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Immune response of mature cows subjected to annual booster vaccination against neonatal calf diarrhoea with two different commercial vaccines: A non-inferiority study

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ABSTRACT

Neonatal calf diarrhoea can have important economic consequences. Scour vaccines are available against some of the most frequent pathogens responsible for this disease: Bovine Rotavirus (BoRV), Bovine Coronavirus (BoCV) and *E. coli* K99. In this multi-centre, randomised, blinded study, adult cows vaccinated with a trivalent vaccine marketed for years (Rotavec™ Corona, MSD Animal Health - RC) prior to last parturition were re-vaccinated 12–15 months later, prior to the upcoming parturition, with either a single injection of a recently marketed vaccine (Bovigen™ Scour, Virbac - BS), or RC. The aim of this trial was to verify whether BS is not inferior to RC for the stimulation of the immune response and the passive transfer to calves in these conditions.

A total of 136 multiparous dairy cows, from 5 different herds and located in 3 countries (France, UK and Germany) were enrolled in the study. Sixty-five cows were vaccinated with BS and 71 with RC. Antibody levels, measured by competitive ELISA and represented as percentage of inhibition (PI), were assessed in the cow's serum (on the day of vaccination: D0 and on days 21, 42 and at calving), in the colostrum and in the serum of calves in the first week of life. Differences in means of PI between groups and the 95% confidence interval (CI) were calculated. The non-inferiority threshold was set at −10%. The relationships between antibody levels in the colostrum and the vaccination-calving interval (VCI) or the inter-booster vaccination interval (IBVI) were also analysed.

All the lower margins of the 95% CI of the difference in means of PI, in all samples and for the 3 pathogens assessed, were above −10%. This result shows that BS is not inferior to RC for the stimulation of the immune response against BoRV, BoCV and *E. coli* K99 and the passive transfer of immunity to calves when this vaccine is administered to their dams previously vaccinated with RC. Furthermore, no correlation was found between PI values in the colostrum and the VCI or IBVI. The ratio of animals with a PI ≥ 95% in the colostrum, among cows with similar intervals, was not significantly different between groups, for all antigens tested.

Therefore, this study shows that a single injection of the heterologous vaccine BS can be used as a booster in cattle previously vaccinated with RC.

1. Introduction

Neonatal calf diarrhoea (NCD) affects mainly calves under 4 weeks of age. It is characterised by a diarrhoea leading to dehydration and acidosis which can have systemic consequences and potentially lead to death (Millemann, 2009). The prevalence of NCD has been estimated around 20% and this disease is a major cause of death in young calves, responsible for more than 50% in some countries (Millemann, 2009;

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Bartels et al., 2010; Lorenz et al., 2011; Cho and Yoon, 2014; Meganck et al., 2015). The loss of calves, the management of the disease and the consequences on the health, growth rate and reproductive potential of surviving calves can lead to a significant economic loss (Millemann, 2009; Cho and Yoon, 2014). The environment, herd size and farm management practices, such as hygiene, feeding, routine use of antibiotics, neonatal care and colostrum management, can influence NCD prevalence in herds (Bendali et al., 1999; Bartels et al., 2010; Meganck et al., 2014). These factors should be evaluated and properly monitored to avoid NCD. The etiological diagnosis of calf diarrhoea can also be sought in order to limit the consequences with the appropriate etiologic or preventive treatment (Millemann, 2009; Meganck et al., 2014, 2015).

The main causative infectious agents of NCD, especially in calves under 12 days of age, are the bovine rotavirus (BoRV), *Cryptosporidium parvum*, the bovine coronavirus responsible for calf diarrhoea (BoCV-CD) and Enterotoxigenic *Escherichia coli* (ETEC), but other pathogens can also be responsible for this disease (Acres et al., 1977; Athanassious et al., 1994; Millemann, 2009; Cho and Yoon, 2014; Meganck et al., 2015). The clinical features and analysis of the environment can help determine the origin of the disease and several diagnostic tools are now available to confirm the presence of one or more suspected pathogens (Bendali et al., 1999; Millemann, 2009; Cho and Yoon, 2014).

Different strains and serotypes of the NCD causative agents have been identified. Rotaviruses are double-stranded RNA viruses which can be classified by groups according to the genotype of their inner capsid protein VP6. They can be further classified according to their outer capsid proteins, mainly VP7 (glycoproteins, G) and VP4 (protease-sensitive, P) proteins (Matthijnssens et al., 2011). NCD is mainly induced by group A rotaviruses with G6 and G10 and P[1], P[5] and P[11] genotypes being the predominant ones in cows (Snodgrass et al., 1990; Cho and Yoon, 2014; Collins et al., 2014). In Europe, the prevalence of BoRV in diarrheic calves can vary from 30% to 60% but a higher prevalence can be seen in other areas (Bartels et al., 2010; Meganck et al., 2014). They are mainly found in calves at 1–2 weeks of age (Millemann, 2009; Bartels et al., 2010; Cho and Yoon, 2014).

Bovine coronavirus (BoCV), an enveloped and single-stranded RNA virus, also generally affects calves under 2 weeks of age (Millemann, 2009; Boileau and Kapil, 2010; Cho and Yoon, 2014). The pathology of BoCV in NCD is often more severe than that of rotavirus, resulting in a mucohaemorrhagic enterocolitis (Boileau and Kapil, 2010). The prevalence of this pathogen in calves with diarrhoea is generally around 8% in Europe (Bartels et al., 2010). Hemagglutinin-esterase (HE) and spike (S) proteins are important for the fusion with the host intestinal cells and these proteins (and others) contain important neutralizing epitopes with a generally low antigenic variability (Clark, 1993; Tsunemitsu et al., 1995; Boileau and Kapil, 2010; Cho and Yoon, 2014).

Among the six major diarrhoeagenic *E. coli* pathotypes, ETEC is the confirmed main causative agent of NCD (Kolenda et al., 2015). This pathogen is responsible for less than 10% of NCD cases in Europe but higher prevalence have been recorded elsewhere (Acres et al., 1977; Bartels et al., 2010; Meganck et al., 2014). The virulence factors of ETEC are its specific cytotoxic toxins and adhesins (DebRoy and Maddox, 2001; Kolenda et al., 2015). It has been shown recently, in a systematic review, that the fimbrial adhesins F5 (or K99), F17, and F41 fimbriae and the heat-stable enterotoxin (ST) were significantly associated with calf diarrhoea (Kolenda et al., 2015). This type of *E.coli* usually affects very young calves (under 5 days of age) and leads to a rapid dehydration.

Cryptosporidium parvum is a protozoan parasite frequently associated with NCD (in 30–60% cases) although infection can also be asymptomatic (Bartels et al., 2010; Cho and Yoon, 2014; Meganck et al., 2014). The oocysts excreted into the faeces can survive for months in the environment and are resistant to most disinfectant. Eliminating this pathogen can therefore be challenging (Cho and Yoon, 2014; Meganck et al., 2015).

Several vaccines have been developed against ETEC, rotavirus and coronavirus but no commercial vaccine is available against *C. parvum* yet (Cresswell et al., 2014). Vaccinating pregnant cows before parturition usually triggers an immune response which leads to the presence of protective immunoglobulins in the colostrum. The calf can then be passively protected if it stands rapidly and is allowed to nurse to satiety, or if the colostrum is fed properly (Kohara et al., 1997; Weaver et al., 2000; Meganck et al., 2015). The vaccines available for calf scours can contain different serotypes, strains or epitope presentations of BoCV, BoRV and ETEC. However, previous studies have shown that the different serotypes of Group A BoRV share similar epitopes and that heterotypic immune response can occur in already exposed cattle. This means that vaccination of adult cows with a single bovine rotavirus serotype will protect against all serotypes to which the cattle has been exposed (Snodgrass et al., 1984, 1991; Brussow et al., 1991; Taniguchi et al., 1991). A cross-reaction between BoCV strains is even more likely since this virus presents a low antigenic variation (Clark, 1993; Tsunemitsu et al., 1995; Boileau and Kapil, 2010). Finally, all vaccines contain the F5 adhesin, the main virulent factor found in calf ETEC responsible for NCD (Nagy and Fekete, 1999; DebRoy and Maddox, 2001; Kolenda et al., 2015; Picco et al., 2015). Therefore, although not demonstrated yet, it should be possible to use a different scour vaccine than the one used for the previous vaccination.

The aim of this multi-centre, randomised, blinded study was to assess antibody responses to BoRV, BoCV and F5 adhesin in adult cows that were vaccinated with a vaccine marketed for years prior to last parturition and revaccinated 12–15 months later, prior to the upcoming parturition, with a single booster-injection of either the same vaccine or a recently marketed new vaccine. This study aimed to evaluate antibody levels were evaluated in the serum of vaccinated dams, in the colostrum and in the serum of new-born calves, in order to evaluate the immune response in cows and the passive transfer in calves. The results of this study should provide evidence for the possibility to efficiently use these two different vaccines on successive vaccination courses.

2. Material and methods

2.1. Ethical approval

This study was approved by the Internal Ethical Review Committee of Virbac (approval # EU-ERC/201602-01)

2.2. Study design

This was a multi-centre, randomized, blinded, reference-controlled study. Animals vaccinated at last parturition with RC were revaccinated prior to the upcoming parturition with either BS or RC. The immune response and passive immunisation of calves will be compared based on antibody levels (assessed by ELISA) found in the serum of cows and calves and in the colostrum.

For randomisation, animals were allocated to either treatment group according the last digit of their ear tag. Since both vaccines require a different volume of administration, the investigator vaccinating the pregnant cows could not be blinded. Blinding was achieved by assigning a different investigator to collect the samples.

2.3. Animals

Healthy pregnant cows from 5 different herds located in 3 countries (France, UK, Germany), with a parity of 2 or more and vaccinated against NCD with RC during the previous pregnancy (generally 12–15 months before depending on the calving-conception interval) were included in the study. Cows enrolled were expected to be due 12 to 3 weeks after vaccination (cows expected to be due outside this time range were not included). Animals were then allocated to vaccination group BS or group RC.