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Effects of exposure to *Bovine viral diarrhoea virus 1* on risk of bovine respiratory disease in Australian feedlot cattle

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ABSTRACT

Viruses play a key role in the complex aetiology of bovine respiratory disease (BRD). *Bovine viral diarrhoea virus 1* (BVDV-1) is widespread in Australia and has been shown to contribute to BRD occurrence. As part of a prospective longitudinal study on BRD, effects of exposure to BVDV-1 on risk of BRD in Australian feedlot cattle were investigated. A total of 35,160 animals were enrolled at induction (when animals were identified and characteristics recorded), held in feedlot pens with other cattle (cohorts) and monitored for occurrence of BRD over the first 50 days following induction. Biological samples collected from all animals were tested to determine which animals were persistently infected (PI) with BVDV-1. Data obtained from the Australian National Livestock Identification System database were used to determine which groups of animals that were together at the farm of origin and at 28 days prior to induction (and were enrolled in the study) contained a PI animal and hence to identify animals that had probably been exposed to a PI animal prior to induction. Multi-level Bayesian logistic regression models were fitted to estimate the effects of exposure to BVDV-1 on the risk of occurrence of BRD.

Although only a total of 85 study animals (0.24%) were identified as being PI with BVDV-1, BVDV-1 was detected on quantitative polymerase chain reaction in 59% of cohorts. The PI animals were at moderately increased risk of BRD (OR 1.9; 95% credible interval 1.0–3.2). Exposure to BVDV-1 in the cohort was also associated with a moderately increased risk of BRD (OR 1.7; 95% credible interval 1.1–2.5) regardless of whether or not a PI animal was identified within the cohort. Additional analyses indicated that a single quantitative real-time PCR test is useful for distinguishing PI animals from transiently infected animals.

The results of the study suggest that removal of PI animals and/or vaccination, both before feedlot entry, would reduce the impact of BVDV-1 on BRD risk in cattle in Australian feedlots. Economic assessment of these strategies under Australian conditions is required.

1. Introduction

Bovine respiratory disease (BRD) is the major cause of clinical disease and death in feedlot cattle worldwide (Edwards, 2010) and in Australian feedlots it has been estimated to cause more than 70% of clinical disease cases and 50% of deaths (Sackett et al., 2006). This multifactorial disease may occur when there is a combination of susceptible animals, infectious agents and stressors. Specific pathogens are not required for development of BRD; it can develop as a result of infections with various combinations of viruses and bacteria. Bovine viral diarrhoea viruses (BVDV) belong to the pestivirus genus within the *Flavivirus* family and have frequently been associated with BRD. Exposure to BVDV has been associated with increased risk of BRD in feedlot cattle populations (Martin and Bohac, 1986; Martin et al., 1990; Dunn et al., 1995; O'Connor et al., 2001b), and BVDV has been regularly isolated from the lungs of cattle that have died from pneumonia (Gagea et al., 2006; Booker et al., 2008b; Fulton et al., 2009a).

There are two recognised species of BVDV that infect cattle, BVDV-1 and BVDV-2. Seroprevalence and virus detection studies have shown that BVDV-1 is common in cattle populations

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worldwide (Martin et al., 1989; O'Connor et al., 2001a; Ridpath, 2010b; Morton et al., 2013). Reported seroprevalences for BVDV-1 at feedlot entry have ranged from 20% to 68% (Martin and Bohac, 1986; Dunn et al., 1995; O'Connor et al., 2001a; Fulton et al., 2002a). Molecular phylogenetic reconstructions have been used to group BVDV-1 into at least 11 genotypes, BVDV-1a to BVDV-1k (Becher et al., 1999; Vilcek et al., 2001). While six additional genotypes have been proposed, further studies are required to clarify their relationship to the other BVDV-1 genotypes (Booth et al., 2013). In comparison, only two BVDV-2 genotypes have been proposed (Becher et al., 1999). While the biological differences between these genotypes are unknown, BVDV-1b is the genotype most frequently associated with BRD in the United States (Fulton et al., 2002b). Only BVDV-1 has been identified in Australia, with the majority of these viruses being classified within the BVDV-1c genotype (Mahony et al., 2005). These viruses remain genetically distinct from genotypes identified in North America and Europe (Ridpath, 2010b; Ridpath et al., 2010).

In a review of the role of BVDV in BRD, Ridpath (2010a) examined the contributions of persistent and transient infections and synergism with other respiratory pathogens. Infection in immunologically competent animals results in cattle becoming transiently infected (TI) with BVDV-1. Infection of bovine foetuses between 28 and 125 days of gestation may result in the birth of immunotolerant persistently infected (PI) animals which continually shed infectious virus into the environment for life (Ridpath, 2010a). Infection of bovine foetuses at a later stage of gestation may result in the birth of apparently normal calves. However, such congenitally infected calves may perform poorly and be at increased risk of disease compared to calves not exposed to BVDV in-utero (Torres, 2014).

Quantitative real time polymerase chain reaction (qPCR) techniques have excellent analytical sensitivity and specificity for detecting BVDV (Bhudevi and Weinstock, 2001) and the cycling threshold (Ct) values obtained from qPCR analyses are related to the amount of viral RNA present in the processed sample. In a review of diagnostic options, Lanyon et al. (2014) noted that qPCR analysis was suitable for the detection of a single PI animal contributing to a pooled test of up to 50 samples. However, relatively low numbers of virus shed during transient infection may also be detected (Bhudevi and Weinstock, 2003). The duration of viraemia due to transient BVDV-1 infection is usually less than 15 days (Fulton, 2013), so repeated sampling and qPCR testing is recommended after a minimum of 28 days to differentiate PI from TI animals (Lanyon et al., 2014). Because qPCR techniques enable the amount of viral nucleic acid present in biological samples to be quantified and because the concentrations of BVDV-1 in discharges shed by TI animals may be lower compared to PI animals, it has been suggested that qPCR may assist in distinguishing between the two (Lanyon et al., 2014). Following infection with BVDV-1, TI animals become seropositive within two to three weeks, while PI animals remain seronegative to antigenically homologous BVDV-1 strains (Lanyon et al., 2014). In populations exposed to a single genotype, serological data may assist in identifying PI animals when used in combination with qPCR testing.

Because PI animals continuously shed large amounts of the virus, they are the major source of BVDV-1 to in-contact animals, (Ridpath, 2010a). BVDV-1 is transmitted through direct contact with infected animals, and to non-contact animals via aerosol (over short distances), and via fomites (Mars et al., 1999; Lindberg et al., 2004; Ridpath, 2010a). With transient infections, mild clinical signs may ensue after an incubation period of 5–7 days (Fulton, 2013). Clinical signs of BRD associated with BVDV-1 infection may develop due to immunosuppression and biological synergism with other infectious agents (Ridpath, 2010a). Although PI animals are the major reservoir for maintenance and transmission of BVDV-1 in cattle populations transmission of BVDV-1 and BVDV-2 from TI animals may also occur. TI animals can shed BVDV-1 and BVDV-2 in nasal secretions (Nickell et al., 2011), and ongoing infection in cattle herds in the absence of PI animals has been documented (Moen et al., 2005). Experimental transmission of BVDV-1a has been demonstrated from apparently recovered and antibody positive animals 98 days post challenge (Collins et al., 2009).

The prevalence of persistent infection in animals arriving at feedlots is low, with reported estimates ranging from less than 0.1% to 0.4%, (Taylor et al., 1995; Loneragan et al., 2005; Fulton et al., 2006). Despite the low prevalence of persistent infection, and the tendency for PI animals to cluster within arrival groups, a small number of PI animals in feedlot settings may result in animals in a large proportion of pens being exposed to BVDV, especially if adjacent pens are considered exposed (Loneragan et al., 2005; Fulton et al., 2009b). Hence, the identification and removal of PI animals has been advocated as a BRD control strategy in cattle populations (Fulton et al., 2009b).

Although seroprevalence studies indicate that BVDV-1 is widespread in Australian cattle populations (Dunn et al., 1995; Durham and Paine, 1997; Taylor et al., 2006), and seroconversion to BVDV-1 has been associated with BRD in Australian feedlot cattle at the animal level (Dunn et al., 1995), there have been no detailed investigations into effects of exposure to PI animals on the occurrence of BRD in Australian feedlot populations. Results from North American studies investigating the impact of the presence of PI animals within feedlots on BRD risk have been variable (Loneragan et al., 2005; O'Connor et al., 2005; Booker et al., 2008a). While it is plausible that prior exposure to BVDV-1 would ameliorate the adverse effect of exposure to PI animals, none of these studies were able to assess the effects of prior exposure to the virus.

1.1. Hypotheses and aims

The following *a priori* hypotheses were formulated based on published literature and plausible biological pathways:

a) The risk of BRD is increased in cohorts (feedlot pens) in which BVDV-1 is infecting animals compared to cohorts in which BVDV-1 is not being transmitted;
b) The risk of BRD is increased if a PI animal is present in the cohort compared to cohorts in which BVDV-1 is being transmitted but no PI animal is present, because in-contact animals in the same pen as PI animals are probably exposed to higher viral loads than animals in pens without PI animals;
c) The effects of exposure to BVDV-1 in feedlot pens vary depending on prior exposure to BVDV-1 PI animals. Animals from the same farm as a PI animal may have been exposed in-utero; such congenitally infected animals may be at increased risk of BRD even if not PI. Animals exposed to BVDV-1 PI animals at a later stage are at reduced risk of BRD compared to animals not previously exposed to BVDV-1 PI animals, provided exposure occurred a sufficient time (at least 4 weeks) prior to exposure in a feedlot pen.
d) Animals with sufficiently high antibody concentrations at induction are protected from increases in BRD risk due to exposure to BVDV-1 at the feedlot
e) PI animals have lower Ct readings in qPCR analyses than TI animals, and hence a single Ct value may be of use in discriminating between PI and TI animals.

The objectives of the current study were to determine the prevalence of persistent infection in animals arriving at Australian feedlots, and test the hypotheses outlined above.

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