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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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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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Topics:	Infectious bovine rhinotracheitis (IBR), Infectious diseases, Respiratory disease, Vaccines
Abstract:	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.

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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?*

1 Bovine respiratory disease (BRD) is a major cause of mortality, production loss, antimicrobial use
2 and compromised animal welfare in cattle globally. On feedlots in the USA, production losses
3 and treatment costs alone during a BRD outbreak (not accounting for time and labour) are
4 estimated at approximately \$14 per animal on the farm (Snowder, 2006) or between \$23-54 in
5 carcass losses per clinically affected animal (Schneider, 2009). In the UK, daily live weight gain of
6 cattle with lung lobe consolidation is estimated to be reduced by 72-202 g/day depending on
7 the degree of consolidation, compared to cattle without any evidence of gross lung pathology
8 (Williams, 2007). Recent economic analysis of the costs of BRD in the UK is not available,
9 however Andrews (2000) calculated an average loss per animal within an affected group of
10 £43.26 for dairy and £82.10 for suckler calves. As BRD outbreaks are often complex and
11 multifactorial, disease prevention can often be problematic (Edwards, 2010), however
12 vaccination is a significant component of most prevention strategies in trying to reduce or
13 mitigate economic losses and animal suffering caused by BRD.
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18 Veterinary vaccines are typically developed and licenced using disease challenge models in small
19 groups of animals under carefully controlled conditions. In the UK, field trials are required to
20 demonstrate product safety, however due to difficulties with designing sufficiently powered
21 studies, may not demonstrate efficacy. Licencing data is rarely made public, although a detailed
22 scientific discussion based on submitted data is available for a minority of veterinary vaccines
23 available in the UK through the European Medicines Agency. Combined with limited data
24 relating to the field efficacy of vaccines targeting BRD (Taylor, 2010), practitioners
25 predominantly rely on the Summary of Product Characteristics (SPC), pharmaceutical company
26 representatives and their own experiences when making vaccination decisions (Richens, 2016).
27 When investigating an SLEE event, it is often difficult for the practitioner to disentangle the
28 performance of the product from the multitude of factors that may contribute to a BRD
29 outbreak. Infectious Bovine Rhinotracheitis (IBR), caused by Bovine Herpes Virus-1 (BoHV-1) is a
30 common pathogen involved in BRD in the UK (Graham, 2013). Awareness of disease is relatively
31 high within the industry, illustrated by a recent survey of UK beef and dairy herds, where BoHV-
32 1 vaccines were used in at least 45% and 60% of herds respectively (Cresswell, 2014). The
33 widespread use of glycoprotein E (gE) deleted (marker) BoHV-1 vaccines that allow BoHV-
34 1 naïve, vaccinated and exposed animals to be differentiated, has facilitated the practitioner in
35 determining whether BoHV-1 is the causative agent during a BRD outbreak (Ackermann, 2006).
36 Here we describe the diagnosis of an outbreak of IBR in a herd vaccinated with a live gE deleted
37 BoHV-1 vaccine.
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CASE PRESENTATION *Presenting features, clinical and environmental history*

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46 A calf fattening unit in the central region of Scotland was populated with 383 weaned spring
47 born calves of various breeds from 3 markets between the 3rd October 2014 and the 3rd
48 November 2014. The cattle were sourced from 96 farms in the Highlands and Islands of Scotland
49 (1-26 calves/farm). Upon arrival on farm in October, the calves were administered a live gE
50 deleted BoHV-1 vaccine and an inactivated *Manheimia haemolytica* vaccine. Despite these
51 products not being licenced to be administered concurrently, both vaccines were administered
52 on the same day at different sites by intra-muscular injection.
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56 The use of unlicensed vaccine combinations is common in veterinary medicine and in many
57 systems is the only practical route by which animals can complete a vaccination course prior to
58 the risk period for disease. Whilst work in veterinary species is limited, there is a strong body of
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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 pyrexia. The farmer had undertaken metaphylaxis 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 pyrexia, with a rectal temperature greater than 40°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

1 pneumonia by the farmer and over 50% of the animals examined were pyrexia, it was
2 recommended that the affected group should be treated metaphalactically for
3 primary/secondary bacterial pneumonia with 20 mg/kg long acting oxytetracycline by intra-
4 muscular injection and 0.5 mg/kg meloxicam by subcutaneous injection, and that the farmer
5 should be prepared to administer the same metaphalactic treatment to any subsequently
6 affected groups if necessary. To minimise the risk of pathogen spread, no movement of stock
7 was to occur between groups in the shared airspace or of at-risk animals from the affected
8 airspace to other groups on the farm.
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11 **DIFFERENTIAL DIAGNOSIS *If relevant***
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14 Primary respiratory disease caused by:

- 15 • BoHV-1
- 16 • BRSV
- 17 • PI3
- 18 • *Pasteurella multocida*
- 19 • *Mycoplamsa bovis /dispar*
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22 Respiratory disease secondary to concurrent immunosuppression due to:

- 23 • Bovine viral diarrhoea virus (BVDV)
- 24 • Fascioliasis
- 25 • Environmental, nutritional or husbandry stressors
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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°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* (Pryslak 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

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

26
27 In this case, a presumptive diagnosis was achieved within 5 days by PCR following BAL and
28 conjunctival swabs, which informed targeted herd management decisions. The BoHV-1 viral PCR
29 used is unable to distinguish between field and vaccine virus (Fiona Howie, personal
30 communication), hence the importance of serology in confirming the active cycling of field virus.
31 More rapid diagnosis would have allowed these decisions to be made earlier and would have
32 reduced the amount of antimicrobials used in this outbreak. This illustrates the need for rapid
33 diagnostic tests to avoid inappropriate antimicrobial use. We also note that only one of the
34 three BAL samples was BoHV-1 virus positive, hence highlighting the need to select an
35 appropriate sample size and the importance of serological surveillance.

38
39 The use of a gE deleted vaccine allowed a more granular analysis of the serological data, by
40 differentiating between vaccination and field virus exposure, hence confirming that field virus
41 was actively cycling and infecting naïve animals. This highlights the necessity of using marker
42 vaccines in the control and surveillance of BoHV-1 and that where vaccines are available that
43 allow differentiation between infected and vaccinated (DIVA) individuals that these should be
44 used preferentially.

46
47 Two of the six animals involved in the serological testing converted to *M. Bovis* during the
48 outbreak. The role of *M. Bovis* as a primary or secondary pathogen in this outbreak warrants
49 discussion. Prysliak and others (2011) described how 6-8 month old calves were more likely to
50 develop clinical disease related to *M. bovis* after exposure to BoHV-1. Given that only two of the
51 six animals tested seroconverted to *M. bovis* compared to five of the six seroconverting to
52 BoHV-1, *M. bovis* is more likely to have been a secondary pathogen in this outbreak.

54
55 The SPC for the vaccine used prior to this outbreak notes that "After a single dose vaccination, a
56 significant reduction of virus shedding duration has been demonstrated upon challenge for 6
57 months. After two doses of vaccine, the intensity and duration of clinical symptoms as well as
58 the titre and duration of virus shedding are significantly reduced following infection". This

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

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

16
17
18 Investigations at the time of the outbreak failed to identify any other concurrent diseases or
19 potential causes of immunosuppression. The growth rate and body condition score of the calves
20 prior to the outbreak were appropriate as was the ration and minerals on offer. Furthermore,
21 abattoir reports showed that active liver fluke was present in less than 2% of animals at
22 slaughter, whilst faecal worm egg count and fluke sedimentation tests indicated that concurrent
23 immunosuppression caused by parasitism was unlikely. Metabolic profiling was not undertaken
24 and may have identified negative energy balance at the time of the outbreak, but given the
25 lowered feed intakes due to respiratory disease, it would not have been possible to determine
26 whether any negative energy balance was primary or secondary to the clinical outbreak.
27 The stocking density, air quality and ventilation were assessed and deemed to be satisfactory for
28 the main shed housing 300 animals. Poor ventilation and air quality could have been a
29 contributory factor to the disease observed in the separate airspace housing the remaining 83
30 animals. The farmer reported going on holiday prior to the outbreak starting and was concerned
31 that a change in management and routine may have occurred during this period. Nothing
32 unusual was reported by the farm staff and it is the authors' opinion that it is unlikely that this
33 precipitated the outbreak.

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38 The prevention of BoHV-1 circulation within a herd should ideally be achieved by appropriate
39 biosecurity measures and protection of stock from pathogen exposure. Where possible, herds
40 should be "closed" and bought in stock should be from a herd known to be negative for BoHV-1.
41 Where the status of the herd of origin is unknown, bought in animals should be isolated and
42 tested for BoHV-1 antibodies and then segregated depending on risk (Van Winden, 2005). With
43 this in mind, vertical integration of farming systems may help to improve biosecurity and
44 mitigate disease risk (Kahan, 2013). That said, the business model of the farm in this case report
45 relies on purchasing calves from a large number of crofters in the North-West of Scotland. These
46 units invariably do not know their disease status and there is a strong tradition of selling calves
47 through markets, where they may be exposed to a variety of pathogens. Within this context,
48 discussions relating to biosecurity have not been tractable and the use of vaccines have become
49 the mainstay of BoHV-1 control.

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52 The economic impact of this outbreak, excluding labour, is summarised in Table 2. The reduced
53 live weight gain is calculated as a result of the overall reduced feed intakes for 383 animals over
54 a two week period. As no animals were weighed during the outbreak and animals were only
55 weighed at the start and end of the housing period (as is common practice) a conservative
56 estimate reduction in daily liveweight gain of 0.5kg/day and the 2015 average market value of
57 approximately £1.80 per kg of live weight have been used.

1 Had the revised vaccination programme been implemented before the outbreak in December
2 2014, the farm would have saved £13,662, assuming effective vaccine efficacy.
3

4 Conclusion

5
6 When investigating an SLEE event, it is often difficult for the practitioner to disentangle the
7 performance of the product from the multitude of factors that may contribute to a BRD
8 outbreak. Penny 2013 noted the importance of investigating, diagnosing and reporting SLEE
9 events correctly. The currently available data provides little guidance for a practitioner dealing
10 with cases on their clients' farms and limits decision making and appropriate herd health
11 planning. This can ultimately impact animal welfare and farm profitability when such disease
12 breakdowns do occur. This case report not only reviews the impact of one such breakdown, but
13 also highlights the need for more data surrounding the subject to be made available to the
14 general practitioner.
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20 **LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required** 21 **field**

- 22 • The importance of appropriate investigation and reporting of veterinary vaccine
23 Suspected Lack of Expected Efficacy (SLEE) events.
- 24 • There is a current paucity of data available to practitioners relating to the field
25 performance of veterinary vaccines.
- 26 • The appropriate recording and usage of this data could help guide herd health planning
27 and limit the impact of disease breakdowns on animal welfare and farm economics.
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 54 **FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document***

55
 56 **Table1: Paired serology results for six acutely affected animals**

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 58 Pre = acute sera, Post = convalescent sera, IBR = Infectious Bovine Rhinotracheitis, g =
 59 glycoprotein, BVDV = Bovine Viral Diarrhoea, PI3 = Parainfluenza 3, BRSV = Bovine
 60

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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<p>TITLE OF CASE <i>Do not include "a case report"</i></p> <p>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.</p>
<p>SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i></p> <p>Keywords: Cattle, Respiratory, Vaccination, Infectious Bovine Rhinotracheitis (IBR), Bovine Herpes Virus (BoHV),</p> <p>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.</p>

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

1 Bovine respiratory disease (BRD) is a major cause of mortality, production loss, antimicrobial use
2 and compromised animal welfare in cattle globally. On feedlots in the USA, production losses
3 and treatment costs alone during a BRD outbreak (not accounting for time and labour) are
4 estimated at approximately \$14 per animal on the farm (Snowder, 2006) or between \$23-54 in
5 carcass losses per clinically affected animal (Schneider, 2009). In the UK, daily live weight gain of
6 cattle with lung lobe consolidation is estimated to be reduced by 72-202 g/day depending on
7 the degree of consolidation, compared to cattle without any evidence of gross lung pathology
8 (Williams, 2007). Recent economic analysis of the costs of BRD in the UK is not available,
9 however Andrews (2000) calculated an average loss per animal within an affected group of
10 £43.26 for dairy and £82.10 for suckler calves. As BRD outbreaks are often complex and
11 multifactorial, disease prevention can often be problematic (Edwards, 2010), however
12 vaccination is a significant component of most prevention strategies in trying to reduce or
13 mitigate economic losses and animal suffering caused by BRD.
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18 Veterinary vaccines are typically developed and licenced using disease challenge models in small
19 groups of animals under carefully controlled conditions. In the UK, field trials are required to
20 demonstrate product safety, however due to difficulties with designing sufficiently powered
21 studies, may not demonstrate efficacy. Licencing data is rarely made public, although a detailed
22 scientific discussion based on submitted data is available for a minority of veterinary vaccines
23 available in the UK through the European Medicines Agency. Combined with limited data
24 relating to the field efficacy of vaccines targeting BRD (Taylor, 2010), practitioners
25 predominantly rely on the Summary of Product Characteristics (SPC), pharmaceutical company
26 representatives and their own experiences when making vaccination decisions (Richens, 2016).
27 When investigating an SLEE event, it is often difficult for the practitioner to disentangle the
28 performance of the product from the multitude of factors that may contribute to a BRD
29 outbreak. Infectious Bovine Rhinotracheitis (IBR), caused by Bovine Herpes Virus-1 (BoHV-1) is a
30 common pathogen involved in BRD in the UK (Graham, 2013). Awareness of disease is relatively
31 high within the industry, illustrated by a recent survey of UK beef and dairy herds, where BoHV-
32 1 vaccines were used in at least 45% and 60% of herds respectively (Cresswell, 2014). The
33 widespread use of glycoprotein E (gE) deleted (marker) BoHV-1 vaccines that allow BoHV-
34 1 naïve, vaccinated and exposed animals to be differentiated, has facilitated the practitioner in
35 determining whether BoHV-1 is the causative agent during a BRD outbreak (Ackermann, 2006).
36 Here we describe the diagnosis of an outbreak of IBR in a herd vaccinated with a live gE deleted
37 BoHV-1 vaccine.
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CASE PRESENTATION *Presenting features, clinical and environmental history*

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46 A calf fattening unit in the central region of Scotland was populated with 383 weaned spring
47 born calves of various breeds from 3 markets between the 3rd October 2014 and the 3rd
48 November 2014. The cattle were sourced from 96 farms in the Highlands and Islands of Scotland
49 (1-26 calves/farm). Upon arrival on farm in October, the calves were administered a live gE
50 deleted BoHV-1 vaccine and an inactivated *Manheimia haemolytica* vaccine. Despite these
51 products not being licenced to be administered concurrently, both vaccines were administered
52 on the same day at different sites by intra-muscular injection.
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54

55
56 The use of unlicensed vaccine combinations is common in veterinary medicine and in many
57 systems is the only practical route by which animals can complete a vaccination course prior to
58 the risk period for disease. Whilst work in veterinary species is limited, there is a strong body of
59
60

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

8
9 The animals also received a 10% fenbendazole oral drench at 7.5mg/kg. The animals were then
10 housed for 5 days and fed a mix of *ad lib* silage and straw. The animals were then turned out on
11 to grass/stubble, where they were trained to eat conserved forage with a gradual increased
12 access to *ad lib* silage and straw, and trough fed concentrate mix at 2.5 kg/head. The homemade
13 concentrate mix was approximately 80% barley, 20% brewer's grains and 150 g per head of a
14 general purpose beef finisher mineral.

15
16
17 The animals were housed in December and continued on the same feeding regime. Three
18 hundred animals were housed in a single airspace in 4 groups of 75 animals with two pens either
19 side of a central feed trough. The remaining animals were in separate airspaces in groups no
20 larger than 30. Upon housing, they all received a multivalent live intra-nasal parainfluenza virus
21 3 (PI3) and bovine respiratory syncytial virus (BRSV) vaccine. Two weeks later these animals had
22 their backs clipped, pour-on ivermectin administered at 500 µg/kg, and a 10 mg/kg
23 subcutaneous injection of nitroxylin.
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27

28 **INVESTIGATIONS *If relevant***

29
30 The Farm Animal Practice at the Royal (Dick) School of Veterinary Studies (R(D)SVS) was
31 contacted in early February by the farmer due to a higher than expected incidence of
32 pneumonia. Thirty individual animals in a separate airspace had been noted by the farmer to
33 have poor feed intakes, hypersalivation and a moist cough with approximately 50% of the
34 animals within the group being pyrexia. The farmer had undertaken metaphylaxis of the group
35 with long acting oxytetracycline at 20 mg/kg and meloxicam at 0.5 mg/kg. He noted that clinical
36 signs resolved within approximately 48 h, apart from a few animals with a persistent moist
37 cough.
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41 Approximately 1 week later the farmer reported a number of animals in a pen of 75 (in the
42 shared airspace) presenting with similar clinical signs as seen previously. At this stage the farmer
43 sought veterinary advice. The farmer provided a history of a similar disease outbreak the
44 previous Christmas. However as the outbreak occurred over Christmas Eve and Christmas Day, a
45 full investigation had not been undertaken and whole farm metaphylaxis had been
46 implemented.
47
48

49 Upon examination, the calves in question appeared to be in good body condition and the
50 housing was well ventilated. More than 50% of the animals in the affected group were pyrexia,
51 with a rectal temperature greater than 40°C. Several animals were observed to be
52 hypersalivating, with a mild serous ocular discharge and light cough. A number of animals
53 remained distant from the feed face and the farmer reported a lack of appetite and reduced
54 feed intakes for the previous 48 hours. One calf examined was extremely dyspnoeic, exhibiting
55 excessive upper respiratory tract noise and marked respiratory effort.
56
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59 As the separate group of 30 animals on farm had already been successfully treated for
60

1 pneumonia by the farmer and over 50% of the animals examined were pyrexia, it was
2 recommended that the affected group should be treated metaphalactically for
3 primary/secondary bacterial pneumonia with 20 mg/kg long acting oxytetracycline by intra-
4 muscular injection and 0.5 mg/kg meloxicam by subcutaneous injection, and that the farmer
5 should be prepared to administer the same metaphalactic treatment to any subsequently
6 affected groups if necessary. To minimise the risk of pathogen spread, no movement of stock
7 was to occur between groups in the shared airspace or of at-risk animals from the affected
8 airspace to other groups on the farm.
9
10

11 **DIFFERENTIAL DIAGNOSIS *If relevant***
12

13
14 Primary respiratory disease caused by:

- 15 • BoHV-1
- 16 • BRSV
- 17 • PI3
- 18 • *Pasteurella multocida*
- 19 • *Mycoplamsa bovis /dispar*
20
21

22 Respiratory disease secondary to concurrent immunosuppression due to:

- 23 • Bovine viral diarrhoea virus (BVDV)
- 24 • Fascioliasis
- 25 • Environmental, nutritional or husbandry stressors
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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°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* (Pryslak 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

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

26
27 In this case, a presumptive diagnosis was achieved within 5 days by PCR following BAL and
28 conjunctival swabs, which informed targeted herd management decisions. The BoHV-1 viral PCR
29 used is unable to distinguish between field and vaccine virus (Fiona Howie, personal
30 communication), hence the importance of serology in confirming the active cycling of field virus.
31 More rapid diagnosis would have allowed these decisions to be made earlier and would have
32 reduced the amount of antimicrobials used in this outbreak. This illustrates the need for rapid
33 diagnostic tests to avoid inappropriate antimicrobial use. We also note that only one of the
34 three BAL samples was BoHV-1 virus positive, hence highlighting the need to select an
35 appropriate sample size and the importance of serological surveillance.

38
39 The use of a gE deleted vaccine allowed a more granular analysis of the serological data, by
40 differentiating between vaccination and field virus exposure, hence confirming that field virus
41 was actively cycling and infecting naïve animals. This highlights the necessity of using marker
42 vaccines in the control and surveillance of BoHV-1 and that where vaccines are available that
43 allow differentiation between infected and vaccinated (DIVA) individuals that these should be
44 used preferentially.

46
47 Two of the six animals involved in the serological testing converted to *M. Bovis* during the
48 outbreak. The role of *M. Bovis* as a primary or secondary pathogen in this outbreak warrants
49 discussion. Prysljak and others (2011) described how 6-8 month old calves were more likely to
50 develop clinical disease related to *M. bovis* after exposure to BoHV-1. Given that only two of the
51 six animals tested seroconverted to *M. bovis* compared to five of the six seroconverting to
52 BoHV-1, *M. bovis* is more likely to have been a secondary pathogen in this outbreak.

54
55 The SPC for the vaccine used prior to this outbreak notes that "After a single dose vaccination, a
56 significant reduction of virus shedding duration has been demonstrated upon challenge for 6
57 months. After two doses of vaccine, the intensity and duration of clinical symptoms as well as
58 the titre and duration of virus shedding are significantly reduced following infection". This

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

8
9
10 Immunosuppression either at the time of vaccination or the time of the outbreak could have
11 been a contributory factor to this outbreak. Whilst the acute sera demonstrated seroconversion
12 to the vaccine, only a small proportion of the herd were sampled, whilst serology gives no
13 indication as to the avidity of the antibody response or magnitude of the T-cell response
14 following vaccination. The possibility of a 'poor quality' response following initial vaccination
15 due to concurrent disease or immunosuppression cannot therefore be excluded.

16
17
18 Investigations at the time of the outbreak failed to identify any other concurrent diseases or
19 potential causes of immunosuppression. The growth rate and body condition score of the calves
20 prior to the outbreak were appropriate as was the ration and minerals on offer. Furthermore,
21 abattoir reports showed that active liver fluke was present in less than 2% of animals at
22 slaughter, whilst faecal worm egg count and fluke sedimentation tests indicated that concurrent
23 immunosuppression caused by parasitism was unlikely. Metabolic profiling was not undertaken
24 and may have identified negative energy balance at the time of the outbreak, but given the
25 lowered feed intakes due to respiratory disease, it would not have been possible to determine
26 whether any negative energy balance was primary or secondary to the clinical outbreak.
27 The stocking density, air quality and ventilation were assessed and deemed to be satisfactory for
28 the main shed housing 300 animals. Poor ventilation and air quality could have been a
29 contributory factor to the disease observed in the separate airspace housing the remaining 83
30 animals. The farmer reported going on holiday prior to the outbreak starting and was concerned
31 that a change in management and routine may have occurred during this period. Nothing
32 unusual was reported by the farm staff and it is the authors' opinion that it is unlikely that this
33 precipitated the outbreak.

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37
38 The prevention of BoHV-1 circulation within a herd should ideally be achieved by appropriate
39 biosecurity measures and protection of stock from pathogen exposure. Where possible, herds
40 should be "closed" and bought in stock should be from a herd known to be negative for BoHV-1.
41 Where the status of the herd of origin is unknown, bought in animals should be isolated and
42 tested for BoHV-1 antibodies and then segregated depending on risk (Van Winden, 2005). With
43 this in mind, vertical integration of farming systems may help to improve biosecurity and
44 mitigate disease risk (Kahan, 2013). That said, the business model of the farm in this case report
45 relies on purchasing calves from a large number of crofters in the North-West of Scotland. These
46 units invariably do not know their disease status and there is a strong tradition of selling calves
47 through markets, where they may be exposed to a variety of pathogens. Within this context,
48 discussions relating to biosecurity have not been tractable and the use of vaccines have become
49 the mainstay of BoHV-1 control.

50
51
52 The economic impact of this outbreak, excluding labour, is summarised in Table 2. The reduced
53 live weight gain is calculated as a result of the overall reduced feed intakes for 383 animals over
54 a two week period. As no animals were weighed during the outbreak and animals were only
55 weighed at the start and end of the housing period (as is common practice) a conservative
56 estimate reduction in daily liveweight gain of 0.5kg/day and the 2015 average market value of
57 approximately £1.80 per kg of live weight have been used.

1 Had the revised vaccination programme been implemented before the outbreak in December
2 2014, the farm would have saved £13,662, assuming effective vaccine efficacy.
3

4 Conclusion

5
6 When investigating an SLEE event, it is often difficult for the practitioner to disentangle the
7 performance of the product from the multitude of factors that may contribute to a BRD
8 outbreak. Penny 2013 noted the importance of investigating, diagnosing and reporting SLEE
9 events correctly. The currently available data provides little guidance for a practitioner dealing
10 with cases on their clients' farms and limits decision making and appropriate herd health
11 planning. This can ultimately impact animal welfare and farm profitability when such disease
12 breakdowns do occur. This case report not only reviews the impact of one such breakdown, but
13 also highlights the need for more data surrounding the subject to be made available to the
14 general practitioner.
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20 **LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required** 21 **field**

- 22 • The importance of appropriate investigation and reporting of veterinary vaccine
23 Suspected Lack of Expected Efficacy (SLEE) events.
- 24 • There is a current paucity of data available to practitioners relating to the field
25 performance of veterinary vaccines.
- 26 • The appropriate recording and usage of this data could help guide herd health planning
27 and limit the impact of disease breakdowns on animal welfare and farm economics.
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 54 **FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document***

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 56 **Table1: Paired serology results for six acutely affected animals**

57
 58 Pre = acute sera, Post = convalescent sera, IBR = Infectious Bovine Rhinotracheitis, g =
 59 glycoprotein, BVDV = Bovine Viral Diarrhoea, PI3 = Parainfluenza 3, BRSV = Bovine
 60

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

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