Limitations of Currently Available Bovine Respiratory Disease Vaccines

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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 efficacious vaccines as a major contribution in reducing the pressure to intensify 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 refrigeration. Additionally, all come with a strong recommendation for a booster to advance immunity and none have been tested for maternal antibody interference. 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.

Keywords: vaccination ; pathogens ; efficacy

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 [1]. 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 [2][3]. 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 [1][4][5]. To compound this problem, several essential farm management practices (discussed earlier) occur during this period increasing corticosteroid levels [6] and essential maternally-derived antibodies (MDA) may interfere with the development of any vaccine-induced immunity [2][7].

2. Route of Administration

The majority of currently approved vaccines against BRD are to be used parenterally (i.e., sub-cutaneously or intramuscularly) and these have been demonstrated as producing protective immune responses [8][9][10][11]. 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 scarring and thus reduced price [12]. More recently, epicutaneous vaccination using skin patches, a non-invasive, needle-free delivery route, has been investigated in mice against RSV with encouraging results [13].

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. Many more intranasal vaccines are getting approved and coming onto the market. Intranasal vaccination induces more localised and protective mucosal immunity through activation of nasal-associated lymphoid tissues (NALT). Although mucosal immunity can also be generated as a consequence of vaginal, anal and oral inoculation, intranasal delivery is preferable due to its many advantages (discussed in context with disadvantages in **Table 1**). 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 [14]. Additionally, Rossi et al. [15] demonstrated strong bronchoalveolar cell-mediated and antibody responses after a single intranasal delivery of a multivalent BRSV, BHV-1 and BPIV-3 vaccine.

Table 1. Main advantages and disadvantages of intranasal vaccination in cattle.

Advantages
More neutral pH and lower 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

3. Type of Vaccines Available:

3.1. Modified-Live (MLV) Vaccines

Modified-live vaccines, also called attenuated vaccines, are those which employ live replicating whole pathogen that has been weakened in the laboratory. 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 [16]. Only two diseases have been successfully eradicated across the globe—smallpox in humans [17] and rinderpest in cattle [18][19]—and both have been achieved using modified-live vaccines, thus illustrating their significant contribution to human and veterinary health.

3.2. Inactivated Vaccines

Inactivated vaccines, also known as killed vaccines, are those which do not contain any live replicating pathogenic material and cannot cause disease. For this reason they have a superior safety profile to their live counterparts [20] and are considered suitable for use in pregnant or lactating animals. The pathogenic agents are destroyed by heat, chemicals or radiation. Furthermore, inactivated vaccines do not require refrigeration and can be lyophilised for transport purposes [21].

3.3. Immunogenicity of Modified-Live and Inactivated Vaccines

As attenuated vaccines broadly mimic the immune response garnered from a natural infection, they are universally recognised for producing stronger, longer lasting and more robust immune responses for many pathogens [21][22][23][24]. Furthermore, it is surmised that modified-live vaccines can initiate cellular responses in a way that inactivated vaccines are not reported as doing [25][26]. Several studies report the benefits of using modified-live vaccines in calves [27][28][29][30]. However, several studies now indicate that evidence on this is conflicting [30][31] and even if this were conclusive, often the immunogenicity advantages gained from MLV are offset by the increased safety risks posed, particularly in neonates.

Conversely, 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 eosinophila [32] and others providing evidence that IFNγ expression is reduced [33]. A further study demonstrated a link between maternal vaccination for BVDV using inactivated vaccines and neonatal pancytopenia—a fatal autoimmune disease contracted from ingesting colostrum [34]. Further, although antibody titres can be high these are often found to be non-neutralising [35]. However, again, in contrast, several studies observed that using inactivated vaccines generated protection and they are at least as efficacious as using modified-live virus [32][36].

3.4. Vaccine-Enhanced Disease

Of particular note for BRSV is the observation that vaccination could actually augment disease. This was first noted in 1967 after a failed vaccine trail using a formalin-inactivated RSV (FI-RSV) vaccine against HRSV [37] which led to investigations in cattle where a similar pathology was reported [38][39]. In this study, one group was vaccinated with a FI-BRSV vaccine while the other was sham-vaccinated. Both groups were challenged with live BRSV post-vaccination. No significant difference in gross lung lesions and in lung function was noted between the two groups, 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 [39] 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 [40] and it is hypothesised that disease escalation is attributed to FI-RSV generation of low affinity antibodies [41] targeted at non-protective epitopes. Consequently, apprehension surrounds trials employing inactivated vaccines and scientists are cautious about developing candidate vaccines using inactivated antigen. Although antibody titres generated from vaccination are not always correlated with reduced disease, vaccination against any other pathogen implicated in BRD does not appear to have had such a detrimental effect [6].

4. Storage Conditions

Incorrect vaccine storage is frequently cited as a main reason for vaccine failure [42]. Correct storage conditions are essential for conserving the three-dimensional structure of antigens, and thus essential for vaccines to retain their potency [43]. However, reliable vaccine storage is often not controlled for in a field setting. Vaccines which could potentially remain immunogenic outside of the cold chain (i.e., not refrigerated) would be greatly beneficial to remote regions, vast farms or areas lacking sufficient infrastructure [44]. 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 [45]. In further support of this, another group demonstrated that dry ice storage for up to 30 days did not detriment stability for a vaccine against East Coast fever—a tick-borne disease of cattle in Eastern and Central Africa with high mortality rates [46]. More recently a study into vaccines for tuberculosis showed that desiccation of liquid vaccine antigen increased thermostability outside of the cold-chain and produced a vaccine antigen more adaptable for mucosal use [47].

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