A review of registered and candidate vaccines for bovine respiratory disease in the UK

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Abstract

Vaccination is widely regarded as a cornerstone in animal or herd health and infectious disease management. Nineteen vaccines against the major pathogens implicated in bovine respiratory disease are registered for use in the UK by the Veterinary Medicines Directorate (VMD). However, despite annual prophylactic vaccination, bovine respiratory disease is still conservatively estimated to cost the UK economy approximately £80 million *per annum*. This review examines the vaccine types available, discusses the surrounding literature and scientific rationale of the limitations and assesses the potential of novel vaccine technologies.

1. Introduction

Bovine respiratory disease complex (BRDC) is the principal cause of mortality in calves from 1-24 months of age across the world. It has a significant impact on the global economy and the National Animal Disease Information Service (NADIS) estimates a cost to the UK of £80 million per annum, with over 1.9 million animals affected (1). This encompasses direct and incidental costs, from mortality, weight loss or carcass blemish and subsequent reduced market price to additional labour

27 expenditure, housing modifications and prophylactic or therapeutic treatments.
28 Although respiratory disease can occur throughout the year, BRDC is largely seasonal
29 in nature with outbreaks occurring within one month of housing in autumn or early
30 winter, thus vaccination usually occurs in late summer.

31

32 As a complex, it tends to progress from viral infection to further secondary bacterial
33 infection. Initially, the immunosuppression arising from stressors and bovine viral
34 diarrhoea virus (BVDV) infection increases vulnerability and thus the likelihood of viral
35 infection. Viral infection has a dual effect on disease progression - first, there is direct
36 damage to the airway epithelial layer and mucociliary escalator, thereby increasing
37 susceptibility to secondary bacterial infection; secondly, the immunosuppressive
38 nature of viral infection can lead to a decrease in the potency of immune responses,
39 thereby potentially increasing opportunity for bacterial pathogens to be inhaled deeply
40 into the lungs, causing lower respiratory tract (LRT) disease. Consequently, immunity
41 is further suppressed potentially aiding invasion from opportunistic non-commensal
42 bacteria. This results in bovine respiratory disease which presents as calf pneumonia
43 which concludes in either calf death or reduced growth after recovery.

44

45 Although viral and bacterial micro-organisms are the etiological agents instigating
46 BRD, several non-microbial aspects have been identified as potential risk factors
47 contributing to the risk of incidence of respiratory disease, discussed below. BRD is a
48 multifaceted complex making it difficult to establish the exact contribution of each
49 potential risk factor in decreasing resistance. However, all contributory risk factors act
50 to elevate stress levels, reducing immunity and thus increase the susceptibility of

51 cattle, particularly neonates. Suitable alleviating mechanisms and infrastructures can
52 reduce the severity and frequency of incidence of BRD.

53 1.1 **Housing:** Housing, more specifically ventilation and stocking density, is often
54 cited as the largest non-microbial risk factor for the development of BRD in 0-
55 3 month old calves (2).

56 1.2 **Transport:** There is a strong link between transport and BRDC-related
57 morbidity (3). In terms of both distance and method, transport is acknowledged
58 as being a major stressor for cattle and calves are the highest risk of respiratory
59 disease just after shipment (4).

60 1.3 **Weather:** Sudden and extreme temperature changes may have more of an
61 impact on the risk of BRDC developing than continually high or low
62 temperatures (4,5). However, evidence of this is inconsistent (6,7).

63 1.4 **Farm management:** Many farm management and animal husbandry practices
64 influence the risk of BRDC developing including pre-movement activities
65 (dehorning, castration, weaning), comingling, vaccination status and intensity
66 of farming (8,9).

67 1.5 **Genetics:** Various studies report Charlois, Simmental, Blonde d'Aquitaine
68 and Aberdeen Angus bulls to have greater resistance to BRDC than other
69 breeds (10). Other authors have suggested that calves intended for use in the
70 beef industry have a lower risk of BRDC development than those in the dairy
71 industry, due to a greater microflora diversity and additional pathogen exposure
72 through cattle markets (11).

73

74 The main contributory pathogens are detailed in Table 1, below. More recently
75 metagenomics analysis highlighted the involvement of up to 21 viruses including
76 Influenza D and bovine rhinotracheitis (12) with the first detection of Influenza D being
77 in the UK in the winter of 2017 (13). Frequently, the bacterial and viral pathogens
78 associated with BRDC interact synergistically to enhance disease (14,15) although
79 often the exact mechanisms remain unclear.

80

81 Due to the complex aetiology surrounding the establishment of BRD it is difficult to
82 ascertain the exact contribution of each pathogen. However, it is recognised that, on
83 a global scale, seropositivity rates against all viral and bacterial associated with BRD
84 are high and can sometimes be up to 100% Europe (16–20). Clinical disease is
85 frequently most severe in calves under 6 months of age, even in those with maternal
86 antibodies (21).

87

88 Table 1: Common viral and bacterial pathogens implicated in BRDC

VIRUSES	BACTERIA	MYCOPLASMA SPP.
Bovine herpesvirus-1 (BHoV)	<i>Mannheimia (Pasteurella) haemolytica</i>	<i>Mycoplasma bovis</i>
Bovine respiratory syncytial virus (BRSV)	<i>Pasteurella multocida</i>	<i>Ureaplasma spp.</i>
Bovine viral diarrhoea virus (BVDV)	<i>Histophilus (Haemophilus) somni</i>	
Bovine parainfluenza virus type-3 (BPIV-3)		
Bovine adenovirus (BAV)		
Bovine coronavirus (BCoV)		

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90

91 **2. Currently available vaccines against BRSV**

92 Nineteen vaccines against BRD are registered for use in the UK by the Veterinary
93 Medicine Directorate (22). Eight vaccines designed to target the viral and bacterial
94 pathogens of BRD are multi or polyvalent and thus designed to target several
95 pathogens in one vaccine, while 11 are monovalent (Section A, Appendix 1). All
96 vaccines available use whole virus, either modified live (attenuated) or inactivated, and
97 all are administered by intramuscular, intranasal or subcutaneous routes. See
98 Appendix 1 for further details on the currently available vaccines within the UK.

99

100 **3. Limitations of currently available BRD vaccines:**

101 Ineffective vaccines, declining employment in the agricultural sector and increasing
102 awareness of antimicrobial resistance has led policymakers to shift the focus onto the
103 development of superior, more successful vaccines as a major contribution to reducing
104 the pressure on the farming sector. Although many vaccines against BRD are currently
105 available on the UK market, they have limitations. Only a few of the vaccines have
106 been registered as suitable for use in pregnant or lactating cows and all require dry,
107 4°C storage out of direct sunlight. Additionally, they all require a booster to advance
108 immunity and none have been tested for maternal antibody interference (22). Only
109 eleven of the vaccines registered for use in the UK are multivalent and only four have
110 been tested and deemed suitable for use alongside other veterinary treatments,
111 frequently with those of the same manufacturer. However, multiple pathogens are
112 considered threats during the neonatal stage and so it is impractical and ineffectual to
113 have monovalent or incompatible medicines. Vaccination against BRD presents many
114 challenges:

115

116 3.1 Age of administration

117 A major challenge to the development of a successful vaccines for BRD is the age at
118 which calves must be vaccinated. Peak viral infection occurs upwards from 1 month
119 so vaccination must take place in the first few weeks of life to allow immunity to
120 develop. However, evidence shows a calf's immune system to be immature at this
121 time, thought to be a carryover from the immunotolerant state induced during
122 pregnancy (23–25). To compound this problem, several essential farm management
123 practices (discussed earlier) occur during this period increasing corticosteroid levels
124 (26) and essential maternally-derived antibodies (MDA) may interfere with the
125 development of any vaccine-induced immunity (27).

126

127 3.2 Route of administration

128 Routes trialled for RSV vaccination include subcutaneous (SC), intravenous (IV),
129 intramuscular (IM), intranasal (IN) all of which have produced protective immune
130 responses during candidate vaccine trials (28–30). However, parenteral vaccines are
131 invasive, require trained personnel for sterile administration and often cause a 'depot
132 effect' at the local site of injection; in cattle this can lead to carcass marking and thus
133 reduced price. Epicutaneous vaccination using skin patches, a non-invasive, needle-
134 free delivery route, has recently been investigated in mice against RSV with
135 encouraging results (31).

136

137 It has also been hypothesised that it might be more rational to vaccinate at the initial
138 site of pathogen entry – intranasally - thereby potentially preventing infection at source

139 and inducing more localised and protective mucosal immunity through activation of
140 nasal-associated lymphoid tissues (NALT). Mucosal immunity can also be generated
141 as a consequence of vaginal, anal and oral inoculation but intranasal delivery is
142 preferable due to the advantages discussed in Table 2. In support of this, a study by
143 Ellis *et al* showed that intranasal administration of BRSV vaccines intended for
144 parenteral use did not reduce the protective efficacy of the vaccines (32). Additionally,
145 Rossi *et al* (33) demonstrated strong bronchoalveolar cell-mediated and antibody
146 responses after a single intranasal delivery of a multivalent BRSV, BHV-1 and BPIV-
147 3 vaccine.

Advantages
Lower pH and levels of enzymatic activity than digestive tract
Prime neonatal calf in the presence of MDA
Needle-free/non-invasive
Induction of systemic and mucosal immunity
User-friendly (potential use in herds/developing world/remote farms)
Disadvantages
Rapid clearance of low affinity antigens
Potential antigen loss during inoculation (impact on cost)
Inefficient uptake
Lack of compatible adjuvants for mucosal vaccines

148 Table 2: Main advantages and disadvantages of intranasal vaccination in cattle

149

150 3.3 Vaccine antigen used

151 3.3.1 *Modified-live (attenuated) virus (MLV) vaccines*

152 Modified live virus (MLV) has been used to successfully globally eradicate Smallpox
153 (34) and Rinderpest (35,36) illustrating the important role MLV has played in world
154 health. Attenuation of pathogenic strains can be obtained by modifying the molecular
155 construction of the genome, using chemical mutagenesis, gene deletion or by

extensive serial passaging in non-host cell culture or embryonated chick eggs. Chemical mutagenesis has also been coupled with low temperatures to develop a cold-adapted temperature-sensitive strain (ctss) of HRSV that can only replicate in the upper respiratory tract (37). Several studies report the benefits of using modified-live vaccines in calves (38–40). However, a later study found no increase in antibody titres when using a live-attenuated BRSV vaccine (41) and similarly, no disparity was noted between inactivated and ML vaccines in a further study (42). Often the immunogenicity advantages gained are often offset by the increased safety risks posed, particularly in neonates.

3.3.2 *Inactivated (killed) virus vaccines*

The immune response garnered from using inactivated vaccines is considered by some as inadequate with suggestions that inactivated vaccines can effectively prime CD4+ T cells but encourage eosinophilia (43) and others providing evidence that IFN γ expression is reduced (44). A further study demonstrated a link between maternal vaccination for BVD using inactivated antigen and neonatal pancytopenia – a fatal autoimmune disease contracted from ingesting colostrum (45). Further, although antibody titres can often be high these can be non-neutralising (46). However, in contrast, several studies observed that using inactivated vaccines generated protection and they are at least as efficacious as using modified-live virus (29,42).

3.3.2.1 Vaccine-enhanced BRSV disease

Of particular note for BRSV is the observation that vaccination could augment disease. This was first noted in 1967 after a failed vaccine trial using a formalin-inactivated RSV

(FI-RSV) vaccine against HRSV (47) which led to investigations in cattle where a similar pathology was reported (48,49). No significant difference in gross lung lesions and in lung function was noted between those receiving a formalin-inactivated BRSV vaccine then challenged with BRSV and those not receiving the vaccine but challenged with BRSV, indicating the failure of the vaccine to provide any protective immunity. Further, although two groups were challenged with the same amount of BRSV, the sham vaccinated cohort demonstrated lower mean clinical scores (49) indicating disease exacerbation arising from vaccination. High titres of non-neutralising antibodies have also been observed, which can be associated with a high IgE titres and an allergic, inflammatory Th2-type response (50) and it is hypothesised that disease escalation is attributed to FI-RSV generation of low affinity antibodies (51) targeted at non-protective epitopes. Consequently, apprehension surrounds trials employing inactivated vaccines and scientists are cautious about developing candidate vaccines using inactivated antigen.

3.4 Storage conditions

Incorrect vaccine storage is frequently cited as a main reason for vaccine failure (52). Correct storage conditions are essential for conserving the three-dimensional structure of antigens, and thus essential for vaccines to retain their potency. Reliable vaccine storage is often not controlled for in a field setting. Vaccines which could remain immunogenic outside of the cold chain (i.e. not refrigerated) would greatly be beneficial especially for remote regions or areas lacking sufficient infrastructure (53). Recently a candidate nanoparticle RSV vaccine derived from an Sf9 insect cell line has been trialled showing that, once re-suspended, the vaccine can remain stable for

< 60 days (54) while storage of an East Coast fever vaccine on dry ice for up to 30 days did not reduce vaccine stability (55).

4. Practical considerations for vaccine development

4.1 Antimicrobial medicines

Metaphylaxis is a commonly employed tactic within farming, primarily regarding mastitis if in cattle, and dihydrostreptomycin, marbofloxacin or oxytetracycline are the most frequently detected antibiotics used in cattle (56). Prophylactic treatment of calves with ceftiofur, rather than after the appearance of clinical signs was shown to reduce the incidence of BRD (57) further supporting this approach. However, this heavy reliance on antibiotics aggravated by the combination of agricultural intensification alongside ineffective vaccines has resulted in production systems coming under scrutiny as a source of escalating antimicrobial resistance. Globally, antimicrobial consumption in animal production is expected to increase by almost 70% by 2030 (58) despite comprehensive UK government efforts to curtail usage (59).

4.2 EU regulations

Regulatory requirements for registering a veterinary vaccine within the EU are less stringent than those necessary to register a human vaccine; a process which is regulated by the Veterinary Medicines Directorate. The legislative requirements are laid down in 2009/9/EC and by the World Organisation for Animal Health (OIE). Vaccine development is geared towards reducing animal use, with current investigations into *in vitro* potency assays (60) and *in silico* systems vaccinology (61).

228 Council directive 81/852/EEC and European Pharmacopoeia further detail
229 requirements, stating that results from laboratory trials should be supplemented with
230 data from field trials. However, when efficacy cannot be demonstrated by laboratory
231 trials, field efficacy trials alone may be acceptable; in particular noting certain diseases
232 where a suitable experimental infection model is non-existent (i.e. BRSV), with
233 diseases that are caused by more than one causal agent or certain diseases where
234 environmental factors play a major role in the aetiology – all characteristics of BRD
235 (62). Only two parameters need to be measured: clinical picture (mortality, morbidity,
236 lesions, weigh) and the serological response, but evidence shows cell-mediated
237 immunity to play an important role against bovine respiratory disease (63,64).
238
239 4.3 Veterinary adjuvants

240
241 **Figure 1: Vaccine antigen type consequence on vaccine safety and immunogenicity**
242
243 Vaccines which are poorly immunogenic often require an additional stimulant as a
244 component to augment efficacy. These can potentially reduce vaccine antigen loads

or administration frequency (65) thus reducing production costs. Removal of the pathogenic fragments of BRSV to leave only purified antigens (i.e. a sub-unit vaccine) will increase the safety profile of the vaccine, increasing the tolerability. However, this can also lead to a reduction in the immunogenicity and the vaccine-induced immune response generated (66). Unlike human medicine, several adjuvants are registered for use in animal vaccines and all currently available vaccines employ aluminium compounds or variants. Despite its potent induction of cell-mediated immunity, the use of Complete or Incomplete Freund's Adjuvant (CFA/IFA) is strictly controlled in veterinary vaccines due to toxicity and the induction of painful side effects. Montanide is emerging as a novel veterinary adjuvant suitable for use in cattle due to the higher lymphoproliferative and antibody responses observed in vaccines in which it is incorporated (67,68).

4.4 Vaccination regimes

Current vaccination regimes rely on a prime/boost regimen to obtain the greatest vaccine-induced immune response (69) and traditionally, boosting occurred with a homologous vaccine. However, recent studies suggest that a boost using a heterologous vaccine can have a more beneficial effect as different arms of the immune system can be induced. Important considerations are the vaccine antigen type (70) and the route of administration of the priming or boosting vaccine (71). Due to the age at which BRD can develop and by extension the age at which vaccination is essential, induction of protective immunity following a single vaccine dose is highly desirable and this has shown promising results in calves with MDA, using a modified live or recombinant BRSV vaccine administered intranasally or intramuscularly (72–

74). However, often little change is detected in virus neutralising antibodies (VNA) titres indicating that single inoculations may only be efficient at priming cell-mediated immunity (75).

4.5 Pre-partum vaccination

Pre-partum vaccination of a heifer or cow is a farm management strategy successfully used to provide immunity for neonates, primarily against enteric pathogens such as *Escherichia coli* (*E. Coli*), rotavirus or coronavirus (76,77). Few report findings of maternal vaccination against BRSV. However, Dudek *et al* observed that maternal vaccination with a multivalent inactivated BRSV/PI3V/*M.haemolytica* vaccine, boosted colostrum immunoglobulin levels and led to increase in blood antibody titres in calves (78).

5. **Candidate BRSV vaccines**

Control strategies surrounding bovine respiratory disease concentrate on seasonal prophylactic antibiotic treatment and the administration of vaccines. Thus far these strategies have failed to prevent disease, with an estimated 1.9 million animals in the UK still affected by bovine respiratory disease annually. With increasing pressures on farms to intensify production alongside more rigid control on antibiotic use, research has focused on developing more efficacious, next generation vaccines.

5.1 Peptide vaccines

There are currently no commercially available peptide vaccines for use in the veterinary field, despite the potential advantages in terms of ease of manufacture and flexibility. However, success has been reported for several candidate peptide vaccines and currently there is much interest in their use in human medicine, particularly against cancers, HIV and diabetes. In farm animals, Foot and Mouth Disease virus (FMDV) seems to command the largest share of research into peptide vaccines, in part due its status as a Specified Animal Pathogen Order (SAPO) level 4 infectious agent and of the economic impact of an outbreak. Greenwood *et al* describe using inert nanobeads conjugated with peptides from FMDV in sheep with higher antibody titres, increased TNF α , IFN γ , IL-6 and greater T cell proliferation observed in immunised animals (79). Vaccines based on epitopes of the FMDV VP1 protein have previously shown promise in swine (80) and Zhang *et al* recently reported success with a peptide vaccine against FMDV documenting 100% protection after prime/boost vaccination and challenge in cattle (81). Bastien *et al* reported a reduction in pathological lesions, compared to unvaccinated controls, when calves were immunised with a peptide encompassing BRSV G₁₇₄₋₁₈₇ (82). This had previously been shown to confer protection in mice (83) and intraperitoneal immunisation of mice with a recombinant protein comprising HRSV G₁₃₀₋₂₃₀ coupled to streptococcal G protein (denoted BBG2Na) protected mice from upper and lower respiratory tract infection (84). However, despite the induction of high antibody titres in these studies, they were non-neutralising; a result repeated in a later study (85) implying that peptide vaccines provide protection by means other than a humoral response.

5.2 Immune stimulatory complexes (ISCOMs)

ISCOMS are comprised of viral glycoproteins, cholesterol, phospholipids and non-toxic saponins from the bark of the Quillaja saponin tree. Tested using the surface antigens of HRSV and BRSV in guinea pigs (86) they have shown promise when used against BRSV in young calves with maternal antibodies (87).

5.3 Virus-like particles (VLP)

Virus-like particles (pseudoviral particles) functionally and structural resemble viruses and present viral antigens in a conformation more akin to a virion. As such there is potential for lower antigenic doses to be used, reducing the cost of the vaccine – an important consideration in veterinary medicine (88). As they do not contain genetic material they are non-infectious, non-replicating and safer than killed or attenuated vaccines. Although there is a lack of literature on VLPs for BRSV, a recent HRSV study indicated robust protection can be provided from a single intranasal inoculation (89).

5.4 Nanoparticle vaccines

To protect peptides from proteolytic degradation by cytosolic aminopeptidases they require formulation with an additional component such as carrier proteins or nanoparticles. Nanoparticles can be relatively inexpensive to manufacture, biodegradable non-toxic and can augment the immunogenicity of subunit vaccines, leading to a potential decrease in antigen load or administration frequency. Further benefits include controlled antigen release, providing protection to antigen in the unfavourable conditions provided by the respiratory tract and the potential removal of the cold chain necessary for vaccine storage (90). Circular nanoring structures derived from a recombinant N protein of HRSV were used as a novel candidate vaccine

against BRSV in young calves, with encouraging results (91). Vaccines based on nanoparticles have also been associated with a reduced need for therapeutic intervention (92) and a recent review highlighted the benefits gained from using natural nanoparticles in livestock vaccines from a One-Health perspective (93).

5.5 DNA vaccines

An early study of an intramuscular DNA vaccine against Influenza A observed proficient stimulation of T and B cell responses, indicating an ability to cross-present antigen (94). However, opinion is divided on their suitability against BRSV as some have proved promising in young calves with maternally-derived antibodies (95) yet some have only been tested in seronegative calves (96). Furthermore, B cell responses have been observed as being slower to develop and ultimately lower in VNA titres than those from natural infection (96) or using a vectored vaccine (97). With DNA vaccines, unlike protein-based vaccines, no mis-folding can occur. Additionally, when the temperature stability and containment or manufacturing advantages gained from DNA vaccines, alongside their proven ability to elicit a cytotoxic response, are taken into consideration this area is worth researching more (98).

5.6 Viral Vectors

Viral vaccine vectors have been shown to capably induce robust cell mediated and humoral responses against BRSV (97) and unlike many other subunit vaccines often do not require an adjuvant to boost immunity, instead relying on the inherent capability of a virus to enter and replicate in a cell. Poxvirus vectors show promise for multivalent vaccine use in cattle, due to the size of exogenous genes which can be accepted and

they enjoy a superior safety profile due to their avian-restricted cytoplasmic replication. Vaccination with a recombinant modified Vaccinia virus Ankara (MVA) has shown much promise (99) and its replication-deficiency makes it all the more suitable for use in the field. Importantly, potential disease-causing immunopathological reactions such as elevated IgE titres and eosinophil influx have not been observed in MVA vaccinated calves, post BRSV challenge (100). Bovine herpesvirus-type 1 (BHV-1) has also been successfully used against BRSV in calves reducing clinical signs, pneumonic lesions and viral loads despite low antibody titres (101) as has bovine adenovirus as a vector (BAV) in mice (102). However, RSV research employing viral vectors as candidate vaccines has focused primarily on HRSV, rather than BRSV. The predominance of studies for HRSV probably reflects the urgency of the medical need to produce a human RSV vaccine.

6. Conclusion

Bovine respiratory disease is a major threat to dairy and beef farming and is the leading cause of mortality and morbidity in cattle over 1 month of age (103). Currently, the commercially available vaccines against BRD are limited in their efficacy, as evidenced by the appearance of clinical disease after vaccination. This may be due to a combination of inappropriate administration route or vaccine storage and the challenges of inoculating in young calves.

In Northern Ireland, agriculture accounts for 1.7 % of Gross Value Added (GVA), approximately 3 times above the UK average, and has been identified as a key future source of economic development in the 'Going for Growth' agri-food strategy (104).

However, the intensification necessary to realise this drive for economic growth has resulted in increasing farm size against a backdrop of decreasing farm numbers (105) and this intensification in productivity may lead to an increasing vulnerability to infectious disease. Thus, alongside increasing pressure on farms to intensify production and more rigid control on antibiotic use, research has focused on developing more efficacious, next generation vaccines.

Author Contributions

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Data Availability Statement

The data presented in this study are collected from the cited literature.

Conflicts of Interest

The authors declare no conflict of interest.

Appendix 1

A – Monovalent vaccines for bovine respiratory disease

(1) Name:	Bovalto Pastobov (2007; Vm 08327/4173)
Multivalent:	N – <i>Mannheimia haemolytica</i> (formerly <i>Pasteurella haemolytica</i>)
Antigen:	Type A1
Recommended age:	Minimum 4 weeks, booster 28 days later
Route of administration:	Sub-cutaneous or intramuscular
Adjuvant/excipients:	Aluminium hydroxide (4.2mg), thiomersal, salts, water

(2) Name:	Bovela lyophilisate (EU/2/14/176/001-016)
Multivalent:	N - BVD (1 – non cyto KE-9; 2 – non cyto NY-93)
Antigen:	Modified live (both strains)
Recommended age:	3 months +
Route of administration:	Intramuscular
Adjuvant/excipients:	Not detailed

(3) Name:	Bovilis BVD suspension (1999; Vm06376/4025)
Multivalent:	N - BVD 1 (non cyto C-86)
Antigen:	Inactivated
Recommended age:	8 months
Route of administration:	Intramuscular
Adjuvant/excipients:	Aluminium 3+ (Alum hydroxide) 6-9mg

(4) Name:	BOVILIS IBR marker inac (2006; vm06376/4053)
Multivalent:	N – BHV-1 (GK/D gE negative strain)
Antigen:	Inactivated
Recommended age:	3 months onwards
Route of administration:	Intramuscular
Adjuvant/excipients:	Alum 3+ (6.0 -8.8mg) formaldehyde 0.6-1mg, trometamol

(5) Name:	BOVILIS IBR MARKER LIVE (2006, vm06376/4032)
Multivalent:	N – BHV-1 (GK/D strain, gE negative)
Antigen:	Live
Recommended age:	2wk (Intranasal) 12wk (Intramuscular)
Route of administration:	Intranasal or Intramuscular
Adjuvant/excipients:	Sorbitol, monosodium glutamate; glycine

(6) Name:	HIPRABOVIS IBR marker live (2011; eu/2/10/114/001)
Multivalent:	N - BHV-1 (gE deleted; Ceddel strain)
Antigen:	Live
Recommended age:	12 wk +
Route of administration:	Intramuscular
Adjuvant/excipients:	Not disclosed

(7) Name:	NASYM (EU/2/19/241/001-004)
Multivalent:	N - BRSV (LYM-56)
Antigen:	Live
Recommended age:	9d (Intranasal) 10w (intramuscular)
Route of administration:	Intranasal OR Intramuscular
Adjuvant/excipients:	Not disclosed

(8) Name:	RISPOVAL IBR MARKER (VM42058/4127, 1999)
Multivalent:	N – BHV-1 (gE deleted, Difivac Strain)
Antigen:	Inactivated
Recommended age:	2w -3 m (if later than use 3 rd booster)
Route of administration:	Sub cut Sub-cutaneous
Adjuvant/excipients:	QUIL A (0.25MG) ALUM HYDROX (14-24MG)

418

(9) Name:	Rispoval Pateurella (VM42058/4128, 1999)
Multivalent:	N – Man.H type A1 (NL 1009 strain)
Antigen:	Inactivated
Recommended age:	12 wk +
Route of administration:	Intramuscular
Adjuvant/excipients:	Liquid paraffin and alum hydrox

419

(10)Name:	Rispoval RS (vm 42058/4129, 2005)
Multivalent:	N - BRSV (RB94)
Antigen:	Live attenuated
Recommended age:	7d – 4m (If 7d then 3 rd booster to counteract MDA)
Route of administration:	Intramuscular
Adjuvant/excipients:	Not detailed

420

(11) Name:	Tracherine (VM42058/4156; 2010)
Multivalent:	N - IBR (RBL106)
Antigen:	Live attenuated
Recommended age:	3w (10wk ideally for reduced MDA interference)
Route of administration:	Intranasal
Adjuvant/excipients:	Not detailed

421

422 B – Poly/Multivalent vaccines for bovine respiratory disease

(12) Name:	Bovalto Respi 3 (2016) (Vm 08327/4273)
Multivalent:	Y – BRSV (Bio-24) and BPI3-V (Bio-23) Man.H (A1)
Antigen:	All inactivated
Recommended age:	In cattle devoid of MDA (~6 months)
Route of administration:	Sub-cutaneous
Adjuvant/excipients:	AH (8.0mg) Quil A (0.4mg) Thiomersal (0.2mg) Formaldehyde (1.0mg)

423

(13) Name:	Bovalto Respi 4 (2016; Vm 08327/4274)
Multivalent:	Y - BRSV (Bio24) BPI3V (Bio23) Man H (A1) BVDV (Bio25)
Antigen:	All inactivated
Recommended age:	2 wk+
Route of administration:	Sub-cutaneous
Adjuvant/excipients:	AH (8.0mg) Quil A (0.4mg) Thiomersal (0.2mg) Formaldehyde (1.0mg)

424

(14)Name:	Bovalto Respi Intranasal (2018; Vm 08327/4289)
Multivalent:	Y - PI3 (Bio23/A) BRSV (Bio24/A)
Antigen:	Modified live (both)
Recommended age:	10 day +
Route of administration:	Intranasal
Adjuvant/excipients:	Not detailed

425

(15)Name:	Bovilis bovipast rsp (1999; Vm 01708/4458)
Multivalent:	Y – BRSV (ev908) PI3 (sf-4 reisinger) Man.H A1 (cross reactive to A6)
Antigen:	All inactivated
Recommended age:	~2 wks of age, prior to housing
Route of administration:	Sub-cutaneous
Adjuvant/excipients:	Alum hydr (37.5mg) Quil A (0.625mg) Thiomersal (0.032-0.58mg)

426

(16)Name:	IMURESP-RP (vm 42058/ 4072 2005)
Multivalent:	Y - PI3 (ts RLB103) IBR (ts RLB106)
Antigen:	Live attenuated
Recommended age:	3-10 wk but 10+ wk preferred
Route of administration:	Intranasal
Adjuvant/excipients:	Not disclosed

427

(17)Name:	Rispoval 3 (vm 42058/4124; 2005)
Multivalent:	Y - PI3 (RLB103) BRSV (375) BVDV (type 1 5960 c + 6309 n-c)
Antigen:	Modified live (PI3, BRSV) inactivated BVD
Recommended age:	12 wk+
Route of administration:	Intramuscular
Adjuvant/excipients:	Alhydrogel 2% 0.8ml (equiv. of 24.36mg alum hydroxide)

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(18)Name:	Rispoval 4 (VM42058/4125, 2001)
Multivalent:	Y – As above (17) including IBR/BHV-1
Antigen:	Inactivated
Recommended age:	12 wk +
Route of administration:	Intramuscular
Adjuvant/excipients:	Not detailed

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(19) Name:	Rispoval RS + PI3 (VM42058/4130)
Multivalent:	Y – BRSV (375) and PI3 (ts RLB103)
Antigen:	Modified Live
Recommended age:	9 day +
Route of administration:	Intranasal
Adjuvant/excipient:	Not disclosed

430 ts = temperature sensitive; c= cytopathic, n-c = non-cytopathic

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