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

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

Although viral and bacterial micro-organisms are the etiological agents instigating BRD, several non-microbial aspects have been identified as potential risk factors contributing to the risk of incidence of respiratory disease, discussed below. BRD is a multifaceted complex making it difficult to establish the exact contribution of each potential risk factor in decreasing resistance. However, all contributory risk factors act to elevate stress levels, reducing immunity and thus increase the susceptibility of
cattle, particularly neonates. Suitable alleviating mechanisms and infrastructures can reduce the severity and frequency of incidence of BRD.

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

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

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

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

1.5 **Genetics:** Various studies report Charlois, Simmental, Blonde d’Aquitaine and Aberdeen Angus bulls to have greater resistance to BRDC than other breeds (10). Other authors have suggested that calves intended for use in the beef industry have a lower risk of BRDC development than those in the dairy industry, due to a greater microflora diversity and additional pathogen exposure through cattle markets (11).
The main contributory pathogens are detailed in Table 1, below. More recently metagenomics analysis highlighted the involvement of up to 21 viruses including Influenza D and bovine rhinotracheitis (12) with the first detection of Influenza D being in the UK in the winter of 2017 (13). Frequently, the bacterial and viral pathogens associated with BRDC interact synergistically to enhance disease (14,15) although often the exact mechanisms remain unclear.

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

Table 1: Common viral and bacterial pathogens implicated in BRDC

<table>
<thead>
<tr>
<th>VIRUSES</th>
<th>BACTERIA</th>
<th>MYCOPLASMA SPP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine herpesvirus-1 (BHoV)</td>
<td>Mannheimia (Pasteurella) haemolytica</td>
<td>Mycoplasma bovis</td>
</tr>
<tr>
<td>Bovine respiratory syncytial virus (BRSV)</td>
<td>Pasteurella multocida</td>
<td>Ureaplasma spp.</td>
</tr>
<tr>
<td>Bovine viral diarrhoea virus (BVDV)</td>
<td>Histophilus (Haemophilus) somni</td>
<td></td>
</tr>
<tr>
<td>Bovine parainfluenza virus type-3 (BPIV-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine adenovirus (BAV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine coronavirus (BCoV)</td>
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</table>
2. **Currently available vaccines against BRSV**

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

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

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

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

3.2 Route of administration

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

It has also been hypothesised that it might be more rational to vaccinate at the initial site of pathogen entry – intranasally - thereby potentially preventing infection at source.
and inducing more localised and protective mucosal immunity through activation of nasal-associated lymphoid tissues (NALT). Mucosal immunity can also be generated as a consequence of vaginal, anal and oral inoculation but intranasal delivery is preferable due to the advantages discussed in Table 2. In support of this, a study by Ellis et al showed that intranasal administration of BRSV vaccines intended for parenteral use did not reduce the protective efficacy of the vaccines (32). Additionally, Rossi et al (33) demonstrated strong bronchoalveolar cell-mediated and antibody responses after a single intranasal delivery of a multivalent BRSV, BHV-1 and BPIV-3 vaccine.

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

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

3.3 **Vaccine antigen used**

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

Modified live virus (MLV) has been used to successfully globally eradicate Smallpox (34) and Rinderpest (35,36) illustrating the important role MLV has played in world health. Attenuation of pathogenic strains can be obtained by modifying the molecular 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 IFNγ 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 trail 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 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).
Council directive 81/852/EEC and European Pharmacopoeia further detail requirements, stating that results from laboratory trials should be supplemented with data from field trials. However, when efficacy cannot be demonstrated by laboratory trials, field efficacy trials alone may be acceptable; in particular noting certain diseases where a suitable experimental infection model is non-existent (i.e. BRSV), with diseases that are caused by more than one causal agent or certain diseases where environmental factors play a major role in the aetiology – all characteristics of BRD (62). Only two parameters need to be measured: clinical picture (mortality, morbidity, lesions, weigh) and the serological response, but evidence shows cell-mediated immunity to play an important role against bovine respiratory disease (63,64).

4.3 Veterinary adjuvants

Vaccines which are poorly immunogenic often require an additional stimulant as a 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–
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 TNFα, IFNγ, 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 G\(_{174-187}\) (82). This had previously been shown to confer protection in mice (83) and intraperitoneal immunisation of mice with a recombinant protein comprising HRSV G\(_{130-230}\) 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 attentuated 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

Conceptualization: J.L.L.; writing—original draft preparation: J.L.L.; writing—review and editing: J.L.L. and M.McM. All authors have read and agreed to the published version of the manuscript.

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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

<table>
<thead>
<tr>
<th>No.</th>
<th>Name:</th>
<th>Multivalent:</th>
<th>Antigen:</th>
<th>Recommended age:</th>
<th>Route of administration:</th>
<th>Adjuvant/excipients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bovalto Pastobov (2007; Vm 08327/4173)</td>
<td>N – Mannheimia haemolytica (formerly Pasteurella haemolytica)</td>
<td>Type A1</td>
<td>Minimum 4 weeks, booster 28 days later</td>
<td>Sub-cutaneous or intramuscular</td>
<td>Aluminium hydroxide (4.2mg), thiomersal, salts, water</td>
</tr>
<tr>
<td>2</td>
<td>Bovela lyophilisa (EU/2/14/176/001-016)</td>
<td>N - BVD (1 – non cyto KE-9; 2 – non cyto NY-93)</td>
<td>Modified live (both strains)</td>
<td>3 months +</td>
<td>Intramuscular</td>
<td>Not detailed</td>
</tr>
<tr>
<td>3</td>
<td>Bovilis BVD suspension (1999; Vm06376/4025)</td>
<td>N - BVD 1 (non cyto C-86)</td>
<td>Inactivated</td>
<td>8 months</td>
<td>Intramuscular</td>
<td>Aluminium 3+ (Alum hydroxide) 6-9mg</td>
</tr>
<tr>
<td>4</td>
<td>BOVILIS IBR marker inac (2006; vm06376/4053)</td>
<td>N – BHV-1 (GK/D gE negative strain)</td>
<td>Inactivated</td>
<td>3 months onwards</td>
<td>Intramuscular</td>
<td>Alum 3+ (6.0 -8.8mg) formaldehyde 0.6-1mg, trometamol</td>
</tr>
<tr>
<td>5</td>
<td>BOVILIS IBR MARKER LIVE (2006, vm06376/4032)</td>
<td>N – BHV-1 (GK/D strain, gE negative)</td>
<td>Live</td>
<td>2wk (Intranasal) 12wk (Intramuscular)</td>
<td>Intranasal or Intramuscular</td>
<td>Sorbitol, monosodium glutamate; glycine</td>
</tr>
<tr>
<td>6</td>
<td>HIPRABOVIS IBR marker live (2011; eu/2/10/114/001)</td>
<td>N - BHV-1 (gE deleted; Ceddel strain)</td>
<td>Live</td>
<td>12 wk +</td>
<td>Intramuscular</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>7</td>
<td>NASYM (EU/2/19/241/001-004)</td>
<td>N - BRSV (LYM-56)</td>
<td>Live</td>
<td>9d (Intranasal) 10w (intramuscular)</td>
<td>Intranasal OR Intramuscular</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>Name:</td>
<td>RISPOVAL IBR MARKER (VM42058/4127, 1999)</td>
<td></td>
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<tr>
<td>Multivalent:</td>
<td>N – BHV-1 (gE deleted, Difivac Strain)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antigen:</td>
<td>Inactivated</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Recommended age:</td>
<td>2w - 3m (if later than use 3rd booster)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Route of administration:</td>
<td>Sub cut Sub-cutaneous</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant/excipients:</td>
<td>QUIL A (0.25MG) ALUM HYDROX (14-24MG)</td>
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<tr>
<th>Name:</th>
<th>RISPOVAL Pateurella (VM42058/4128, 1999)</th>
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</thead>
<tbody>
<tr>
<td>Multivalent:</td>
<td>N – Man.H type A1 (NL 1009 strain)</td>
</tr>
<tr>
<td>Antigen:</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Recommended age:</td>
<td>12 wk +</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Adjuvant/excipients:</td>
<td>Liquid paraffin and alum hydrox</td>
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<th>Name:</th>
<th>Rispoval RS (vm 42058/4129, 2005)</th>
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<tbody>
<tr>
<td>Multivalent:</td>
<td>N - BRSV (RB94)</td>
</tr>
<tr>
<td>Antigen:</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Recommended age:</td>
<td>7d – 4m (if 7d then 3rd booster to counteract MDA)</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Adjuvant/excipients:</td>
<td>Not detailed</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Name:</th>
<th>Bovalto Respi 4 (2016; Vm 08327/4274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen:</td>
<td>All inactivated</td>
</tr>
<tr>
<td>Recommended age:</td>
<td>2 wk+</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Sub-cutaneous</td>
</tr>
<tr>
<td>Adjuvant/excipients:</td>
<td>AH (8.0mg) Quil A (0.4mg) Thiomersal (0.2mg) Formaldehyde (1.0mg)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Name:</th>
<th>Bovalto Respi Intranasal (2018; Vm 08327/4289)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivalent:</td>
<td>Y - P13 (Bio23/A) BRSV (Bio24/A)</td>
</tr>
<tr>
<td>Antigen:</td>
<td>Modified live (both)</td>
</tr>
<tr>
<td>Recommended age:</td>
<td>10 day +</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Adjuvant/excipients:</td>
<td>Not detailed</td>
</tr>
<tr>
<td><strong>(15)</strong> Name:</td>
<td><strong>Bovilis bovipast rsp (1999; Vm 01708/4458)</strong></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Multivalent:</strong></td>
<td>Y – BRSV (ev908) PI3 (sf-4 reisinger) Man.H A1 (cross reactive to A6)</td>
</tr>
<tr>
<td><strong>Antigen:</strong></td>
<td>All inactivated</td>
</tr>
<tr>
<td><strong>Recommended age:</strong></td>
<td>~2 wks of age, prior to housing</td>
</tr>
<tr>
<td><strong>Route of administration:</strong></td>
<td>Sub-cutaneous</td>
</tr>
<tr>
<td><strong>Adjuvant/exipients:</strong></td>
<td>Alum hydr (37.5mg) Quil A (0.625mg) Thiomersal (0.032-0.58mg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(16)</strong> Name:</th>
<th><strong>IMURESP-RP (vm 42058/ 4072 2005)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivalent:</strong></td>
<td>Y - PI3 (ts RLB103) IBR (ts RLB106)</td>
</tr>
<tr>
<td><strong>Antigen:</strong></td>
<td>Live attenuated</td>
</tr>
<tr>
<td><strong>Recommended age:</strong></td>
<td>3-10 wk but 10+ wk preferred</td>
</tr>
<tr>
<td><strong>Route of administration:</strong></td>
<td>Intranasal</td>
</tr>
<tr>
<td><strong>Adjuvant/exipients:</strong></td>
<td>Not disclosed</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>(17)</strong> Name:</th>
<th><strong>Rispoval 3 (vm 42058/4124; 2005)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivalent:</strong></td>
<td>Y - PI3 (RLB103) BRSV (375) BVDV (type 1 5960 c + 6309 n-c)</td>
</tr>
<tr>
<td><strong>Antigen:</strong></td>
<td>Modified live (PI3, BRSV) inactivated BVD</td>
</tr>
<tr>
<td><strong>Recommended age:</strong></td>
<td>12 wk+</td>
</tr>
<tr>
<td><strong>Route of administration:</strong></td>
<td>Intramuscular</td>
</tr>
<tr>
<td><strong>Adjuvant/exipients:</strong></td>
<td>Alhydrogel 2% 0.8ml (equiv. of 24.36mg alum hydroxide)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(18)</strong> Name:</th>
<th><strong>Rispoval 4 (VM42058/4125, 2001)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivalent:</strong></td>
<td>Y – As above (17) including IBR/BHV-1</td>
</tr>
<tr>
<td><strong>Antigen:</strong></td>
<td>Inactivated</td>
</tr>
<tr>
<td><strong>Recommended age:</strong></td>
<td>12 wk +</td>
</tr>
<tr>
<td><strong>Route of administration:</strong></td>
<td>Intramuscular</td>
</tr>
<tr>
<td><strong>Adjuvant/exipients:</strong></td>
<td>Not detailed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>(19)</strong> Name:</th>
<th><strong>Rispoval RS + PI3 (VM42058/4130)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivalent:</strong></td>
<td>Y – BRSV (375) and PI3 (ts RLB103)</td>
</tr>
<tr>
<td><strong>Antigen:</strong></td>
<td>Modified Live</td>
</tr>
<tr>
<td><strong>Recommended age:</strong></td>
<td>9 day +</td>
</tr>
<tr>
<td><strong>Route of administration:</strong></td>
<td>Intranasal</td>
</tr>
<tr>
<td><strong>Adjuvant/exicipants:</strong></td>
<td>Not disclosed</td>
</tr>
</tbody>
</table>

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