

Bovine Respiratory Syncytial Virus (BRSV) Pneumonia in Beef Calf Herds Despite Vaccination

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Larsen LE, Tegtmeier C, Pedersen E: Bovine respiratory syncytial virus (BRSV) pneumonia in beef calf herds despite vaccination. Acta vet. scand. 2001, 42, 113-121. – The present report describes the clinical, pathological, serological and virological findings in calves from 2 larger Danish beef herds experiencing outbreaks of pneumonia. The calves had been vaccinated with an inactivated bovine respiratory syncytial virus (BRSV) vaccine 2 months prior to the outbreak. The clinical signs comprised nasal discharge, pyrexia, cough and increased respiratory rates. A total of 28 calves died in the 2 herds. The laboratory investigations revealed that BRSV was involved and probably initiated both outbreaks. Furthermore, the serological results suggested that the vaccine induced only sparse levels of antibodies probably due to the presence of maternally derived antibodies at the time of vaccination. Necropsy findings in 5 calves revealed changes typical for infectious pneumonia with involvement of BRSV. In conclusion, vaccination of calves against BRSV in 2 Danish beef herds failed to protect the calves against severe or even fatal BRSV mediated respiratory disease 2 months later.

Bovine respiratory syncytial virus; BRSV; vaccination; enzootic pneumonia; serology, calves.

Introduction

Respiratory disease is one of the most important health problems in young Danish cattle with substantial financial losses for the industry (Tegtmeier *et al.* 1999, Uttenthal *et al.* 1996). Thus, approximately 20% of the materials from bovines submitted to The Danish Veterinary Laboratory (DVL) for necropsy originate from cattle with a history of respiratory symptoms. Bovine respiratory syncytial virus (BRSV) has been recognised in recent years as the major viral component of the bovine respiratory disease (BRD) complex (Larsen 2000). This is based on the high prevalence of seropositive individuals (Uttenthal *et al.* 2000, Uttenthal *et al.* 1996) and the strong correlation between respiratory disease and detection of the virus in diagnostic samples (Larsen *et al.* 1999). BRSV has a predilection for the lower respiratory tract and may

damage the respiratory tract epithelium directly followed by changes induced by, i.e. inflammatory mediators (Kimman *et al.* 1989a) and/or it may increase the ability of bacteria to invade the lung and cause a secondary bacterial infection (Babiuk *et al.* 1988). So far it has not been possible to prove a clear link between protection and level of actively produced or passively acquired antibodies in natural BRSV infection. Thus, calves less than 6 months are most frequently infected with BRSV despite the presence of maternally derived antibodies. Furthermore, reinfections occur even in sero-positive calves (Van der Poel *et al.* 1993). Antibodies may be partly protective, however, since the incidence and severity of disease seems to be inversely related to the level of specific maternal antibodies (Kimman *et al.* 1988). Several inac-

tivated and modified live BRSV vaccines are commercially available in North-America and Europe, yet none have been registered for use in Denmark (September, 2000). In 1997 approximately 20 Danish beef herds, with confirmed BRSV positive status, received a temporary permission to use an inactivated vaccine against BRSV in calves. The present report describes the clinical, pathological, serological and virological findings in vaccinated calves in 2 Danish beef herds experiencing outbreaks of pneumonia in January 1998.

Materials and methods

Herds and animals

Two beef cattle herds, each producing approximately 1000 calves a year were included. In herd A, new calves, aged 2-4 weeks were purchased from different sources every second month. The calves were reared in groups in 2 different housing systems: An indoor-system where the calves were kept in groups of 45 and an outdoor system where the calves were kept in groups of 15 in calf hutches. In herd B, the calves were purchased and reared as described for herd A. After 5-6 months, however, the calves from this herd were transferred to a separate farm nearby and kept there in a traditionally indoor system and slaughtered at 7-9 months of age. The veterinarian described the management in both farms as "excellent".

Vaccine and vaccination

According to the specifications supplied by the vendor, each 2-ml dose of the betapropiolactone-inactivated vaccine contained at least 0.80 SN.U (1 SN.U is the quantity necessary to obtain 1 log₁₀ sero-neutralising antibodies in the guinea-pig) of inactivated BRSV in aluminium hydroxychloride and saponin adjuvant.

In both herds all calves received 2 subcutaneous vaccinations (2 ml per calf per vaccination), 4 and 7 weeks after arrival, respectively accord-

ing to the manufacture's guidelines. The vaccination program was finalised December the 1st 1997.

Clinical signs and treatments

All calves were inspected daily for signs of disease. On indication, the rectal temperature was measured (data not shown). In the case of clinical signs or increased rectal temperature the veterinarian inspected the calves and eventually initiated treatment with antibiotics.

Sampling

Nasal swabs for virology and plain blood samples for serology were taken from 10 calves with clinical signs of respiratory disease in each of the 2 herds as previously described (*Utten-thal et al.* 1996). A second blood sample was taken 3-4 weeks later from the same calves.

Necropsy and microbiology

Five dead calves in herd B were necropsied on location. The macroscopic findings were recorded and the lungs transported to the DVL where bacteriological and mycoplasma examination, and histological processing was performed as previously described (*Tegtmeier et al.* 1999). For virology, material from the necropsied calves and nasal swabs were tested for the presence of BRSV, bovine corona virus (BCV), bovine parainfluenza-3 (PI-3) virus, and bovine viral diarrhoea virus (BVDV) by antigen ELISA as previously described (*Utten-thal et al.* 1996, *Meyling* 1982). Tests for infectious bovine rhinotracheitis (IBR) virus are not routinely performed since Denmark is considered free from this infection.

Serology

The serum samples were tested for the presence of specific antibodies against BRSV, including IgG1, IgG2, IgM and IgA isotypes and BRSV neutralising serum antibodies (SNT) as de-

Table 1. Virological and serological findings in vaccinated calves during acute outbreak of respiratory disease in herd A (a) and herd B (b). Nasal swabs were taken at the acute phase (20/26 Jan) and paired serum samples were taken at the acute phase and one month later (18/19 Feb). The nasal swabs were analysed for the presence of bovine respiratory syncytial virus (BRSV), bovine corona virus (BCV) and parainfluenza-3 virus (PI-3) antigen (Ag) by ELISA. Serum samples were analysed for the presence of antibodies against BRSV (IgM, IgA, IgG₁, IgG₂ isotypes) and neutralising antibodies (SNT), BCV (Ab) and PI-3 (Ab). Significant change in antibody titers were defined as either sero-conversion (from 0 to any titer) or at least four-fold rises. Dead: The calf died between the two sampling dates. NA: Not applicable. * Insufficient amount of sample for testing.

Table 1a

Calf #	BRSV Ag		BRSV-IgM		BRSV-IgA		BRSV-IgG1			BRSV-IgG2			BRSV-SNT		
	20 Jan	20 Jan	19 Feb	20 Jan	19 Feb	20 Jan	19 Feb	Rise	20 Jan	19 Feb	Rise	20 Jan	19 Feb	Rise	
332	+	0	Dead	0	Dead	0	Dead	NA	0	Dead	NA	64	Dead	NA	
338R	0	0	0	0	40	80	2560	YES	0	2560	YES	16	2048	YES	
325	+	0	*	0	0	40	160	YES	0	*	NA	16	1024	YES	
340	0	0	0	0	20	160	1280	YES	40	2560	YES	64	256	YES	
244N	0	0	Dead	0	Dead	40	Dead	NA	0	Dead	NA	8	Dead	NA	
416	0	0	0	0	20	20	2560	YES	0	640	YES	4	128	YES	
421H	0	0	0	0	160	20	160	YES	0	10240	YES	16	2048	YES	
426H	0	0	0	0	0	40	160	YES	40	160	YES	256	32	No	
407H	0	0	0	0	0	0	320	YES	0	1280	YES	2	1024	YES	
436H	0	0	0	0	0	40	5120	YES	0	40	YES	8	2048	YES	

Calf #	BCV Ag	BCV Ab		Rise	PI-3 Ag		PI-3 Ab	
	20 Jan	20 Jan	19 Feb		20 Jan	20 Jan	19 Feb	Rise
332	0	800	Dead	NA	0	0	Dead	NA
338R	0	12800	12800	NO	0	0	0	NO
325	0	1600	3200	NO	0	8	8	NO
340	0	3200	1600	NO	0	8	8	NO
244N	0	3200	Dead	NA	0	8	Dead	NA
416	0	1600	1600	NO	0	0	0	NO
421H	0	3200	3200	NO	0	0	0	NO
426H	0	800	6400	YES	0	0	0	NO
407H	0	1600	1600	NO	0	0	0	NO
436H	0	3200	6400	NO	0	0	0	NO

scribed elsewhere (*Uttenhal et al.* 2000). In addition, the paired serum samples were tested for antibodies against BCV and PI-3 as previously described (*Uttenhal et al.* 1996).

Results

Clinical signs and treatments

No adverse effects were seen in any of the calves in the 2 herds following vaccination.

In both herds, severe outbreaks of respiratory disease started in January 1998. The clinical signs comprised nasal discharge, pyrexia, coughing, elevated respiratory rates and marked depression. Almost all calves between 4 and 7 months of age were more or less affected and a total of 8/500 and 20/250 calves died during the outbreak in herd A and B, respectively. The outbreak ceased within 2 weeks

Table 1b

Calf #	BRSV Ag			BRSV-IgM		BRSV-IgA		BRSV-IgG1			BRSV-IgG2			BRSV-SNT		
	26 Jan	26 Jan	18 Feb	26 Jan	18 Feb	26 Jan	18 Feb	Rise	26 Jan	18 Feb	Rise	26 Jan	18 Feb	Rise		
1064/5	0	0	0	*	40	* \geq 1280	10240	NA	*	5120	NA	64	2048	YES		
2535/5	0	0	Dead	80	Dead	2560	Dead	NA	80	Dead	NA	2048	Dead	NA		
2537/5	0	0	0	0	0	320	320	NO	0	320	YES	128	256	NO		
642/5	0	0	Dead	0	Dead	1280	Dead	NA	0	Dead	NA	64	Dead	NA		
829/5	0	640	0	80	20	640	160	NO	20	160	YES	64	32	NO		
1057	0	0	0	0	0	1280	2560	NO	0	640	YES	256	128	NO		
821	0	0	Dead	80	Dead	1280	Dead	NA	20	Dead	NA	2048	Dead	NA		
799	0	0	Dead	0	Dead	320	Dead	NA	0	Dead	NA	64	Dead	NA		
795	0	320	Dead	80	Dead	5120	Dead	NA	0	Dead	NA	1024	Dead	NA		
1317	0	0	0	0	20	640	2560	YES	20	160	YES	8	148	YES		

Calf #	BCV Ag		BCV Ab		PI-3 Ag		PI-3 Ab	
	26 Jan	26 Jan	18 Feb	Rise	26 Jan	26 Jan	18 Feb	Rise
1064/5	0	*	\geq 25600	NA	0	*	0	NA
2535/5	0	6400	Dead	NA	0	0	Dead	NA
2537/5	0	3200	12800	YES	0	0	0	NO
642/5	0	800	Dead	NA	0	0	Dead	NA
829/5	0	800	\geq 25600	YES	0	0	8	YES
1057	0	1600	\geq 25600	YES	0	0	0	NO
821	0	6400	Dead	NA	0	16	Dead	NA
799	0	3200	Dead	NA	0	0	Dead	NA
795	0	3200	Dead	NA	0	8	Dead	NA
1317	0	12800	12800	NO	0	8	0	NO

in both herds, however prolonged treatments (primarily antibiotics) of few severe affected calves were necessary for additional 1-2 weeks.

Laboratory findings

Herd A

The results of the virological and serological analysis are detailed in Table 1a. BRSV antigen was detected in nasal swabs from 2 out of 10 sampled animals of which one died. None of the tested calves had IgM or IgA antibodies against BRSV at the first sampling day, whereas 4 out of 8 calves had moderate levels of IgA one month later. The initial IgG1 titers were low (between 0 and 160) increasing to titers 160-

5120 one month later. IgG2 was absent in 8 out of 10 calves at the first sampling and low (titer 40) in the remaining 2 calves, however the titers increased to very high titers at the second sampling (up to 10240). Thus, all surviving calves had significant titer rise in BRSV specific IgG1 and IgG2 antibodies between the 2 samplings. Similarly, the level of neutralising antibodies (SNT) increased from rather low to very high titers (up to 2048) in all but one calf between the 2 samplings. BCV or PI-3 antigen were not detected in any of the calves and only one calf had significant rise in BCV specific antibodies between the 2 samplings. None of the calves showed rise in PI-3 specific antibodies.

Table 2. Results of post mortem diagnostic examinations of lungs from five calves that died during the outbreak in herd B. The lungs were examined macroscopic and microscopic and samples were tested for the presence of bacteria, mycoplasmas and virus.

Animal ID	Virus	Bacteria	Mycoplasma	Histopathology
1408	Negative	<i>M. haemolytica</i>	<i>U. diversum</i> <i>M. dispar</i>	Fibrino-necrotizing bronchopneumonia
2131	Negative	<i>M. haemolytica</i>	<i>U. diversum</i> <i>M. bovirhinis</i>	Fibrino-necrotizing bronchopneumonia
1083	BRSV	No bacterial pathogens isolated	<i>U. diversum</i>	Suppurative bronchopneumonia
0782	BRSV	No bacterial pathogens isolated	<i>U. diversum</i> <i>M. bovis</i>	Suppurative bronchopneumonia
1004	Negative	No bacterial pathogens isolated	<i>U. diversum</i>	Suppurative bronchopneumonia

M. haemolytica: Mannheimia haemolytica; *M. dispar*: Mycoplasmas dispar, *M. bovis*: Mycoplasmas bovis, *M. bovirhinis*: Mycoplasmas bovirhinis, *U. diversum*: Ureaplasma diversum.

Herd B

The results of the virological and serological analysis are detailed in table 1b. No virus specific antigen was detected in nasal swabs from any of the 10 sampled animals. As 5 of the 10 calves died between the 2 sampling days, paired serum samples were available from only 5 calves. Four of the 10 tested calves had IgM and/or IgA antibodies against BRSV at the first sampling day. In addition, 3 out of 5 calves had low levels of IgA one month later including the 2 calves that were IgA negative at the first sampling. The initial IgG1 titers were high (between 320 and 5120) and only one calf out of 5 had significant rise in IgG1 titers between the 2 samplings. IgG2 was present in low levels in only 4 out of 10 calves at the first sampling and increased to moderate to high titers at the second sampling in all calves tested. The level of neutralising antibodies (SNT) varied between titer 8 and 2048 at the first sampling and increased in only two calves, which had initial low titers. There was no clear correlation between level of BRSV specific antibodies in

the initial sample and the fate of the calf, i.e. calves with low as well as high SNT titers died between the 2 sampling days. Three out of 5 calves had significant rise in BCV specific antibodies between the 2 samplings. One of the calves seroconverted to PI-3 virus (titer 0 → 8). At necropsy, acute bronchopneumonia characterized by red consolidated tissue, interstitial edema and marked interstitial emphysema was observed in all 5 cases. The results of the histopathological and microbiological findings are summarized in Table 2. *Mannheimia (Pasteurella) haemolytica* (*M. haemolytica*), *Mycoplasma dispar* (*M. dispar*), *Mycoplasma bovirhinis* (*M. bovirhinis*), *Mycoplasma bovis* (*M. bovis*) and *Ureaplasma diversum* (*U. diversum*) was isolated either alone or concomitantly from one or more of the 5 cases. Histological examinations revealed a fibrinous-necrotizing pneumonia in 2 cases whereas the remaining three cases were diagnosed as suppurative bronchopneumonias. In all cases, variable numbers of syncytial cells were seen.

Discussion

The detection of BRSV antigen in 2 calves, and the serological responses in the majority of calves strongly indicated that BRSV was involved in the outbreak in herd A. Similarly, the presence of BRSV antigen in 2 of the necropsied calves, and the serological responses suggested that this was also true for the outbreak in herd B.

Previous studies on the pathogenesis of BRSV infection have shown that BRSV antigen may be detected in nasal swabs material from days 2-3 until days 8-10 post infection (Larsen et al. 1999, Vilcek et al. 1994). Studies on the kinetics of BRSV specific antibody isotypes in serum have revealed that IgM and IgA may be present from day 8-10 until days 14-25 (Kimman et al. 1988). IgG1 being detectable from days 10-17, peaking on days 24-38 and remaining detectable for up to 8 months (half-life 21-32 days) (Schrijver et al. 1996, Kimman et al. 1988). The IgG2 isotype did not appear in serum until days 25-86, peaking on days 38-90 and lasting for at least 9 months. Thus, the detection of antigen in the nasal cavity and the lack of IgM and IgA at the first sampling in herd A indicated these samples were taken shortly after infection, i.e. prior to day 8-10.

Contrary to the situation in herd A, the lack of antigen in nasal swabs and the presence of IgM and IgA in herd B indicated that the first samples were taken later than 8-12 days after infection. At this time detectable amounts of IgG1 and SNT antibodies may have been produced in response to the active infection, especially in vaccinated calves (see below). The relatively high titers of IgG1 and SNT encountered in herd B at the first sampling do not necessarily represent antibodies induced by the vaccine. Similarly, the low IgG1 and SNT titers at the first sampling in herd A may represent either residues of maternal derived antibodies or antibodies induced by the vaccine.

Whatsoever, the low titers indicated either that the vaccine induced only low levels of antibodies or that these had vanished by the time of sampling (approximately 2 months after last vaccination). The failure of the vaccine to induce higher titers of antibodies may be due to either poor immunogenicity or the presence of moderate or high levels of maternally derived antibodies at the time of vaccination. Thus, presence of maternally or naturally acquired antibodies have been shown to suppress both the local and systemic antibody responses following experimental BRSV infection (Ciszewski et al. 1991, Kimman et al. 1987). Interestingly, these studies also revealed that a memory response might be mounted even in the absence of a detectable primary response in seropositive calves. Therefore, vaccinated calves may display a stronger and more rapid systemic antibody response at challenge. Indeed, the high IgG1, IgG2 and SNT titers in the second sample in both herds were in surplus of the titers normally seen in naturally infected calves (Utenthal et al. 2000).

Published field trials, with live or inactivated BRSV vaccines, revealed different levels of protection (Fulton et al. 1995, Kubota et al. 1992, Howard et al. 1987, Verhoeff & van Nieuwstadt 1984, Mohanty et al. 1981) while others found that vaccination enhanced disease in calves (Gershwin et al. 1998, Kimman et al. 1989b). Kimman and co-workers investigated the effect of routes of administration and maternal antibodies on the protective effect of modified live and inactivated vaccines (Kimman et al. 1989c). Intramuscular administration, especially in calves that possessed maternal antibodies, proved least effective in inducing protection and intranasal inoculation of live virus in colostrum deprived calves proved most effective.

Multiple infectious agents: *M. haemolytica*, *M. dispar*, *M. bovirhinis*, *M. bovis* and *U. diversum*

were isolated from one or more of the 5 lungs, in addition to the BRSV antigen detected in 2 cases. These findings were in accordance with previous microbiological studies on pneumonic calf lung tissue, where multiple pathogens frequently were isolated (Tegtmeier *et al.* 1999). The presence of one or more of the isolated microorganisms may likely have contributed to the development and severity of pneumonia. However, viral agents, such as BRSV, are usually considered the primary pulmonary pathogen, capable of destroying the respiratory epithelial lining to a degree allowing other agents to colonize (Babiuk *et al.* 1988). In a former study (Tegtmeier *et al.* 1999), performed on pneumonic lung tissue submitted to the DVL for diagnostic purposes, BRSV antigen was often detected in cases of suppurative bronchopneumonias, in which syncytial cells and interstitial emphysema could be observed. Syncytial cells and interstitial emphysema were features present in all 5 cases necropsied in the present study, thereby indicating that BRSV was, or had been, present in the examined lungs.

The significant rise in BCV specific antibodies in 3 out of 5 calves in herd B and the presence of high titers of BCV antibodies in most of the other sampled calves in both herds confirm previous findings, that BCV is common in Danish cattle (Larsen *et al.* 1999). However, the association between the presence of BCV and BCV antibodies and outbreak of respiratory disease is still controversial (Martin *et al.* 1998). Experimental infections with BCV failed to induce fulminate respiratory disease (Heckert *et al.* 1991), but the detection of BCV in nasal swabs and specific rise in BCV titers were strongly correlated to outbreaks of respiratory disease in a large survey recently performed in 20 Danish dairy herds (Alban *et al.* 1999). Thus, presently BCV may be considered involved in the BRD complex, but the virus is probably not capable of inducing fulminate res-

piratory disease without the presence of other contributing factors. Interpretation of BCV serological and virological data is further complicated by the fact that the diagnostic assays employed did not distinguish between BCV strains involved in BRD and strains involved in enteric infections.

In conclusion, the data obtained in the present investigation strongly indicated that BRSV was involved, and probably initiated, both outbreaks of BRD despite prior vaccination with an inactivated BRSV vaccine. The company withdrew the vaccine from the European market in the early spring of 1998.

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Sammendrag

Bovin Respiratorisk Syncytial Virus (BRSV) lungebetændelse i slagtekalvesætninger på trods ad vaccination.

Artiklen beskriver de kliniske, patologiske, serologiske og virologiske fund i kalve fra 2 større danske slagtekalvesætninger i forbindelse med udbrud af alvorlig lungebetændelse. Kalvene var vaccineret med en inaktiveret vaccine mod bovine respiratorisk syncytial virus (BRSV) to måneder tidligere. De kliniske symptomer omfattede nasal flåd, feber, hoste og forøget respirationsfrekvens. I alt 28 kalve døde i

de to besætninger. Laboratorieundersøgelser viste at BRSV var involveret og formodentligt udløste begge udbrud. Ydermere viste resultaterne af de serologiske tests, at vaccinen kun inducerede lave mængder af antistoffer; formodentlig på grund af tilstedeværelse af maternelle antistoffer på vaccinations-tidspunktet. Obduktion af fem kalve viste forandringer typisk for lungebetændelse forårsaget af BRSV. På baggrund af de beskrevne fund kunne det konkluderes, at vaccination med en inaktiveret BRSV vaccine ikke beskyttede kalvene mod alvorlig og fatal lungebetændelse to måneder efter sidste vaccination.

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