In field review of Bovalto® Respi 3 and 4 efficacy in different production systems

Matthew Yarnall[1], Edmond Jolivet[2], Mathieu Chevalier[2], Arnaud Bolon[2], Marie-Pascale Tiberghien[3], Milan Huňady[4], Corinne Philippe[2]

[1] Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany
[2] Boehringer Ingelheim, Lyon, France
[3] Consulting, Cortambert, France
[4] Bioveta, Ivanovice na Hané, Czech Republic

Received November 17, 2021
Accepted June 14, 2022

Abstract

Three field studies (Phase 4, immediate efficacy) were conducted with an inactivated, adjuvanted, tri or quadri-valent respiratory vaccine for cattle (bovine respiratory syncytial virus [BRSV], parainfluenza 3 virus [Pi3V], *Mannheimia haemolytica* ± bovine viral diarrhoea virus [BVDV]), compared to competitor vaccines, in three different production systems: allotted fattening bulls, beef calves on their farm of birth, allotted veal calves. Mortality, morbidity, pre and post-vaccinal serological data (ELISA and virus neutralising titres) were compared between groups. There were no significant differences in mortality and morbidity between the groups. In the fattening bulls study, significantly fewer bovine respiratory disease treatments were administered to animals in the Bovalto group. Virus neutralising titre results were not different between groups, except for BVDV in Study 3 where a BVDV outbreak was observed.

Cattle, vaccination, respiratory disease

Bovine respiratory disease (BRD) is a major health and economic issue in cattle farming, particularly in young stock. Despite the depth of research into the causal pathogens of BRD, and advances in management and vaccination, morbidity is still a major challenge (Smith et al. 2020). In addition to the necessary studies conducted for registration purposes, post-licensing studies are a useful complement to confirm vaccine efficacy in a variety of cattle rearing systems. The purpose of the studies described below was to compare, under field conditions and in different production systems, the immediate efficacy of Bovalto Respi 3 and Respi 4 with that of other registered vaccines.

Materials and Methods

Three separate studies were conducted with Bovalto Respi 3 and 4 in France and Belgium, by different investigators, in different production systems. Each study comprised a Bovalto Respi group (3 or 4) and a competitor vaccine group (Rispoval 3 or Bovilis Bovigrip). The studies started at the time of vaccine administration and observations lasted two to three months.

The vaccines are described in Table 1, and an overview of study design is shown in Table 2. In Studies 1 and 3, informed consent from the owners was requested and obtained; in Study 2 this was not specified.

Study 1

Study 1 (Marie 2016) was conducted in young fattening bulls during the winter period. The animals recruited into the study were Charolais, Charolais cross, and Blonde d'Aquitaine breeds, aged approximately 10 months and weighing 300–400 kg. They were collected into a sorting centre and split into 21 pens over 4 farms, each pen containing bulls of similar breed, age and weight. Within each pen animals were allocated at random to Bovalto Respi 4 or Rispoval 3. The 1st vaccine injection (following the Marketing Authorisation (MA) recommendations for each vaccine) was given by an investigator at the sorting centre, after which the animals were moved to their intended fattening farm. The 2nd injection was given at the fattening farm after a 3-week interval, by an investigator also following the MA recommendations for the administration of each vaccine. The farmers, who were blind to treatment group, monitored the animals, noted the presence of BRD symptoms as appropriate - such as cough, polypnoea/dyspnoea, rectal temperature and anorexia - with regular visits from an investigator. Farmers

Address for correspondence:
Matthew Yarnall
Boehringer Ingelheim Vetmedica GmbH
Binger Strasse 173, 55216 Ingelheim, Germany
Phone: +44 1344 741 397
matt.yarnall@boehringer-ingelheim.com

Table 1. Vaccines used in the studies - marketing authorisations

	Bovalto Respi 4	Bovalto Respi 3	Rispoval 3	Bovilis Bovigrip
Manufacturer	Boehringer Ingelheim Animal Health		Zoetis	MSD Animal Health
Components	BRSV (inactivated) Pi3V (inactivated) MH		BRSV (MLV) Pi3V (MLV)	BRSV (inactivated) Pi3V (inactivated) MH (inactivated)
	BVDV (inactivated)	None	BVDV (inactivated adjuvanted	None
Presentation	Ready-to-use		Pellet dissolved with solution	Ready-to-use
Route of administration	Sub-cutaneous injection		Intra-muscular injection	Sub-cutaneous injection
Dose volume	2 ml		4 ml	5 ml
Vaccination regimen (primo-vaccination)	2 injections 3 weeks apart		2 injections 3-4 weeks apart	2 injections 4 weeks apart

BRSV - bovine respiratory syncytial virus; Pi3V - parainfluenza 3 virus; MLV - modified live virus vaccine; MH - *Mannheimia haemolytica*; BVDV - bovine viral diarrhoea virus

Table 2. Study design overview.

	Study 1 (Bovalto Respi 4)	Study 2 (Bovalto Respi 3)	Study 3 (Bovalto Respi 4)
Animals	Young bulls 10 months of age (♂) in 19 pens, 4 fattening units	Beef calves from 2 weeks of age (♂/♀) in their farm of birth,	Veal calves from 10 days of age (♂/♀) in one fattening unit
Comparator	Rispoval 3, Zoetis (BRSV, Pi3V, MH)	Bovilis Bovigrip, MSD Animal Health (BRSV, Pi3V, BVDV)	
Vaccination regimen	Rispoval: 2 inj. 3 wks apart Bovalto 4: 2 inj. 3 wks apart	Bovipast: 2 inj. 4 wks apart Bovalto 3: 2 inj. 3 wks apart	2 inj. 25 days* apart for all vaccinates
Maternally -derived antibodies	Not applicable	Yes (young animals with access to maternal colostrum)	
Design	Two groups: 4 fattening unit and 19 pens, each contained similar numbers of animals from each vaccine group (shared airspace, 2 batches/pen)	Two groups: sequential inclusion based on birth date and eartag Both vaccine groups shared the same airspace.	Three groups: two vaccine groups and one untreated roup Each vaccine group was housed in a separate airspace (3 in total)
Bias control	Farmer(s) blind to the vaccine administered		
Animals included	n = 178/179 per group	n = 62 per group + 1 Bovalto animal	n = 95/96 per group (+ 20 untreated controls)
Animals not excluded	n = 165/166 per group	n = 62 per group	n = 95/96 per group (+ 20 untreated controls)
Study duration	60 days monitoring	35-77 days monitoring Depending on birth date	92 days
Variables measured	√ Mortality √ BRD morbidity √ Number of BRD treatments √ Average daily weight gain	√ Mortality √ Morbidity √ Serology (antibodies to vaccinal antigens)	

*This was chosen as the half-way compromise between the MA recommendations for both vaccines
BRSV - bovine respiratory syncytial virus; Pi3V - parainfluenza 3 virus; BVDV - bovine viral diarrhoea virus; MH - *Mannheimia haemolytica*; BRD - bovine respiratory disease; inj - injections; wks - weeks

initiated antibiotic treatment on individual animals with BRD symptoms where they thought it was necessary. The observation period lasted for 60 days after 1st vaccine administration. No serology evaluation was carried out. Postmortem investigations were conducted by the Autopsy Service of Nantes Veterinary School.

Study 2

Study 2 was conducted on a Charolais beef cow farm, comprising approximately 180 cows housed in 3 sheds, each building containing 60 to 80 cows and their calves. Calves born on site during the winter period were sequentially enrolled into the study from 2 weeks of age and were allocated to a treatment group (Bovalto Respi 3 or Bovilis Bovigrip) on an alternate basis using ear tag numbers. Vaccination was carried out by one of the investigators, according to the MA recommendations. The farmer and farm staff were blind to the vaccine given. Same as for Study 1, the farmer monitored calf health, particularly for signs of BRD. Blood samples were taken at intervals, to follow antibody response to antigens present in the vaccines. The animals were monitored for 35 to 77 days (depending on their order of birth).

Study 3

Study 3 took place in a veal calf fattening unit, where the experimental animals were calves of dairy breeds, aged 10 days or more, arriving to the unit after allotment. Three groups were assembled (Bovalto Respi 4; Bovilis Bovigrip; untreated control) and each group was maintained in a separate airspace. Before vaccination, calves were acclimatised for one week, during which time they received a metaphylactic treatment of oxytetracycline plus aspirin, administered orally with the milk replacer. Vaccination was carried out by one of the investigators following MA recommendations. The control group received no treatment. A single inter-vaccination interval of 25 days was selected and applied to all vaccinated animals. Farmers (blind to the treatment group) noted any clinical signs, including those indicative of respiratory disease. Blood samples were taken at intervals, to follow antibody response to antigens present in the vaccines. The animals were monitored for 92 days following the 1st vaccine injection. Additional metaphylactic treatments were administered to all animals on D21-D22 (oral suspension tilmicosin); D32 to D37 (oral amoxycillin plus aspirin) and D67 to D74 (doxycycline + aspirin). These treatments were considered representative of routine treatments administered on the farm during a calf-rearing cycle.

Serology (Studies 2 and 3)

Competitive ELISA tests were used to assess serological response to all vaccine antigens. Results were expressed as negative, doubtful or positive. In addition, virus neutralising titres (VNTs) for BRSV and Pi3V were conducted approximately 2 weeks after the 2nd vaccine injection, in order to compare the vaccine groups with a biologically relevant test. No laboratory investigation was conducted in Study 1.

Data analysis

Mortality data were compared between vaccine groups, using Fisher's exact test (due to the small numbers); morbidity data were compared between groups in all studies, using Chi-squared tests or Fisher's exact test. In Study 1, the odds ratio of animals treated against BRD (vs not treated) was calculated across vaccine groups, using multivariate regression modelling methods.

Serology data: for each vaccine component within each study, the proportion of individuals with negative, doubtful and positive responses to ELISA analysis was compared between vaccines and time points using Chi-squared tests. In addition, within each study VNTs conducted at single time points were compared between vaccines using Analysis of Variance methods. In Study 3, repeated measure analyses were conducted on ELISA titres.

The level of significance for all tests was set at $P < 0.05$.

Results

Exclusions

Study 1: twenty-six animals (13 from each vaccine group) from two pens on fattening farm 1 were excluded from the study on Day 8, because they had received a metaphylactic antibiotic treatment; this left 331 animals in 19 pens in the study (166 and 165 in the Bovalto and Rispoval vaccine groups respectively).

Study 2: one calf from the Bovalto group was excluded from the clinical signs analysis, because of an acute arthritis that was treated with multiple injections of a macrolide antibiotic, which could have masked respiratory signs; however this calf remained in the serological data analysis.

Study 3: no animals were removed from the study post inclusion.

Overall, the exclusions noted were not thought to introduce any bias to the data analysis.

Mortality and respiratory morbidity

Mortality and respiratory morbidity are summarised in Figs 1–3. Mortality was low in Studies 1 and 3 and non-existent in Study 2; no significant difference between groups was detected.

Average morbidity ranged from ≈ 2% in Study 2, to 10 % in Study 3 and 15% in Study 1; no significant difference between vaccine groups was detected in any of the studies.

In Study 1, with regards to BRD treatment, a significant vaccine effect was detected (odds ratio of 0.49, $P = 0.04$): Bovalto Respi 4-vaccinated calves received significantly fewer treatments for BRD (10.8%) than the animals vaccinated with Rispoval 3 (18.1%).

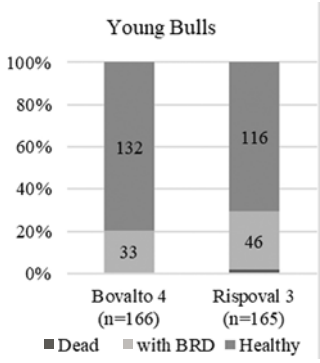


Fig. 1. Study 1

Mortality: non-significant; morbidity: no significant difference between groups; bovine respiratory disease (BRD) treatment: animals treated with Bovalto Respi 4 had a lower incidence of treatment (10.8%) compared to those treated with Rispoval 3 (18.1%) ($P = 0.04$)

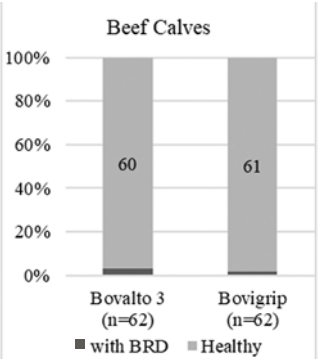


Fig. 2. Study 2

Mortality: none observed; morbidity: low in both groups, no significant difference between groups
BRD - bovine respiratory disease

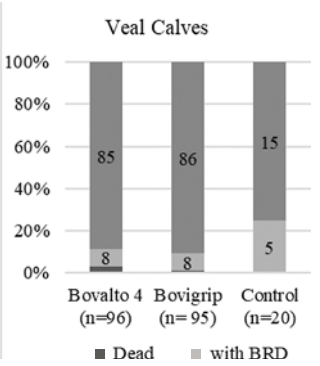


Fig. 3. Study 3

Mortality and morbidity: no significant difference detected
BRD - bovine respiratory disease

Serology

Serology (Studies 2 and 3) results are summarised in Figs 4, 6, 8, 10, 12 (Study 2) and 5, 7, 9, 11 ,13 and 14 (Study 3).

BRSV: approximately 80% of the animals in Study 2 were positive or doubtful at the 1st sampling, presumably due to antibodies of maternal origin. After vaccination (D end), no animal remained negative in either group. The proportion of ELISA positives was significantly higher for Bovilis Bovigrip. However, the VNT results showed no significant difference between groups. There were similar findings in Study 3, with relatively low levels of ELISA antibodies observed in all groups at D0, followed by a rise in vaccinated animals at D42 and D92, apparently slightly higher for the Bovilis group than for the Bovalto group, although non-significantly. Again, the VNTs between animals of the 2 vaccine groups at D42 did not differ. Control animals did not seroconvert throughout the study and their VNTs were significantly lower than those of the vaccinates.

Pi3V: approximately 65% of the animals in Study 2 were positive or doubtful at the 1st sampling. After vaccination, almost all animals were ELISA positive in both vaccine groups, with no difference between groups. The VNTs also showed no difference between the groups. In Study 3, the initial ELISA antibody titres were relatively low in all 3 groups,

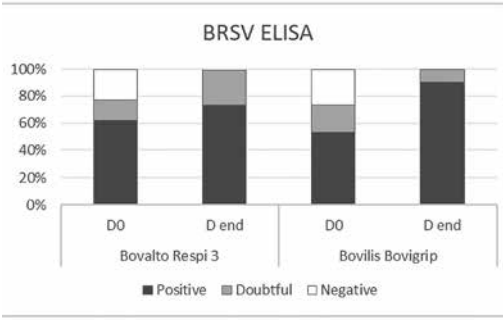
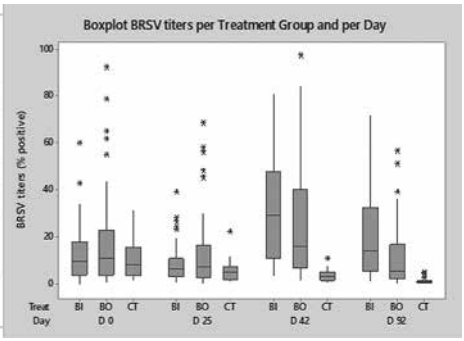


Fig. 4. Study 2. Proportion of animals positive, doubtful or negative for BRSV ELISA titres in each group at Day 0 and Day end

The proportion of animals showing BRSV ELISA antibodies was similar between groups at D0, and significantly higher for Bovilis at D end (P = 0.003). BRSV - bovine respiratory syncytial virus



BI - Bovilis; BO - Bovalto; CT - control

Fig. 5. Study 3. Boxplot of BRSV ELISA titres per vaccine group at all timepoints monitored (D0, D25, D42, D92)

BRSV ELISA titres in the control group differed significantly from (lower than) those of the two vaccinated groups, which rose at D42 and D92; titres in the Bovilis group appeared higher than in the Bovalto group although this was not significant in the repeated measure analysis conducted after excluding the control group. BRSV - bovine respiratory syncytial virus

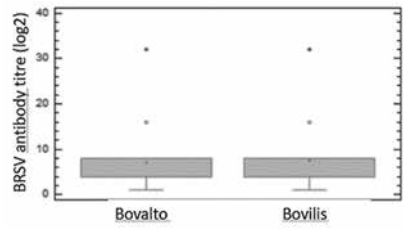


Fig. 6. Study 2. BRSV VNTs determined at Day end for animals of both vaccine groups

Animals in both vaccine groups showed modest and similar VNTs at the end of the study, perhaps indicative of a lack of challenge on the farm during the period. BRSV - bovine respiratory syncytial virus; VNT – virus neutralizing titre

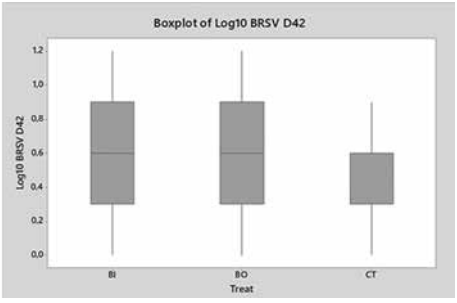


Fig. 7. Study 3. Boxplot of BRSV VNTs determined at Day 42 for all study animals

The untreated group significantly different from (lower than) the two vaccinated groups (P = 0.011). No difference was found between the vaccine groups. BRSV - bovine respiratory syncytial virus; VNT – virus neutralizing titre

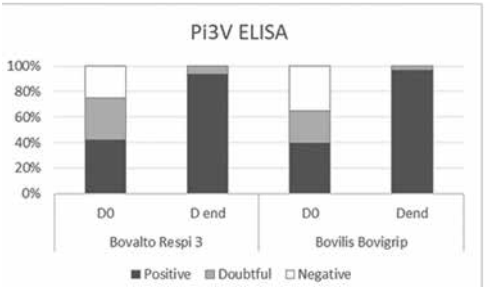


Fig. 8. Study 2. Proportion of animals positive, doubtful or negative for Pi3V ELISA titres in each group at Day 0 and Day end

Animals in both vaccine groups showed similar Pi3V ELISA antibody concentrations both at D0 and at Dend. Pi3V - parainfluenza 3 virus

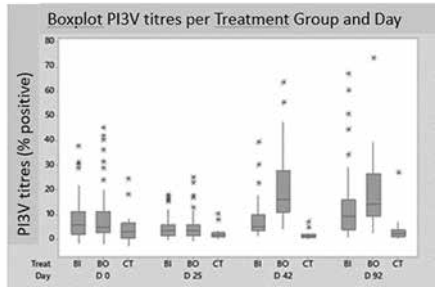


Fig. 9. Study 3. Boxplot of Pi3V ELISA titres per vaccine group at all timepoints monitored (D0, D25, D42, D92)

Pi3V ELISA titres in the control group differed significantly from (lower than) those of the two vaccinated groups, which rose at D42 and D92; titres in the Bovalto group were higher than in the Bovilis group in the repeated measure analysis conducted after excluding the control group. Pi3V - parainfluenza 3 virus

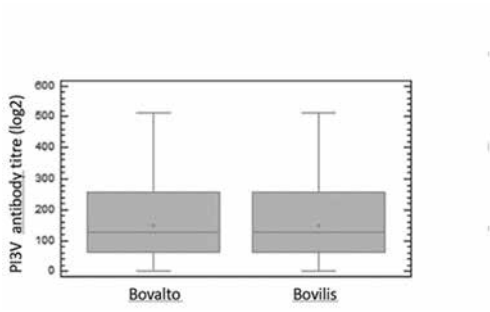


Fig. 10. Study 2. Pi3V VNTs determined at Day end for animals of both vaccine groups

Animals in both vaccine groups showed similar Pi3V VNT antibody concentrations at D end. Pi3V - parainfluenza 3 virus ; VNT - virus neutralizing titre

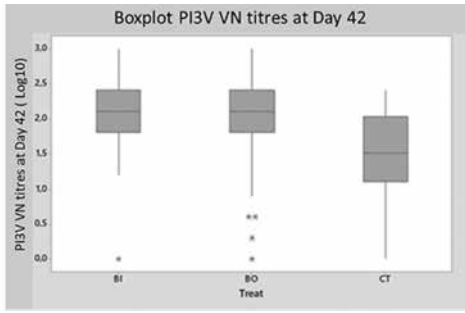


Fig. 11. Study 3. Boxplot of Pi3V VNTs determined at Day 42 for all study animals per vaccine group

The control group was significantly different from (lower than) the two vaccinated groups ($P = 0.008$). No difference was found between the vaccine groups. Pi3V - parainfluenza 3 virus ; VNT - virus neutralizing titre

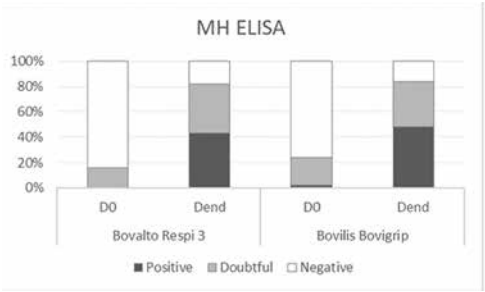


Fig. 12. Study 2. Percentage of animals positive, doubtful or negative for MH ELISA titres in each group at Day 0 and Day end

At D0, a large proportion of animals were negative for MH ELISA in both groups, suggesting no maternally-derived immunity. After vaccination, animals in both groups demonstrated a good response. MH - *Mannheimia haemolytica*

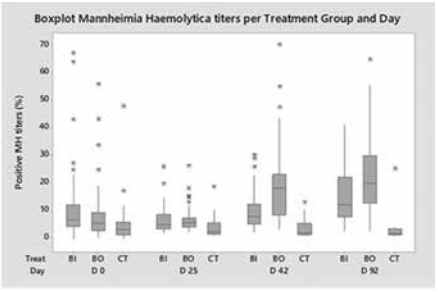


Fig. 13. Study 3. Boxplot of MH ELISA titres determined per vaccine group at all timepoints monitored (D0, D25, D42, D92)

The control group was significantly different from (lower than) the two vaccinated groups ($P < 0.05$); MH Elisa titres in the Bovalto group significantly higher than Bovilis at Day 42 and 92 ($P < 0.05$). MH - *Mannheimia haemolytica*

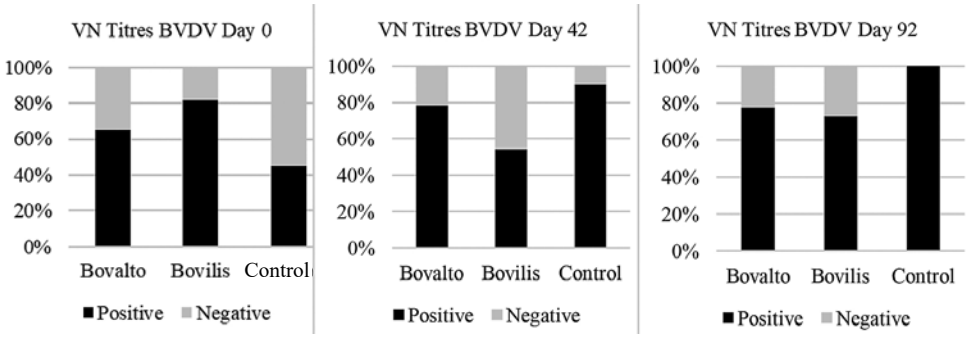


Fig. 14. Study 3. Proportion of animals positive or negative for BVDV VN titres in each group at D0, D42, and D92. BVDV - bovine viral diarrhoea virus

At D0, fewer animals in the control group had virus neutralizing (VN) antibodies to BVDV than in both the treated groups. The proportion of positive animals was highest in the Bovilis group (80%), followed by Bovalto (65%). Antibodies at D0 were assumed to be of maternal origin.

At D42, surprisingly the proportion of positive animals in the control group had increased from 43% to 90%; this was thought to indicate circulation of a BVDV wild strain.
In the Bovilis group the proportion of positive animals fell to 52%, consistent with a progressive loss of maternal antibodies and the absence of a BVDV component in the vaccine.
In the Bovalto group the proportion of positive animals had increased to 79%, consistent with a moderate, vaccine-induced increase.

At D92, all animals from the control group had now seroconverted.
In the Bovilis group the proportion of seropositive animals increased to 71%, suggesting a (wild strain) BVDV exposure.
The Bovalto group showed a proportion of positive animals similar to D42, consistent with post vaccinal levels in the absence of a wild strain exposure.

and increased in the vaccinated animals, significantly more so in the Bovalto than in the Bovilis group. Virus neutralisation titres at D42 showed no difference between vaccine groups but the control group was significantly lower than both vaccine groups.

Mannheimia haemolytica: in Study 2, ELISA antibodies at D0 were low in animals from both groups; they increased post-vaccination in both groups in a similar manner. In Study 3, ELISA antibody levels were relatively low at D0, and increased post-vaccination in both vaccine groups, (significantly more in the Bovalto than in the Bovilis group) while the control animals remained low.

BVD VNTs in Study 3 were monitored because Bovalto Respi 4 includes a BVDV component (unlike Bovilis Bovigrip). The results are shown in Fig. 14. The Bovalto group showed an increase in the proportion of positive animals from 60% on D0 to 80% on D42 and remaining at 80% on D92 whereas, unexpectedly, the proportion of positive animals in the control group increased (from 42% positive on D0 to 85% on D42 and 100% on D92) and in the Bovilis group fluctuated (from 80% positive on D0 down to 50% on D42 but up again to 80% on D92).

Discussion

The low mortality figures observed during these 3 studies were indicative of a low to moderate respiratory disease pressure, despite the relatively greater at-risk winter period selected in Studies 1 and 2.

Morbidity was highest in the fattening bulls study, where the risk factors (Kurcubic 2018) were concentrated, and similar to incidence previously reported in the same area and type of production (Assié et al. 2009). Morbidity data in the veal calf unit would be expected to be high as well, with similar risk factors, in addition to suspected low colostrum uptake on their farm of origin. However, it is a frequent practice to apply blanket oral treatments to all calves in a unit when clinical signs of illness are detected, as was the case here: this may have contributed to an apparent lowering of morbidity. Morbidity on the breeding farm was reported to be much lower than observed on the same farm in previous years, when no vaccination had been applied.

There was no significant difference between vaccine groups in mortality and morbidity figures in any of the studies. This suggests that the clinical efficacy of the vaccines was similar. Alternatively or in addition, it could also be the effect of overlapping herd immunity. It is well recognised (Inman and Hudson 2009) that in vaccine studies, commingling vaccinated and unvaccinated animals can simultaneously increase challenge on the vaccinates and protect the unvaccinated animals from challenge. Nevertheless, the EMEA/CVMP (2001) note of guidance for the conduct of vaccine field studies recommends commingling because separate airspaces between groups may not provide similar pathogen challenge conditions to all groups. There is also the possibility that the monitoring period was too short to enable the vaccines to develop their full effects. Finally, it could also be that the sample size in each study was too modest for the detection of differences in proportions. *Post hoc* power calculations indicated that the number of animals used in Study 1 would be sufficient to detect a difference in morbidity of 10% between groups using a 5% significance level and 80% power, whereas the actual observed difference was 4%. Chamorro and Palomares (2020) conducted a review of published evidence available regarding the effect of vaccination against BRD and found much uncertain or conflicting evidence.

In Study 1, animals vaccinated with Bovalto Respi 4 received significantly fewer antibiotic treatments against BRD than animals vaccinated with Rispoval 3, despite the lack of significantly different morbidity incidence. This could mean that the clinical signs observed were less severe. This reduced treatment rate was thought to be possibly due to

a protective effect of the MH component, present in Bovalto Respi 4 but absent from Rispoval 3, as previously observed by Assié et al. (2009) in a similar production system. This observation is important in the context of reducing antimicrobials use in cattle production.

In Study 2, a proportion of the 2-week-old calves had significant levels of maternally-derived antibodies, particularly to BRSV and Pi3V. This obviously did not prevent a good serological response to vaccination.

Regarding the BVD VN titres in Study 3, it is evident that animals in the control group were exposed to a wild strain of BVD from before D42 – causing a titre increase – and the Bovilis group experienced a similar outbreak after D42. Results in the Bovalto group were consistent with antibodies of maternal origin at D0 not preventing a good vaccine response, as seen at D42 and D92; wild BVD strain exposure in that group was thought unlikely, because antibody titres would have been expected to rise further. As the animals of each group were housed in different airspaces, virus spread was probably uneven.

BVDV is a legitimate component in a multivalent respiratory vaccine for cattle, given the epidemiological features and immunosuppressive properties of the virus (Houe 1999). However, in Europe several countries and regions are currently deploying BVDV control and/or eradication plans (Metcalfe 2019), and respiratory vaccines without a BVD component are required in such areas.

There were a few apparent divergences in the conclusions relating to serology investigations, ELISA vs VNT: ELISA methods are very frequently used in field studies, for convenience and cost reasons, in preference to VNT determinations. Although it is possible to demonstrate a good correlation between ELISA and VNT (Cooke et al. 2020), VNT remains the 'gold standard' when there are discrepancies, because it is considered a biologically more relevant test.

The difference in sensitivity seen with ELISA methods may be due to interference with maternally derived antibody; however, as seen with VNT, this suspected diagnostic interference was not clinically relevant. In practice, one method of overcoming this potential interference and reducing the onset of immunity is by the use of the prime-boost effect (Chamorro et al. 2016). This involves the use of a live followed by a killed form of the same antigen, which provides synergistic enhancement of immunity to the target pathogen (Ellis et al. 2018). This also has the benefit of eliciting a significant serological response to the 1st dose of a multivalent inactivated vaccine containing the same strains of Pi3V and BRSV, in this case Bovalto Respi 4, suggesting a secondary immune response or booster effect to the initial intranasal live vaccine, Bovalto Respi Intranasal (Metcalfe et al. 2019).

Acknowledgements

All three studies were financed by Boehringer Ingelheim and all authors are in a direct or indirect (MPT) employment of Boehringer Ingelheim.

References

Assié S, Seegers H, Makoschey B, Désiré-Bousquié L, Bareille N 2009: Exposure to pathogens and incidence of respiratory disease in young bulls on their arrival at fattening operations in France. Vet Rec **165**: 195-199

Chamorro MF, Palomares RA 2020: Bovine respiratory disease vaccination against viral pathogens, modified-live versus inactivated antigen vaccines, intranasal versus parenteral, what is the evidence? Vet Clin Food Anim **36**: 461-472

Chamorro MF, Woolums A, Waltz PH 2016: Vaccination of calves against common respiratory viruses in the face of maternally derived antibodies (IFOMA). Anim Health Res Rev **17**: 79-84

Cooke RF, Paiva R, Pohler KG 2020: Technical note: Using enzyme-linked immunosorbent assays to evaluate humoral responses to vaccination against respiratory viruses in beef cattle. J Anim Sci **98**:skaa249

Ellis J, Gow S, Berenik A, Lacoste S, Erickson N 2018: Comparative efficacy of modified-live and inactivated vaccines in boosting responses to bovine respiratory syncytial virus following neonatal mucosal priming of beef calves. Can Vet J **59**: 1311-1319

EMEA/CVMP/852/99 2001: Note for Guidance Field Trials with Veterinary Vaccines. London, UK. 8 p. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-field-trials-veterinary-vaccines_en.pdf
Houe H 1999: Epidemiological features and economical importance of bovine virus diarrhoea virus (BVDV) infections. Vet Microbiol **64**: 89-107
Inman C, Hudson C 2009: Cattle immunology: vaccination and immunological testing. UK Vet **14**: 1-4
Kurcubic V, Dokovic R, Ilic Z, Petrovic M 2018: Etiopathogenesis and economic significance of bovine respiratory disease complex (BRDC). Acta Agric Serb **23**: 85-100
Marie A 2016: Comparaison de l'efficacité en condition terrain de deux vaccins contre les bronchopneumonies infectieuses chez les jeunes bovins en ateliers d'engraissement. Thèse de Doctorat Vétérinaire, Faculté de Médecine, Nantes, F, 122 p.
Metcalfe L, Philippe-Reversat C, Esteves Lopes R, Chevalier M 2019: Booster effect of an inactivated quadrivalent BRD vaccine following an intra-nasal inoculation: leading them by the nose - Poster presented at the European Bovine Congress (EBC), 's-Hertogenbosch, The Netherlands Sept 11-13, 2019
Metcalfe LVA 2019: An update on the status of BVD control and eradication in Europe. J Veter Sci Med **7**: 4
Smith RA, Step DL, Woolums AR 2020: Bovine respiratory disease: looking back and looking forward, what do we see? Vet Clin North Am Food Anim Pract **36**: 239-251