous administration of vaccines and that there is no increase in either vaccine failure rates or adverse events when vaccines are administered concurrently (CDC 2016). The SPC for the live gE deleted BoHV-1 vaccine used states that "a decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis". This was done so in this herd, in conjunction with the market authorisation holder, and therefore the use of the vaccine as described in this case report is compliant with the SPC.

The animals also received a 10% fenbendazole oral drench at 7.5mg/kg. The animals were then housed for 5 days and fed a mix of *ad lib* silage and straw. The animals were then turned out on to grass/stubble, where they were trained to eat conserved forage with a gradual increased access to *ad lib* silage and straw, and trough fed concentrate mix at 2.5 kg/head. The homemade concentrate mix was approximately 80% barley, 20% brewer's grains and 150 g per head of a general purpose beef finisher mineral.

The animals were housed in December and continued on the same feeding regime. Three hundred animals were housed in a single airspace in 4 groups of 75 animals with two pens either side of a central feed trough. The remaining animals were in separate airspaces in groups no larger than 30. Upon housing, they all received a multivalent live intra-nasal parainfluenza virus 3 (PI3) and bovine respiratory syncytial virus (BRSV) vaccine. Two weeks later these animals had their backs clipped, pour-on ivermectin administered at 500 µg/kg, and a 10 mg/kg subcutaneous injection of nitroxynil.

INVESTIGATIONS ***If relevant***

The Farm Animal Practice at the Royal (Dick) School of Veterinary Studies (R(D)SVS) was contacted in early February by the farmer due to a higher than expected incidence of pneumonia. Thirty individual animals in a separate airspace had been noted by the farmer to have poor feed intakes, hypersalivation and a moist cough with approximately 50% of the animals within the group being pyrexic. The farmer had undertaken metaphalaxis of the group with long acting oxytetracycline at 20 mg/kg and meloxicam at 0.5 mg/kg. He noted that clinical signs resolved within approximately 48 h, apart from a few animals with a persistent moist cough.

Approximately 1 week later the farmer reported a number of animals in a pen of 75 (in the shared airspace) presenting with similar clinical signs as seen previously. At this stage the farmer sought veterinary advice. The farmer provided a history of a similar disease outbreak the previous Christmas. However as the outbreak occurred over Christmas Eve and Christmas Day, a full investigation had not been undertaken and whole farm metaphylaxis had been implemented.

Upon examination, the calves in question appeared to be in good body condition and the housing was well ventilated. More than 50% of the animals in the affected group were pyrexic, with a rectal temperature greater than 40^{o}C. Several animals were observed to be hypersalivating, with a mild serous ocular discharge and light cough. A number of animals remained distant from the feed face and the farmer reported a lack of appetite and reduced feed intakes for the previous 48 hours. One calf examined was extremely dyspnoeic, exhibiting excessive upper respiratory tract noise and marked respiratory effort.

As the separate group of 30 animals on farm had already been successfully treated for

pneumonia by the farmer and over 50% of the animals examined were pyrexic, it was recommended that the affected group should be treated metaphalactically for primary/secondary bacterial pneumonia with 20 mg/kg long acting oxytetracycline by intra-muscular injection and 0.5 mg/kg meloxicam by subcutaneous injection, and that the farmer should be prepared to administer the same metaphalactic treatment to any subsequently affected groups if necessary. To minimise the risk of pathogen spread, no movement of stock was to occur between groups in the shared airspace or of at-risk animals from the affected airspace to other groups on the farm.

DIFFERENTIAL DIAGNOSIS ***If relevant***

Primary respiratory disease caused by:

- BoHV-1
- BRSV
- PI3
- *Pasteurella multocida*
- *Mycoplamsa bovis /dispar*

Respiratory disease secondary to concurrent immunosuppression due to:

- Bovine viral diarrhoea virus (BVDV)
- Fascioliasis
- Environmental, nutritional or husbandry stressors

TREATMENT *If relevant*

Further investigation and ancillary testing.

Broncho-alveolar lavage (BAL) was performed on 3 animals and submitted to the local veterinary diagnostic labs that day for viral PCR (BoHV-1, BRSV, PI3) and bacterial culture and sensitivity. Serum and faeces were collected from these 3 animals, as well as a further 3 calves. Animals selected for these samples were acutely affected, previously untreated, noticed as not feeding that morning, with a rectal temperature of greater than 40^{o}C and tachypnoea, but no nasal discharge.

Faecal worm egg counts and fluke sedimentation were negative when assessed that evening in the practice laboratory. Serum samples were stored in a freezer, for the assessment of paired serology 3 weeks later.

Four days after the initial reported outbreak, one animal from the original affected group died. A field post mortem revealed inflammation of the lungs, larynx and pleural surfaces. The trachea was filled with a necrotic diptheretic exudate containing caeseous suppurative material. Two conjunctival swabs were taken, one from the dead animal and another from an additional animal presented for clinical examination and submitted for respiratory virus PCR (BoHV-1, PI3 and RSV). No other samples were submitted from these two animals. During this visit, the farmer had remarked that the mild clinical signs seen in the initial outbreak had been observed in 3 of the 4 groups housed in the affected airspace, and metaphylactic treatment within these groups had been undertaken.

The results from the BAL were available 5 days after the initial outbreak. All animals were negative for BRSV and PI3. One animal was positive for BoHV-1 and *Pasteurella multocida* (sensitive to all antibiotics tested except tylosin) was cultured from another animal. The conjunctival swab from the live animal was also found to be positive for BoHV-1. The conjunctival swab from the dead animal was negative for BoHV-1. A presumptive diagnosis of primary IBR was made.

A live gE deleted BoHV-1 vaccine was administered intranasally to all animals on farm. In total, 280 animals were treated with oxytetracycline and meloxicam. The farmer reported that clinical signs were significantly reduced approximately 48 hours after treatment and that no new cases occurred. Eight animals developed chronic disease and were described as ‘persistent coughers’ by the farmer. Feed intakes returned to normal approximately 2 weeks after treatment. Overall one animal death was reported and 8 affected animals developed symptoms consistent with chronic suppurative pneumonia (ill thrift, suppurative nasal discharge, persistent cough with excessive abdominal effort and increased respiratory rate). These chronic cases were placed on a 4 week course of daily intramuscular procaine penicillin at 10 mg/kg. In total, 1.7 kg of oxytetracycline, 50 g of meloxicam and 600 g of procaine penicillin were used during the outbreak.

OUTCOME AND FOLLOW-UP

Definitive diagnosis

Paired serology was completed after obtaining a second serum sample 3 weeks after the initial outbreak. The results (Table 1) demonstrate that all of the animals were seropositive to BoHV-1

glycoprotein B (gB), whilst two of the animals were seropositive to BoHV-1 gE prior to the outbreak, hence indicating that four of the animals were naïve to field virus but had been vaccinated. Five of the six animals seroconverted to BoHV-1 gE during the outbreak, hence demonstrating an immune response to the field virus.

All of the animals were seronegative to Bovine Viral Diarrhoea Virus (BVD) and seropositive to PI3 and RSV prior to the outbreak, which is consistent with vaccination and/or natural exposure. No animals demonstrated a rising titre to BRSV, whilst only one animal demonstrated a rising titre to PI3. Two of the six animals seroconverted to *M. bovis* during the outbreak. Experimental studies have shown that BoHV can exacerbate respiratory disease due to *M. bovis* (Prysliak 2011). A diagnosis of a primary breakdown of IBR in a live gE deleted BoHV-1 vaccinated herd was made.

The farmer was advised to alter his vaccination regime in future years as follows: intranasal administration using a live gE deleted BoHV-1 vaccine upon arrival in October and a second intramuscular administration of the same vaccine at housing in December. This protocol is advised by the SPC for use of the vaccine in animals 'at immediate risk of IBR' and was implemented in 2015. No respiratory disease has since been observed or reported by the farmer, whilst total mortality in the 2015/16 housing period was 1%. It is worth noting that the single dose vaccination protocol used prior to the outbreak was in accordance with the SPC's advice on vaccine administration to calves over 3 months of age.

DISCUSSION ***Include a very brief review of similar published cases***

A Suspected Adverse Reaction (SAR) to a veterinary pharmaceutical product is any observation in animals that is unfavourable and unintended and that occurs after any (label or off-label) use of a veterinary medicine. This includes SLEE events or reactions in humans (Anon 2007). Of the 399 Veterinary Medicines Directorate (VMD) recorded adverse events in UK cattle during 2014, 168 (42%) of these were SLEE events and 141 of these (84%) were related to vaccines (Anon 2016). Unfortunately, the VMD does not report the name of the products involved or the sales volumes of each product.

To the authors' knowledge, the annual pharmacovigilance review by the VMD (Anon 2016) is the only data describing vaccine SARs or SLEE events in the UK. This limited data is broken down by species and then by product groups only, with a brief description of predominant clinical signs and a few comments describing general trends. No details of suspected predisposing factors for SLEE events or confirmed case related data are available. The currently available data provides little guidance for a practitioner dealing with cases on their clients' farms. The data relating to these SARs must be recorded as it is reported to the competent authority (the VMD in the case of the UK) and the marketing authorization holder. Specific data related to SARs and SLEE events will also be held by product manufacturers obtained during field trials conducted when a product is licenced. Until this information is made publicly available for all products in the market, practitioners will not possess the necessary information to make informed decisions regarding the use of veterinary vaccines.

Due to the differences in veterinary vaccines used in the USA and the EU, case-based data relating to SSLE events from the USA are of limited relevance to practitioners within the EU. There has been some discussion in the literature regarding the appropriate investigation of SLEE

events related to BoHV-1 vaccination. Allcock and others (2010) have reported two SLEE events in dairy herds vaccinated using a live marker BoHV-1 vaccine. These cases were diagnosed on the basis of clinical signs, response to booster vaccination and fluorescent antibody testing (FAT) of conjunctival swabs. Penny (2013) noted that BoHV-1 FAT testing has a poor specificity and outlined the importance of investigating, diagnosing and reporting SLEE events correctly, specifically that confirmation of active BoHV-1 circulation requires serological testing for BoHV-1 gE and gB titres as well as the use of PCR from either BAL fluid, nasopharyngeal swabs or post-mortem samples. Due to epithelial destruction as the disease progresses, BoHV-1 is often not isolated from animals that have died during an IBR outbreak, with histopathology of the respiratory tract also often unrewarding. This highlights the importance of sampling animals early in the disease course and underpinned the rationale behind performing BALs on carefully selected animals in the acute stages of infection in this outbreak. To improve the chances of a satisfactory diagnosis, the authors would recommend that post mortem examinations are undertaken at a recognised veterinary investigation centre, however this was not feasible in this outbreak. A definitive aetiological diagnosis for the animal that died cannot therefore be made, however the gross post-mortem findings and testing of other animals within the same management group support a presumptive diagnosis of IBR. To our knowledge, this is the only published case report of an SLEE in a BoHV-1 vaccinated herd to use both PCR and serology to confirm circulating BoHV-1 as the primary pathogen related to the clinical signs seen. This highlights the need to increase the reporting of SLEE investigations using appropriate diagnostic tests. Only then can the predisposing factors leading to SLEE events be thoroughly investigated and the field performance of veterinary vaccines understood.

In this case, a presumptive diagnosis was achieved within 5 days by PCR following BAL and conjunctival swabs, which informed targeted herd management decisions. The BoHV-1 viral PCR used is unable to distinguish between field and vaccine virus (Fiona Howie, personal communication), hence the importance of serology in confirming the active cycling of field virus. More rapid diagnosis would have allowed these decisions to be made earlier and would have reduced the amount of antimicrobials used in this outbreak. This illustrates the need for rapid diagnostic tests to avoid inappropriate antimicrobial use. We also note that only one of the three BAL samples was BoHV-1 virus positive, hence highlighting the need to select an appropriate sample size and the importance of serological surveillance.

The use of a gE deleted vaccine allowed a more granular analysis of the serological data, by differentiating between vaccination and field virus exposure, hence confirming that field virus was actively cycling and infecting naïve animals. This highlights the necessity of using marker vaccines in the control and surveillance of BoHV-1 and that where vaccines are available that allow differentiation between infected and vaccinated (DIVA) individuals that these should be used preferentially.

Two of the six animals involved in the serological testing converted to *M. Bovis* during the outbreak. The role of *M. Bovis* as a primary or secondary pathogen in this outbreak warrants discussion. Prysliak and others (2011) described how 6-8 month old calves were more likely to develop clinical disease related to *M. bovis* after exposure to BoHV-1. Given that only two of the six animals tested seroconverted to *M. bovis* compared to five of the six seroconverting to BoHV-1, *M. bovis* is more likely to have been a secondary pathogen in this outbreak.

The SPC for the vaccine used prior to this outbreak notes that “After a single dose vaccination, a significant reduction of virus shedding duration has been demonstrated upon challenge for 6 months. After two doses of vaccine, the intensity and duration of clinical symptoms as well as the titre and duration of virus shedding are significantly reduced following infection”. This

outbreak occurred approximately 4 months after a single injection, therefore it could be argued that the vaccine was performing according to the expectations of the SPC by reducing viral shedding but not necessarily the intensity and duration of clinical symptoms. That said, the vaccine did not perform according to the client's and prescribing veterinary surgeon's expectations. This was reported to the market authorisation holder who supported the investigation of this outbreak, provided additional vaccine free of charge and reported the event to the VMD.

Immunosuppression either at the time of vaccination or the time of the outbreak could have been a contributory factor to this outbreak. Whilst the acute sera demonstrated seroconversion to the vaccine, only a small proportion of the herd were sampled, whilst serology gives no indication as to the avidity of the antibody response or magnitude of the T-cell response following vaccination. The possibility of a 'poor quality' response following initial vaccination due to concurrent disease or immunosuppression cannot therefore be excluded.

Investigations at the time of the outbreak failed to identify any other concurrent diseases or potential causes of immunosuppression. The growth rate and body condition score of the calves prior to the outbreak were appropriate as was the ration and minerals on offer. Furthermore, abattoir reports showed that active liver fluke was present in less than 2% of animals at slaughter, whilst faecal worm egg count and fluke sedimentation tests indicated that concurrent immunosuppression caused by parasitism was unlikely. Metabolic profiling was not undertaken and may have identified negative energy balance at the time of the outbreak, but given the lowered feed intakes due to respiratory disease, it would not have been possible to determine whether any negative energy balance was primary or secondary to the clinical outbreak.
The stocking density, air quality and ventilation were assessed and deemed to be satisfactory for the main shed housing 300 animals. Poor ventilation and air quality could have been a contributory factor to the disease observed in the separate airspace housing the remaining 83 animals. The farmer reported going on holiday prior to the outbreak starting and was concerned that a change in management and routine may have occurred during this period. Nothing unusual was reported by the farm staff and it is the authors' opinion that it is unlikely that this precipitated the outbreak.

The prevention of BoHV-1 circulation within a herd should ideally be achieved by appropriate biosecurity measures and protection of stock from pathogen exposure. Where possible, herds should be "closed" and bought in stock should be from a herd known to be negative for BoHV-1. Where the status of the herd of origin is unknown, bought in animals should be isolated and tested for BoHV-1 antibodies and then segregated depending on risk (Van Winden, 2005). With this in mind, vertical integration of farming systems may help to improve biosecurity and mitigate disease risk (Kahan, 2013). That said, the business model of the farm in this case report relies on purchasing calves from a large number of crofters in the North-West of Scotland. These units invariably do not know their disease status and there is a strong tradition of selling calves through markets, where they may be exposed to a variety of pathogens. Within this context, discussions relating to biosecurity have not been tractable and the use of vaccines have become the mainstay of BoHV-1 control.
The economic impact of this outbreak, excluding labour, is summarised in Table 2. The reduced live weight gain is calculated as a result of the overall reduced feed intakes for 383 animals over a two week period. As no animals were weighed during the outbreak and animals were only weighed at the start and end of the housing period (as is common practice) a conservative estimate reduction in daily liveweight gain of 0.5kg/day and the 2015 average market value of approximately £1.80 per kg of live weight have been used.

Had the revised vaccination programme been implemented before the outbreak in December 2014, the farm would have saved £13,662, assuming effective vaccine efficacy.

Conclusion

When investigating an SLEE event, it is often difficult for the practitioner to disentangle the performance of the product from the multitude of factors that may contribute to a BRD outbreak. Penny 2013 noted the importance of investigating, diagnosing and reporting SLEE events correctly. The currently available data provides little guidance for a practitioner dealing with cases on their clients' farms and limits decision making and appropriate herd health planning. This can ultimately impact animal welfare and farm profitability when such disease breakdowns do occur. This case report not only reviews the impact of one such breakdown, but also highlights the need for more data surrounding the subject to be made available to the general practitioner.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- The importance of appropriate investigation and reporting of veterinary vaccine Suspected Lack of Expected Efficacy (SLEE) events.
- There is a current paucity of data available to practitioners relating to the field performance of veterinary vaccines.
- The appropriate recording and usage of this data could help guide herd health planning and limit the impact of disease breakdowns on animal welfare and farm economics.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Table1: Paired serology results for six acutely affected animals

Pre = acute sera, Post = convalescent sera, IBR = Infectious Bovine Rhinotracheitis, g = glycoprotein, BVDV = Bovine Viral Diarrhoea, PI3 = Parainfluenza 3, BRSV = Bovine

Respiratory Syncytial Virus. The symbols + and ++ denote a positive or rising antibody titre.

Table 2. Approximate costs incurred during the disease outbreak.

OWNER'S PERSPECTIVE *Optional*

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	M. bovis		IBR gB		IBR gE		BVDV		PI3		BRSV	
Animal	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	-	-	+	+	+	+	-	-	+	+	+	+
2	-	-	+	++	-	+	-	-	+	+	+	+
3	-	-	+	++	-	+	-	-	+	+	+	+
4	-	+	+	++	-	+	-	-	+	++	+	+
5	-	+	+	++	+	++	-	-	+	+	+	+
6	-	-	+	+	-	+	-	-	+	+	+	+

Initial Vaccine costs	**£1,271**
Total Treatment spend	£6,966
Oxytetracycline	£2,856
Procaine penicillin	£360
Meloxicam	£3,750
Repeat Vaccination	£1,271
Total POM-V Spend	**£9,502**
Reduced live weight	**£5,040**
Death of one animal	**£1000**
Vet fees	**£278**
Diagnostics	**£344**
Total cost of this IBR outbreak	**£16,164**