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Immunity to bovine herpesvirus 1: II. Adaptive immunity and vaccinology

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Abstract

Bovine herpesvirus 1 (BHV-1) infection is widespread and causes a variety of diseases. Although similar in many respects to the human immune response to human herpesvirus 1, the differences in the bovine virus proteins, immune system components and strategies, physiology, and lifestyle mean the bovine immune response to BHV-1 is unique. The innate immune system initially responds to infection, and primes a balanced adaptive immune response. Cell-mediated immunity, including cytotoxic T lymphocyte killing of infected cells, is critical to recovery from infection. Humoral immunity, including neutralizing antibody and antibody-dependent cell-mediated cytotoxicity, is important to prevention or control of (re-)infection. BHV-1 immune evasion strategies include suppression of major histocompatibility complex presentation of viral antigen, helper T-cell killing, and latency. Immune suppression caused by the virus potentiates secondary infections and contributes to the costly bovine respiratory disease complex. Vaccination against BHV-1 is widely practiced. The many vaccines reported include replicating and non-replicating, conventional and genetically engineered, as well as marker and non-marker preparations. Current development focuses on delivery of major BHV-1 glycoproteins to elicit a balanced, protective immune response, while excluding serologic markers and virulence or other undesirable factors. In North America, vaccines are used to prevent or reduce clinical signs, whereas in some European Union countries marker vaccines have been employed in the eradication of BHV-1 disease.

Keywords: bovine herpesvirus 1 (BHV-1), adaptive immunity, vaccine, envelope glycoprotein, differentiating infected from vaccinated animals (DIVA), immune suppression

1. Introduction

Bovine herpesvirus 1 (BHV-1) causes important diseases of cattle globally (Gibbs and Rweyemamu, 1977; Beer, 2012). Infection and the resultant immunosuppression contribute to the bovine respiratory disease complex (BRDC), which has a large economic impact on the cattle industry in USA (Jones and Chowdhury, 2007; Anon, 2011a).

The bovine immune response to infection is robust, broad-based, and long-lasting, perhaps due to persistent infection (Babiuk *et al*., 1996; Engels and Ackermann, 1996; Kaashoek *et al*., 1996a). The response begins with internal and external signaling by infected cells, and proceeds through stimulation of innate and adaptive immune cells, resulting in cytotoxic T lymphocyte (CTL) and virus neutralizing (VN) antibody (Ab) to clear the infection and prevent re-infection.

BHV-1 infection is commonly diagnosed serologically. Serosurveys have been conducted in Africa (Straub, 1990; El Hussein *et al*., 2005), South Asia (Nandi *et al*., 2009), East Asia (Kampa *et al*., 2004; Yan *et al*., 2008), Australia (St. George *et al*., 1967; Smith *et al*., 1995), North America (Kahrs *et al*., 1964; Elazhary *et al*., 1984), South America (Straub, 1990), and Europe (Wuyckhuise *et al*., 1994).

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Serological testing and removal of infected animals have been successfully used to eliminate BHV-1 from Denmark, Switzerland, and Austria (Ackermann and Engels, 2006).

BHV-1 disease is widely vaccinated against, on multiple continents. A variety of vaccines have been employed, such as replicating and non-replicating or conventional and genetically engineered (Turin *et al.*, 1999). Many of the vaccines have had problems or issues in application, including virulence, immunosuppression, recrudescence, or failure to protect. In North America, the aim is disease suppression, whereas in many EU countries vaccination is used in eradication campaigns (van Drunen Littel-van den Hurk, 2006). BHV-1's large genome size has resulted in investigation of its use as a viral vector for vaccination against other cattle diseases (Kit *et al.*, 1991; Schrijver *et al.*, 1997; Kweon *et al.*, 1999).

The molecular characterization of BHV-1 and its infection, and useful extrapolations from human alphaherpesvirus (αHV) infections, have led to the use of BHV-1, as a model for vaccine and other technologies. The cost and pervasiveness of BHV-1 disease and the mixed record of vaccination success mean the knowledge gained and tools developed from research and development are likely to find practical and impactful application. For these reasons, examination of the bovine immune response to infection with and vaccination against BHV-1 is important and relevant.

2. The bovine adaptive immune response to BHV-1

2.1 The mammalian and bovine immune response to alphaherpesvirus infection

The bovine immune system is of interest because of the economic importance of cattle to pastoral communities and commercial enterprises globally. Its similarities to and differences from the better-studied mouse and human immune systems are only beginning to be understood. Some features appear to be fundamental and are conserved (Hirano *et al.*, 2011), allowing useful generalizations or extrapolations. However, there are also differences in strategies [e.g., for generation of diversity of lymphocyte (LC) antigen (Ag) receptors and immunoglobulins (Igs)] between mammalian orders, families, genera, and species. It has been noted that 'cattle- specific evolutionary breakpoint regions have a higher density of species-specific variations in genes having to do with lactation and immune responsiveness' (The Bovine Genome Sequencing and Analysis Consortium *et al.*, 2009). The interactions of stress, nutrition, and fertility with the innate and adaptive immune systems are important for cattle (Salak-Johnson and McGlone, 2007; Lippolis, 2008).

Most of what is known about mammalian immunity to αHV was first elucidated in the human herspesvirus 1 (HHV-1)-mouse system, and then confirmed or expanded in HHV-1/2-human and other systems, e.g., suid herpesvirus 1 (SHV1)-mouse or -swine. The bovine immune response to BHV-1 has been well reviewed at intervals (Rouse and Babiuk, 1978; Wyler *et al.*, 1989; Tikoo *et al.*, 1995a; Babiuk *et al.*, 1996; Engels and Ackermann, 1996; Muylkens *et al.*, 2007).

The response begins with internal and external (cytokine) signaling by infected cells. Innate immune cells including macrophages (Mϕ), polymorphonuclear neutrophils (PMN), plasmacytoid dendritic cells (pDC), and natural killer (NK) cells are recruited to the site and activated. These immune cells secrete more cytokines, kill virus-infected cells, and bridge to the adaptive response, including by presenting Ag to LCs. It has been noted that innate and adaptive immune cells have a complex interaction in αHV infections (Schuster *et al.*, 2011).

Starting at day 5, and peaking days 7–10, helper T cells activate Mϕ and NK cells, and promote the proliferation of specific CTLs. Finally, beginning at day 10 and peaking after the infection is largely resolved, VN and other Abs are detectable. They likely help with clearing extracellular virus and with cellular cytotoxicity. Ab can then protect the host from reinfection (by recrudescence or another exposure), and can protect the neonate via colostrum. The main adaptive immune response to the virus and virus-infected cells is to the viral envelope GPs: gB, gC, and gD.

The bovine adaptive immune response to BHV-1 and vaccination to prevent the diseases it causes are the foci of this review. The BHV-1 life cycle and bovine innate immune response to the virus are the subject of another review (Levings and Roth, 2013).

2.2 Adaptive immune system components and activities

The adaptive immune response is characterized by: (1) the specificity of T- and B-LC receptors due to gene segment rearrangement and assembly, mutation, and clonal selection; and (2) the memory of the response (Bonilla and Oettgen, 2010). B cells recognize surface epitopes with the immunoglobulin B-cell receptor (BCR). T cells, by means of the T-cell receptor (TCR), recognize peptides that are the products of protein breakdown in another cell and displayed on that cell's surface in a complex with a major histocompatibility complex (MHC) molecule (Murphy *et al.*, 2008). The adaptive response is commonly described as having two 'arms', cell-mediated and humoral, enabled by T-helper 1 and 2 responses, respectively. The involvement of T cells in both 'arms' means that, unlike the innate response, the adaptive response is 'MHC-restricted.'

MHC restriction describes the phenomena of T cells only being stimulated by peptides bound to 'self' MHC. They only kill infected cells with the same MHC type I or

proliferate when presented with Ag by cells of the same MHC type II. This has been demonstrated in cattle using multiple viral systems, including studies of genetic variation in strength and character of immune response to pathogens, and determination of key amino acid (aa) residues in MHC- binding pockets for vaccine design (Collen and Morrison, 2000; Glass, 2004; Baxter *et al.*, 2009; Gerner *et al.*, 2009; Glass *et al.*, 2012).

However, for LCs to proliferate, become effector cells, and generate memory cells, a 'second signal' beyond Ag recognition by BCR or TCR is needed, such as binding by a co-receptor and stimulation by cytokine. A third signal is also proposed for efficient stimulation (Curtsinger *et al.*, 1999; Ruprecht and Lanzavecchia, 2006).

The bovine response to BHV-1 is balanced, including generation of CTL and VN Ab. CTLs are considered important for virus clearing and recovery from an infection, and Abs in the prevention of BHV-1 (re-)infection (Babiuk *et al.*, 1996).

2.2.1. Antigen presenting cells

Dendritic cells (DCs), Mϕs, and B cells can serve as antigen presenting cells (APC), because in addition to presenting Ag peptides on MHC I or II, when activated during an infection they express the co-stimulatory molecules needed to activate T cells (Renjifo *et al.*, 1999; Murphy *et al.*, 2008). They migrate to the local draining lymph node to do so. DCs have the unique ability to sensitize (prime) naïve T cells. Mϕs and B cells present engulfed and soluble Ag, respectively, to primed effector T cells (Murphy *et al.*, 2008).

Conventional DCs (cDCs) are so named to differentiate them from pDC, which have a different origin and distribution in tissues. cDCs, also known as myeloid DCs, include migratory cells and lymphoid-resident cells (Freer and Matteucci, 2009). cDC: (1) have specialized mechanisms for Ag capture and processing; (2) migrate to defined sites in lymphoid organs to initiate immunity; and (3) rapidly mature in response to a variety of microbial and other stimuli (e.g., cytokines produced by innate immune cells) (Steinman and Hemmi, 2006). After activation, cDC produce interleukin (IL)-12 and IL-15 that stimulate interferon (IFN)-γ secretion by NK cells, and promote differentiation of $CD4^+$ and $CD8^+$ T cells (Lambotin *et al.*, 2010). So, they serve as a major link between innate and adaptive immunity. cDCs are continuously produced and positioned at the skin, mucosal surfaces, and in the blood, so they are likely to rapidly encounter and be activated by invading pathogens (Murphy *et al.*, 2008). cDCs can be infected by viruses themselves, can phagocytize infected cells, or can micropinocytose Ag. Migrating cDC may also transfer Ag to lymph node resident DC (Murphy *et al.*, 2008; Singh and Cresswell, 2010).

cDCs are equipped with a set of varied pathogen recognition receptors (PRR), such as toll-like receptors (TLR) in the endosome and retinoic acid-inducible gene I (RIG-I)-like receptors (RLR) in the cytosol. Damage-associated molecular patterns (DAMP) may also activate immature DC (Nace *et al.*, 2012). Stimulation changes the chemokine receptors on the cDC, which in turn results in their ability to migrate to the peripheral lymphoid tissue to activate naïve T cells (Murphy *et al.*, 2008). Activated DCs also present many peptide-MHC complexes and co-stimulatory molecules, such as B7.1 (CD80) or B7.2 (CD86), for which T-cells express complementary CDs (e.g., CD28) (Murphy *et al.*, 2008).

cDCs comprise two main subsets: $CD8^-$, which are efficient at presenting exogenous Ag on MHC II to $CD4^+$ T cells; and $CD8^+$, which present Ag on MHC I to $CD8^+$ T cells (Reizis *et al.*, 2011). Presentation to naïve $CD8^+$ T cells is known as cross-priming, and presentation to stimulated ones is known as cross-presentation (Singh and Cresswell, 2010). Cross-presentation is important for the response to viruses that do not infect APCs directly. The dominant mechanism for cross-presentation is translocation of Ags to the cytosol, where proteasomal degradation generates peptides, which are then transported via the transporter associated with antigen processing (TAP) and bind to newly synthesized MHC I (Singh and Cresswell, 2010). DC can also regulate T cell differentiation with IL (Freer and Matteucci, 2009). cDCs produce IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α (Murphy *et al.*, 2008). DCs performed better than monocytes as APCs for BHV-1 (measured by stimulation of T-cell proliferation *in vitro*). The DCs were not BHV-1-infected (Renjifo *et al.*, 1999).

Mϕs from BHV-1-infected cattle were shown to express increased levels of MHC II (Tikoo *et al.*, 1995a), and Ag presentation by bovine alveolar Mϕs was shown to stimulate proliferation of T cells *in vitro*. Bovine alveolar Mϕ and monocytes are permissive to BHV-1 infection (Renjifo *et al.*, 1999), resulting in the impairments described in another review focused on the innate immune system (Levings and Roth, 2013).

B cells can internalize Ag bound to the BCR, and process it in the endosome (triggering TL7 and TLR9, a third signal for the B cells), leading to presentation of Ag on MHC II (Lanzavecchia and Sallusto, 2007).

2.2.2. Lymphocytes

LCs are the effector cells of the adaptive immune system. Study of leukocyte differentiation molecules has shown that many of those identified in human beings and mice (e.g., CD-2, −3, −4, −8) are highly conserved in structure and function across mammalian species (Davis and Hamilton, 1998).

2.2.3. T lymphocytes

T-cell receptors are constituted of two chains, each of which is coded by recombined gene segments (resulting in high diversity). The gene segments are variable (V), junction (J), diversity (D), and constant (C). The proteins are made by recombination of VJC (α and γ chains) and

VDJC (β and δ chains) genes (Murphy *et al.*, 2008). Nucleotide deletion and substitution at the V(D)J junction by exonuclease and terminal deoxynucleotide transferase activity increases the diversity achieved during recombination. Consequentially much of the variability is focused in the complementarity determining region (CDR) 3, encoded by the V(D)J junction (Connelley *et al.*, 2008). The CDR3s of both chains are central in the binding site and key to Ag recognition (Murphy *et al.*, 2008).

Human and murine TCRs are predominantly $\alpha-\beta$. There are 40–70 variable α or β gene segments, many J segments, and the D gene for the β chain is frequently read in three frames. The pairing, recombination, and junctional diversity together lead to a diversity of 10^{18} (Murphy *et al.*, 2008). The contribution of $\gamma\delta$ TCR to TCR diversity in humans is minimal.

For cattle it was assumed that the high levels of $\gamma\delta$ diversity observed meant $\alpha\beta$ diversity was likely to be low, but this appears not to be the case. Over 400 genes have been observed in the $\alpha-\delta$ locus (Reinink and Van Rhijn, 2009) and 48 functional Vβ genes of 17 subfamilies were identified. Clonal expansions were distributed over a large number of Vβ subfamilies, although a limited number of clonotypes dominated the response (Connelley *et al.*, 2008).

2.2.4. Bovine γδ T cells

Unlike in human beings and mice, $\gamma\delta$ T cells are a major population of T cells in cattle, particularly in calves, where they account for 60% of peripheral blood leucocytes (PBLs) (Chen *et al.*, 2009). There is more gene diversity (VDJC γ; VJC δ) in ruminants and some other species than in mice and humans (Reinink and Van Rhijn, 2009), and multiple γ genes are used (Guzman *et al.*, 2012). $\gamma\delta$TCRs interact with non-classical MHCs in mice and humans; it is believed unlikely that $\gamma\delta$TCR interact with classical MHC in cattle (Reinick and Van Rhijn, 2009).

Two populations of $\gamma\delta$ T cells have been found (MacHugh *et al.*, 1997): $WC1^+$, $CD2^-$, $CD4^-$, $CD8^-$; and $WC1^-$, $CD2^+$, $CD8^{+/-}$. $WC1^+$, $CD2^-$, $CD4^-$, $CD8^-$ cells are present in peripheral blood, marginal zones of the spleen, dermal, and epidermal layers of the skin and lamina propria of the gut. The majority of $WC1^-$, $CD2^+$ $CD8^{+/-}$ cells is localized in the red pulp of the spleen. The two populations use different families of TCR genes (MacHugh *et al.*, 1997; Blumerman *et al.*, 2006). Up to 90% of $\gamma\delta$ T cells in PBL are $WC1^+$ (Baldwin *et al.*, 2000). $WC1^+$ $\gamma\delta$ T cells are believed to be inflammatory, and $WC1^-$ $\gamma\delta$ T cells regulatory (Meissner *et al.*, 2003; Chen *et al.*, 2009).

WC1 is a transmembrane glycoprotein encoded by a large, multi-gene family, part of the group B scavenger receptor cysteine-rich (SRCR) superfamily (Herzig and Baldwin, 2009; Herzig *et al.*, 2010). Its function is unknown but may serve as a functional homolog of CD4 and CD8 on $\alpha\beta$ T cells, regulating $\gamma\delta$ T-cell response or affecting signaling from outside the cell (Chen *et al.*, 2009). Isoforms WC1.1 and WC1.2 have been identified. The largely non-overlapping populations of $\gamma\delta$ T cells bearing them decrease with age differently and appear to have distinct immunological roles (Rogers *et al.*, 2005).

Pathogen-associated molecular patterns (PAMPs) prime bovine $\gamma\delta$ T cells, as observed by an increase in receptors in the absence of IFN-γ secretion (Jutila *et al.*, 2008). A population of $WC1^+$ $\gamma\delta$ T cells increased expression of MHC II, processed Ag, and demonstrated NK cell-like killing in response to infection with foot-and-mouth disease virus (FMDV) (Toka *et al.*, 2011). A large population of $CD8^+$ T cells in cattle is $\gamma\delta$ T cells (MacHugh *et al.*, 1997), and a subset of $CD8^+$ $\gamma\delta$T cells home to mucosal tissues due to selective expression of adhesion molecules and chemokine receptors (Wilson *et al.*, 2002).

A population of peripheral blood $\gamma\delta$ T cells increased rapidly upon inoculation with or exposure to BHV-1 (Amadori *et al.*, 1995). Vaccination with one dose of modified live BHV-1 generated $\gamma\delta$ T cells in the peripheral blood of cattle that became activated in response to live BHV-1 in culture (using CD25 as a marker) (Endsley *et al.*, 2002). Of two populations of bovine $\gamma\delta$ T cells studied ($CD2^-$ and $CD2^+$), one ($CD2^-$/$D62L^+$) was reduced after vaccination with product containing inactivated BHV-1 and other viruses (Vesosky *et al.*, 2003).

2.2.5. CD8, CD4 and T-cell types

Double-positive thymocytes that have been positively selected develop into either $CD4^+$ or $CD8^+$ T cells, as determined by the MHC-restriction specificity of their TCR (Singer *et al.*, 2008). $CD8^+$ cells become CTLs. $CD4^+$ cells can differentiate into T-helper 1 (Th1), T-helper 2 (Th2), T-helper 17 (Th17) or T regulatory (Treg) cells (Murphy *et al.*, 2008). IL-12, IL-18, TNF-α and IFN-α are associated with skewing naïve T cells to Th1. Th2 cells are produced in the absence of such cytokines and in the presence of IL-19. Transforming growth factor (TGF)-β promotes the generation of Treg cells, whereas IL-6 inhibits the generation of Treg and induces Th17 cells (Freer and Matteucci, 2009). Th1 cells activate Mϕs, including increasing their ability to kill intracellular pathogens (such as BHV-1). Th2 cells provide help in B-cell activation and class switching. Th17 cells enhance neutrophil response, and Treg cells suppress the T cell response (Murphy *et al.*, 2008).

IFN-γ is produced by Th1 $CD4^+$ and $CD8^+$ CTL effector T cells as part of the adaptive immune response (Schoenborn and Wilson, 2007). IL-12 produced by APC stimulates T cells to produce IFN-γ (Jaime-Ramirez *et al.*, 2011). It is 'a predominant response after BHV-1 infection' (Campos *et al.*, 1989) and is necessary for the activation of non-MHC restricted cytotoxic activities mediated by Mϕ.

Bovine CTLs (Hogg *et al.*, 2011), Th1s, and Th2s have been characterized. Although a strict Th1/Th2 dichotomy was not observed, a biased immune response was indicated when the cytokines expressed by cloned Th cells with different Ag specificities were compared

(Brown *et al.*, 1998). There is evidence for bovine Treg activity in populations of $CD4^+$, $CD25^+$ and of $WC1^+$, $CD4^+$, $CD25^+$ $\gamma\delta$ T cells (Coussens *et al.*, 2012).

2.2.6. CD8 T cells

$CD8^+$ T cells predominantly recognize peptide–MHC I complexes (because CD8 binds best to MHC I), and kill the cells that bear them. The peptides are bound primarily at the ends of the MHC binding groove. MHC I is present on all cells and are normally loaded with self-peptide fragments generated by proteasomes via TAP (Murphy *et al.*, 2008). Typically, viral proteins are processed into peptides in the cytoplasm by proteasomes. They bind to the TAP1-TAP2 heterodimer, and after the dimer undergoes conformational changes, are transported into the endoplasmic reticulum lumen where they are loaded onto MHC I molecules (Neefjes *et al.*, 1993; Knittler *et al.*, 1999). The MHC I–peptide complexes are presented on infected cell or APC surfaces. IL-12 and IFN-I have been proposed as the third signal for human CD8 (Curtsinger *et al.*, 1999; Curtsinger and Mescher, 2010).

CTLs kill by releasing perforin, which helps deliver granzymes into the target cell, granzymes, which are proproteases that are activated intracellularly to trigger apoptosis in the target cell, and granulysin (in human beings). CTLs also carry the membrane-bound effector molecule Fas ligand (CD178), which binds to Fas (CD95) on a target cell to activate apoptosis in the Fas-bearing cell. This latter mechanism may be less important for virus-infected cell killing than for killing LC after the response is over (Murphy *et al.*, 2008).

Granzymes trigger apoptosis by activating caspases. For example, granzyme B cleaves and activates caspase 3, which triggers a cascade ending in DNAse. The DNAse degrades both cellular and viral DNA. Granzyme B also triggers apoptosis through actions that result in the release of apoptosis-inducing molecules, including cytochrome *c* (Murphy *et al.*, 2008). Bovine $CD8^+$ T cells express perforin (increasing with age) (Hogg *et al.*, 2011) and have demonstrated MHC I-restricted killing *in vitro* (Guzman *et al.*, 2008).

BHV-1-encoded proteins appear on the cell surface to serve as targets within 3–4 h after infection (Babiuk *et al.*, 1975, 1996). gC and gD were demonstrated targets for $CD8^+$ CTL (Denis *et al.*, 1993), although when cells were infected with vaccinia expressing BHV-1 gB, gC, or gD, memory T-cell populations did not react with them (Hart *et al.*, 2011). Bovine CTL killing was MHC I-restricted and BHV-1-specific (Splitter *et al.*, 1988; Hart *et al.*, 2011). Cell-mediated immunity (CMI) responses peaked 7–10 days after infection and correlated with recovery (Babiuk *et al.*, 1996). CTLs likely play a role in control of recrudescence from latency in αHVs (Jones and Chowdhury, 2007).

Herpesviruses (HV) have multiple mechanisms to evade CTL killing (Ploegh, 1998), and in some cases even closely related viruses such as αHV use different molecules for the same mechanism, or different mechanisms for the same molecule (Koppers-Lalic *et al.*, 2008; Deruelle and Favoreel, 2011). It should be noted that although in BHV-1 infection $CD4^+$ T cells are killed preferentially, $CD8^+$ numbers decreased in PBMC in infection, resulting in decreased CMI (Winkler *et al.*, 1999).

The BHV-1 gN homolog encoded by UL49.5 (Liang *et al.*, 1993) interferes with peptide transport for MHC loading (Hinkley *et al.*, 1998). It binds to TAP, inhibits its peptide transport, and results in TAP degradation (Koppers-Lalic *et al.*, 2005; Lipińska *et al.*, 2006). The BHV-1 UL49.5 protein is predicted to be composed of an N-terminal 22 aa signal sequence, a luminal 32 aa domain, a 25 aa transmembrane domain, and a 17 aa cytoplasmic tail (Liang *et al.*, 1993; Lipińska *et al.*, 2006). UL49.5 binds TAP via its transmembrane domain and inhibits TAP conformational transitions (Loch *et al.*, 2008; Verweij *et al.*, 2008). Deletion of the entire cytoplasmic tail or the terminal two aa of UL49.5 eliminates TAP degradation (Loch *et al.*, 2008), and it was determined that a 3-aa luminal sequence signals the aa in the cytoplasmic tail to initiate both inhibition and degradation of TAP (Wei *et al.*, 2011). Infection with BHV-1 with deletions in both luminal and terminal sequences induced more rapid onset (but similar peak levels) of VN Ab and CMI in calves than infections with wild-type BHV-1 (Wei *et al.*, 2012). The suppression of MHC I Ag presentation results in BHV-1 immune evasion in the initial stages of infection (Koppers-Lalic *et al.*, 2001, 2005, 2008; Gopinath *et al.*, 2002), which is consistent with the previously observed transient suppression of CMI early in infection (Ohmann and Babiuk, 1985; Tikoo *et al.*, 1995a). It is of interest that the gN homologs of various varicelloviruses employ diverse mechanisms to interfere with TAP activity (Koppers-Lalic, 2007; Deruelle and Favoreel, 2011).

Other BHV-1 factors inhibit CTL killing. BHV-1 gG is a chemokine-binding protein that prevents homing of LCs to sites of infection (Jones and Chowdhury, 2007). BHV-1 viral host shutoff (VHS) protein shuts down synthesis of MHC I (and MHC II), reducing Ag presentation (Koppers-Lalic *et al.*, 2001; Gopinath *et al.*, 2002; Muylkens *et al.*, 2007). The latency-related (LR) alternate transcript binds BH3-interacting domain death agonist (Bid), which is specifically cleaved by granzyme B. In this way LR proteins impair the CTL-induced death of infected neurons (Jones and Chowdhury, 2007).

Other αHV immune evasion activities may be assumed for BHV-1, but have not yet been demonstrated. Despite low aa sequence similarity, the US3 homologs show 'substantial functional conservation' (Deruelle and Favoreel, 2011). HHV-1 US3 has multiple immune evasion activities, and many of these have also been observed in SHV1. US3 interferes with: (1) fas-mediated apoptosis; (2) MHC I presentation of Ag, as do the homologs HHV3 open reading frame (ORF) 66 and SHV1 US3; and (3) endocytosis of gB in HHV-1, which has not been shown for BHV-1 (Deruelle and Favoreel, 2011).

The HHV3 US3 homolog ORF66 retains mature MHC I complexes in the cis/medial Golgi (Griffin *et al.*, 2010). HHV-1 gD also blocks apoptosis (Roizman and Taddeo, 2007).

In other cases, αHV anti-CTL or anti-apoptosis factors have no homolog in BHV-1. HHV-1 gJ blocks CTL (Roizman and Taddeo, 2007), but has no homolog in BHV-1 (Schwyzer and Ackermann, 1996; Schmitt and Keil, 1998). HHV-1 infected cell protein (ICP) 47 (IE12) inhibits MHC I expression (Bauer and Tampé, 2002), but has no homolog in BHV-1 (Ambagala *et al.*, 2004). Finally, HHV-1 US11-encoded proteins including ICP 34.5 interact with protein kinase R (PKR) and Beclin 1, both inhibiting autophagy and presentation of GPs on the cell surface (Shah *et al.*, 2009; Cavignac and Esclatine, 2010; Taylor *et al.*, 2011), but there are no homologs in BHV-1 (Schwyzer and Ackermann, 1996; Schmitt and Keil, 1998; Henderson *et al.*, 2005).

BHV-1 infection leads to programmed cell death, with p53 and caspases activated (Devireddy and Jones, 1999). Penetration of the cell is not needed (Hanon *et al.*, 1999). The induction or blocking of apoptosis is a matter of timing for the host and αHV (Srikumaran *et al.*, 2007). Early in the cell infection, apoptosis destroys viral components (including progeny DNA), obviating their assembly and release. Thus, when danger signals and immune cells induce apoptosis, there is an advantage to the host. After assembly, however, apoptosis may be advantageous to release of the virus (Nguyen and Blaho, 2009). The balance may also be cell type dependent.

2.2.7. $CD4^+$ T cells

$CD4^+$ T cells predominantly recognize peptide–MHC II complexes (because CD4 binds best to MHC II) and are activated by or activate the cells that bear them. MHC II are borne primarily by APC, and bind proteasome-degraded peptides along their length (Murphy *et al.*, 2008). IL-1 has been proposed as the third signal for human CD4 (Curtsinger *et al.*, 1999; Curtsinger and Mescher, 2010). $CD4^+$ Th1 can bear Fas ligand, which triggers death of the Fas-bearing cell (Murphy *et al.*, 2008).

During BHV-1 infection, $CD4^+$ T cells are considered to be essential for virus clearance *in vivo*. CD4 T cells, but not γδ T cells or $CD8^+$ T cells, were identified as the limiting cell type in Ag-induced proliferation in BHV-1 infection (Denis *et al.*, 1994). They are required for the generation of Ab-producing cells, MHC II-restricted $CD4^+$ CTL (Wang and Splitter, 1998), and other cytotoxicity activity (Renjifo *et al.*, 1999). Th1s secrete IL-2, IL-12, IFN-γ and Th2s secrete IL-4, IL-5, IL-6 and IL-10 to drive the Ab response (Campos *et al.*, 1994). $CD4^+$ T cells were cytotoxic against Mϕs pulsed with BHV-1 peptides, acting through Fas and in an MHC II-restricted fashion (Wang and Splitter, 1998). The association of BHV-1 Ab response and MHC II genotype has been studied (Juliarena *et al.*, 2009).

BHV-1 gB, gC, gD, and viral protein (VP) 8 are recognized by CD4 T helper cells from immune cattle (Hutchings *et al.*, 1990; Leary and Splitter, 1990). gE, gI, and gG were shown not to be significant for lymphoproliferative responses (Denis *et al.*, 1996). T-cell heterohybridomas specific for gB, gC, and gD have been generated (Nataraj and Srikumaran, 1994), and T-cell epitopes have been mapped on BHV-1 gB (Gao *et al.*, 1999) and gD (Tikoo *et al.*, 1995b).

BHV-1 infects and results in apoptosis of $CD4^+$ T cells, including activated ones (Griebel *et al.*, 1990; Eskra and Splitter, 1997; Winkler *et al.*, 1999). $CD4^+$ but not $CD8^+$ T cells were shown to be infected, and gD (γ1, leaky-late) but not gC (γ2, late) transcripts were detected, indicating a non-productive infection (Winkler *et al.*, 1999). UV-irradiated BHV-1 suppressed IL-2 and (heterologous) Ag-induced proliferative responses (Hutchings *et al.*, 1990). Anti-gB or gD Ab was able to block this effect. BHV-1 has other mechanisms of reducing $CD4^+$ T-cell responses. BHV-1 VHS (UL41) causes a decrease of MHC II (and MHC I) presentation (Muylkens *et al.*, 2007). Light (L)-particles (Dargan *et al.*, 1995) have been observed in BHV-1 infected MDBK cells and are believed to be involved in immune evasion (Meckes and Raab-Traub, 2011). They do this by shuttling HLA-DR (MHC II) to the exosomal secretion pathway instead of the cell surface.

2.2.8. B lymphocytes

Naive B-cell activation is dependent on three signals: (1) BCR binding by Ag, followed by (2) cognate interaction with helper T cells through an immunological synapse, and (3) TLR stimulation (Ruprecht and Lanzavecchia, 2006; Lanzavecchia and Sallusto, 2007; Murphy *et al.*, 2008). The B-cell 'co-receptor complex' includes CD21 [C receptor 2 (CR2)], CD19, and CD81. If the cleaved C fragment C3d is bound to Ag, the complement can bind CR2, the Ag can bind BCR, and the complex of the two can result in augmented signal (Murphy *et al.*, 2008). Some repeating Ags (T-cell independent Ag) and anti-idiotypic Ab are able to provide multiple signals by cross-linking BCR.

BCR binding up-regulates TLRs (Ruprecht and Lanzavecchia, 2006) and MHC II (Ratcliffe and Mitchison, 1984), which are keys to subsequent signals. Specific activation of the B cell by its cognate T cell (a helper T cell primed by the 'same' Ag) consists of ILs and ligand (T-cell CD40L to bind B-cell CD40) (Murphy *et al.*, 2008). The T cells must recognize Ag on the B cell in association with MHC (Ratcliffe and Mitchison, 1984). The T-cell – B-cell immunological synapse is enriched in the center for TCR–MHC–peptide and CD40-CD40L, and 'sealed' at the periphery by interaction of T-cell LFA-1 and B-cell ICAM-1 (Murphy *et al.*, 2008). The T and B cells polarize their secretory and endocytic/exocytic machinery, respectively, toward the synapse (Duchez *et al.*, 2011). Th2s provide help in B-cell activation and secrete the B-cell growth factors IL-4, IL-5, IL-9, and IL-13. In cattle, IL-2 was

observed to drive the Ab response, but other factors may drive it to one class or another (e.g., IgG1 with IL-4 or IgG2 with IFN-γ) (Estes and Brown, 2002; Estes, 2010). The roles of cytokines in the mouse were not found to extrapolate well to cattle.

2.2.9. Immunoglobulins

Ig generation, classes and subclasses, and strategies for their use may vary between mammalian species. For example, the ileal Peyer's patch is a likely bursa equivalent in cattle (Meyer *et al.*, 1997). The concentration of different Ig classes in milk and colostrum varies considerably according to species, breed, age, stage of lactation, and health status. In many species, absorption of Igs is selective and receptor mediated. In ruminants, absorption is non-selective during the first 12–36 h after parturition (Marnila and Korhonen, 2011). Ig subclasses do not match between species because the species diverged before the classes or subclasses subdivided (Butler, 1995). IgG1 is the primary secretory Ig in cattle.

Diversity of Ag specificity is generated by five main mechanisms: (1) combinations of different variable-light (VL) and -heavy (VH) domains; (2) combinations of different V, diversity (D), and J genes; (3) addition and deletion of nucleotides at junctions of V, (D), and J genes during recombination; (4) somatic hypermutation; and (5) gene conversion. Different species have been found to use different strategies to generate diversity (reviewed in Butler, 1997). Primates and rodents express a large number of V, D, and J genes and emphasize combinatorial mechanisms as well as templated (Ag-driven) somatic hypermutation (mutations in 'hotspots' while the B-lymphocyte is in the germinal center) (Teng and Papavasiliou, 2007). Artiodactyls, lagomorphs, and chickens, conversely, express few V, D, and J genes and emphasize untemplated somatic mutation and gene conversion.

Bovine Ig genes (C, then V, then J and D) were located on chromosomes (Zimin *et al.*, 2009), using homology to mouse and human genes and the identification of flanking, conserved recombination signal sequences (RSS) (reviewed in Butler, 1995, 1997). It was determined that cattle express one VH family (Saini *et al.*, 1997; Niku *et al.*, 2012). Bovine light (L) chains are predominantly lambda type, with only a few sub-families of genes, and only a few sub-sub-families are used (Sinclair *et al.*, 1995). One J gene is predominantly expressed in each of H (Saini *et al.*, 1997; Zhao *et al.*, 2003) and L (Pasman *et al.*, 2010) chains. Three D genes have been identified, with varying lengths that contribute to varying length H chain CDR3, including the extremely long ones found in IgM only (Shojaei *et al.*, 2003).

Ig effector function is in the crystallizable fragment (Fc), or C domains. Key Ig effector functions in the immune response to BHV-1 include VN, C fixation, and Ab-dependent cell-mediated cytotoxicity (ADCC). These functions are important late in the immune response, and protect the host from further primary or later re-infection. They are effective against virions and infected cells.

2.2.10. Virus neutralization by Ab

Ab neutralization of animal virus infectivity can occur by multiple mechanisms (Klasse and Sattentau, 2002; Reading and Dimmock, 2007). Extracellular Ab may (1) aggregate virions and reduce the number of infectious centers, (2) mimic a cell receptor to bind virions and lead to premature virion steps (e.g., release of the genome), (3) inhibit virion attachment by blocking receptor engagement, (4) inhibit fusion, either at the cell membrane or in an endocytotic vesicle, or (5) bind to a cell-surface protein and result in the transduction of a signal into the cell that aborts the infection. Post-entry neutralization can occur by transmission of a signal via the virus surface protein to the virion core. Transcytosing IgA may neutralize virus when their respective vesicles fuse. Ab may bind nascent virions and block their budding or release from the cell surface (Reading and Dimmock, 2007).

In the bovine immune response to BHV-1, Ab is the key to binding GPs and preventing attachment. This can occur to prevent extracellular virus from infecting host cells late in primary infection, during re-activation, and upon secondary exposure. Ab can coat the virus as it is being shed (Pastoret *et al.*, 1979).

In the primary response, gB, gC, and gD are the primary inducers and targets of neutralizing Ab (Turin *et al.*, 1999). The response is expanded in recrudescence or secondary exposure – it is elevated against the major GPs, and responses to minor GPs like gE 'become detectable.' Dubuisson *et al.* (1992) examined the neutralization mechanisms of monoclonal Ab (MAb) to gB, gC, and gD. The majority of MAbs did not prevent attachment. Few MAbs to gB were effective. Anti-gD MAb worked as well after attachment as before, which was likely due to gD's role in penetration. C enhanced the activity of almost all of the gB and gC MAb, but not the gD MAb. The conformational change of HHV-1 gD when it binds receptor provides a new neutralization site (Lazear *et al.*, 2012).

Passive immunity Ab protected against fatal multisystemic BHV-1 disease in newborn calves (Turin *et al.*, 1999), but did not prevent initial viral replication, resulting in latency. This results in seronegative latent carrier (SNLC) animals after the maternal Ab declines (Lemaire *et al.*, 2000a; Nandi *et al.*, 2009). Experimental passive transfer of Ab did not protect completely, although it prevented death from challenge (Marshall and Letchworth, 1988).

αHV evade neutralizing Ab using three mechanisms (Favoreel *et al.*, 2006): (1) Fc receptor Ab binding (by gE/gI, which is not apparent for BHV-1) (Whitbeck *et al.*, 1996); (2) endocytosis of GPs, or Ag-Ab complex internalization by same mechanism; and (3) hiding from Abs

through intracellular retention of viral proteins and directed egress to intimate cell–cell contacts. The synapse can be seen as an example of the latter (Favoreel *et al.*, 2006). In HHV-1, cell-to-cell transmission depends on gE–gI, which binds to components of cell junctions (while gD localizes to apical surface) (Dingwell and Johnson, 1998). BHV-1 gC includes Ig-related domains. The low gC reactivity of bovine antisera may be explained by molecular mimicry (Fitzpatrick *et al.*, 1989, 1990). Finally, syncytial strains of HHV-1 avoid neutralization by not using extracellular virus to infect neighboring cells. This was stated to not occur with wild-type viruses, however (Roizman *et al.*, 2007).

2.2.11. Ab-dependent cell-mediated cytotoxicity

Ab binding to determinants on virus-infected cells may lead to those cells being killed in a non-MHC restricted manner. PMNs are the most effective mediators of ADCC. Mϕs also contribute, and LCs do not (Rouse *et al.*, 1976; Grewal *et al.*, 1977). IFN and C enhance the activity (Rouse and Babiuk, 1977). IgM is inactive in ADCC alone, but can enable ADCC-C-mediated lysis, which may be important early in the humoral response. BHV-1 infection of Mϕs limits their ability to perform ADCC (Ohmann and Babiuk, 1986). The FcγR of HHV-1 blocked ADCC (Lubinski *et al.*, 2011).

2.2.12. Other Ab activities

Ab label Ag on virions and virus-infected cells for activity by C, phagocytes, and NK cells (Favoreel *et al.*, 2006). Ab to viral Ag can trigger the classic pathway of C activation on virions and infected cells. It is not believed this is important early in infection because high amounts of each were needed for activity *in vitro* (Babiuk *et al.*, 1975; Rouse and Babiuk, 1977). Cattle have differences from humans and mice in their FcR (particularly Fcγ2R), possibly because of the different role of IgG re: mucosal surfaces (Kacskovics, 2004). NK and other immune cells bear FcR. Ab can also neutralize the immunosuppressive effects induced by BHV-1 against T cells (Hutchings *et al.*, 1990).

The BHV-1 evasion methods for these activities would be the same or similar to those cited for neutralization or innate C activation (Muylkens *et al.*, 2007), including viral FcR and C3bR. Fc receptors, when present on αHV, can serve to shield the Ag with normal Ig, or result in Ig bridging (Ag–Ab–Fc) to prevent C activation. SHV1-infected cells can shed or internalize Ab–Ag–C complexes (Favoreel *et al.*, 2003).

2.3. Other immune response considerations

2.3.1. Immune response in latency and reactivation

The role of the immune system in preventing reactivation from latency is controversial. There is a chronic inflammatory (immune) response in latently infected TGs, with elevated $CD8^+$ and cytokine/chemokine expression. This was interpreted as maintaining viral latency and suppressing reactivation of HHV-1 (Theil *et al.*, 2003). This role in control of reactivation from latency in αHVs was noted and believed potentially due to viral protein expression in rare cells in the TG (Jones and Chowdhury, 2007). This has been called 'spontaneous molecular reactivation'. IFN-γ was also believed to play a role (Jones, 2003). However, it has been reported that the latency associated transcript (LAT) of HHV-1 is responsible for $CD8^+$ CTL functional exhaustion in TGs (Chentoufi *et al.*, 2011). Also, $CD8^+$ T cells surround only a small proportion of LAT^+ neurons, but micro RNA (miRNA) are present in all of the LAT^+ cells (Held *et al.*, 2011).

2.3.2. Mucosal immunity

The selective localization of mucosal LC to specific tissues is due to their expression of chemokine receptors and the differential expression of cognate chemokines and tissue-specific addressins by epithelial cells (Czerkinsky and Holmgren, 2012). T cells ($CD4^+$ and $CD8^+$) primed by DCs in the local LN are influenced to home, based on receptors (Ciabattini *et al.*, 2011). The chemokine/chemokine receptor pairs CCL25/CCR9 and CCL28/CCR10 have been shown to be important to trafficking of Ab-secreting cells to mucosal tissues. The expression of these molecules is different in cattle than in humans and mice, suggesting different mechanisms for accumulation in specific mucosal tissues (Distelhorst *et al.*, 2010).

2.3.3. Consequences of BHV-1 immunosuppression

The impact of BHV-1-encoded immunosuppression factors on the outcome of the virus infection is clear, but there may also be impacts on other infections. The contribution of BHV-1 infection to 'shipping fever' (and BRDC), indicated in the field by co-infections (Martin *et al.*, 1980) and demonstrated experimentally (Jericho and Langford, 1978), is complex, but is believed to include the immune and inflammatory response to BHV-1 (Hodgins *et al.*, 2002; Ellis, 2009) as well as immunosuppressive effects previously cited in this review and elsewhere (Levings and Roth, 2013) for multiple aspects of the bovine immune response to BHV-1. Reduced immune functions associated with anti-bacterial activities were described in BHV-1 infection. They include impaired function of alveolar Mϕ (Fc and C receptor activity, phagocytosis, PMN chemotaxis and respiratory burst), and LC (proliferation, cytotoxicity), with reduction of IL-2 levels (Forman *et al.*, 1982; Filion *et al.*, 1983; McGuire and Babiuk, 1984; Ohmann and Babiuk, 1985; Tikoo *et al.*, 1995a; Roth and Perino, 1998).

Some experiments have measured specific immunosuppressive effects relative to secondary bacteria. BHV-1 infection depressed LC blastogenic responses to *Mannheimia haemolytica* and *Pasteurella multocida* and delayed the anti-*M. haemolytica* Ab response. The PMN infiltration of *P. multocida*-infected lungs was reduced,

although the antibacterial activity of PMNs was not significantly affected (Filion *et al.*, 1983; McGuire and Babiuk, 1984). It could be expected that any of the non-agent-specific immunosuppressive effects of BHV-1 infection described would facilitate secondary infection, including: inhibition of IFN signaling; chemokine or C3b (or Ab) binding; and infection, function depression, and/or killing of Mϕs, PMNs, APCs, and T cells.

3. Vaccination

3.1. General BHV-1 vaccinology

Nucleosidic antiviral drugs have been used to treat human herpesviral infections since the 1970s, and have been tested and applied for limited applications in veterinary species, including for HV infections (Rollinson *et al.*, 1988; Wilkins *et al.*, 2003; van der Meulen *et al.*, 2006; Henninger *et al.*, 2007). However, widespread clinical use of antiviral drugs is not common in veterinary medicine (Kahn *et al.*, 2005). Administration of IFN (Cummins *et al.*, 1993) or IFN inducers (Theil *et al.*, 1971) to reduce the clinical signs of BHV-1 infection has been limited to experimental trials. Anti-herpesviral immunomodulators such as host defense proteins (Jenssen, 2009), double-negative 'intracellular immunization' (Mühlbach *et al.*, 2009), and gene therapy (Chase *et al.*, 1990; Bunnell and Morgan, 1998) are not currently used in food animal medicine. Rather, biosecurity and vaccination are the primary control measures for the diseases caused by BHV-1.

BHV-1 is a good candidate for conventional and new vaccines (van Drunen Littel-van den Hurk, 2006). Although there are subtypes of BHV-1 (Metzler *et al.*, 1985), the subtypes are broadly immunologically cross-reactive and there is limited antigenic variation within a geographic region. Also, BHV-1 is a stable virus, has a limited host range, and has a viremic phase (van Drunen Littel-van den Hurk, 2006). In natural infection there is a strong, long-lasting and well-balanced Th1/Th2 immune response to protective Ags, possibly due to persistent infection (Kaashoek *et al.*, 1996a). There is also a significant response to other viral proteins that can serve as markers. BHV-1 is easily grown (rapidly, to high titers) in cell cultures, facilitating production of many types of BHV-1 vaccines.

Conventional modified live virus (MLV) and killed virus (KV) BHV-1 vaccines have been used for many years (Kendrick *et al.*, 1957; Kolar *et al.*, 1972). However, problems due to the nature of the virus (e.g., MLV immunosuppression), vaccine technologies (KV efficacy), or control program needs (vaccine markers) encouraged the use of new technologies to develop 'second generation veterinary viral vaccines' (reviewed in Meeusen *et al.*, 2007; Zhao and Xi, 2011). The emphasis has been on delivery of major GPs, and on use of major or minor GPs as negative markers (Babiuk *et al.*, 1996; Baranowski *et al.*, 1996; Turin *et al.*, 1999). The goal of vaccination is a well-balanced immune response, similar to that of protection due to natural infection.

There is such a wide variety of BHV-1 vaccines (in practice and particularly in the literature), that it can be helpful to describe them as belonging to categories. The most common divisions are: conventional and molecular; replicating and non-replicating; and marker and non-marker. Vaccines can also be categorized by route (intranasal [IN], intramuscular [IM], etc.) or administration technique (e.g., aerosol, injection, 'gene gun'). The divisions are not absolute; e.g., some molecular vectors (e.g., canarypox in mammals or alphavirus replicons) do not replicate in the host but non-productively infect cells and express Ag on the cell surface similar to live vaccines (Taylor *et al.*, 1995; Vander Veen *et al.*, 2012). Further, in some cases vaccines may be best used in combination regimens, called 'prime-boost,' e.g., MLV and KV gene-deleted vaccines (Muylkens *et al.*, 2007), or DNA and subunit vaccines (van Drunen Littel-van den Hurk *et al.*, 2008).

The 'differentiating infected from vaccinated animals' (DIVA) strategy (van Oirschot, 1999) usually employs a vaccine that is missing an antigenic marker, or a positive marker can also be added (Chowdhury, 1996), combined with a complementary diagnostic assay for that marker. A diagnostic assay for protective vaccine Ag that is present in both the vaccine and field virus is also employed. Marker vaccines can range from a live virus with a mutation or deletion in a single gene to single glycoprotein subunit vaccines. A desirable negative marker protein is one that is not needed for *in vitro* production, not critical for protection, present in all wild-type viruses, and that induces a rapid, strong, long-lasting response in both naïve and vaccinated animals (Kaashoek *et al.*, 1996b; van Drunen Littel-van den Hurk, 2006). Also, the companion diagnostic should be sensitive and specific. Widely employed BHV-1 marker companion diagnostics have occasionally demonstrated problems with each of these characteristics (van Oirschot *et al.*, 1999; Muylkens *et al.*, 2007).

The extensive research on BHV-1 and the bovine immune response to it has resulted in reports on a wide variety of experimental vaccines in the literature. Many of them are briefly described below. However, the currently licensed vaccines in the US and EU include only MLV and KV vaccines of cell culture passaged virus, gE-deleted virus, or temperature sensitive (ts) mutant virus, administered IM, subcutaneously, or IN.

3.2. Non-replicating vaccines

3.2.1. Killed virus

Conventional KV vaccines have been used for decades (Kolar *et al.*, 1972). They have the advantage of safety, including in pregnant cattle. However, typically two

immunizations are needed, the immune response is primarily humoral, and the duration of immunity is shorter than for MLV vaccines (Tikoo *et al.*, 1995a; van Drunen Littel-van den Hurk, 2007). The adjuvants commonly added to increase immunogenicity can introduce problems of their own (Spickler and Roth, 2003).

The conventional KV BHV-1 vaccine is produced through physicochemical inactivation of infected cell culture fluids. Agents used have included formalin, beta-propiolactone, binary ethylene amine, ethanol, UV irradiation, and heat (Haralambiev, 1976; Levings *et al.*, 1984; van Drunen Littel-van den Hurk, 2006). The vaccine includes all components of the virus (and cell culture), but there is the concern that inactivation could damage key epitopes (Jones and Chowdhury, 2007). A marker vaccine can be produced using the same inactivation methods when the production virus is gene-deleted (e.g., gE-) (Kaashoek *et al.*, 1995; Strube *et al.*, 1996).

3.2.2. Subunit

Subunit vaccines containing the major GPs (gB, gC, gD) have proven effective. These included detergent extracts of virus preparations to solubilize envelope GPs (Lupton and Reed, 1980), including incorporation of the extracts into immune stimulating complexes (ISCOMs) (Trudel *et al.*, 1988). Individual GPs have also been purified from such extracts for vaccine use using affinity chromatography (Babiuk *et al.*, 1987). gB, gC, and gD subunit vaccines were each protective, with gD eliciting the highest Ab titers and best protection (Babiuk *et al.*, 1987).

The GPs for subunit vaccine use have also been produced using various expression systems. Vaccinia and adenovirus systems in mammalian cells, and baculovirus systems in insect cells yielded protective GPs due to their glycosylation. *Escherichia coli* systems produced partial protection (van Drunen Littel-van den Hurk *et al.*, 1993). A truncated, secreted version of gD was produced in a bovine cell line (Kowalski *et al.*, 1993) and shown protective (van Drunen Littel-van den Hurk *et al.*, 1994). When the adjuvant CpG was incorporated into the vaccine, no virus was shed after challenge (Ioannou *et al.*, 2002).

3.2.3. Anti-idiotype

Anti-idiotype (anti-Id or Ab2) immunizations for HV (Kennedy *et al.*, 1984; Gurish *et al.*, 1988; Tsuda *et al.*, 1992; Zhou and Afshar, 1995), and BHV-1 in particular have been reported. Srikumaran *et al.* (1990), Hariharan *et al.* (1991), and Orten *et al.* (1991) used neutralizing murine MAb as Ab1 to generate bovine polyclonal Ab (PAb), bovine MAb, or rabbit PAb Ab2 respectively, which in turn were used to elicit neutralizing Ab3 in mice. Orten *et al.* (1993) immunized calves with an Ab2 (rabbit PAb anti-Id to murine anti-gB and gD MAb), resulting in a slight reduction of clinical signs and one calf producing BHV-1-neutralizing antibodies.

3.3. Replicating vaccines

3.3.1. Modified live (attenuated) virus

MLV vaccines have been used for BHV-1 disease since 1956 (Kendrick *et al.*, 1957). MLV in general are generated by passage in cell culture, sometimes in heterologous cell culture (Quinlivan *et al.*, 2011). This allows for mutations or deletions in genes important to viral fitness, but that are not essential to *in vitro* replication. The main advantage of MLV is that they replicate in the host's target cells, so Ag is presented on MHC I (eliciting CTLs), as well as on MHC II (eliciting humoral immunity) (van Drunen Littel-van den Hurk, 2007). After one dose of MLV, when PBLs were exposed to live BHV-1, CD25 was increased in CD^{4+}, CD^{8+}, and $\gamma\delta$ T cells (Endsley *et al.*, 2002). BHV-1 MLVs also typically elicit substantial duration of immunity (van Drunen Littel-van den Hurk, 2007).

BHV-1 conventional MLV problems have included those specific to BHV-1 disease. These include virulence (e.g., in small calves or pregnant animals) (Whetstone *et al.*, 1986; Bryan *et al.*, 1994; Jones and Chowdhury, 2007; O'Toole *et al.*, 2012), latency (Pastoret *et al.*, 1980; Whetstone *et al.*, 1986), and immunosuppression, including a reduction in the response to another vaccine administered simultaneously (Harland *et al.*, 1992). Other problems common to all MLVs can also occur. These include reversion to virulence (Belknap *et al.*, 1999), lack of efficacy due to overattenuation, and adventitious agents. The latter is particularly likely if the vaccine is produced in host cells or with host ingredients (Wessman and Levings, 1999; Falcone *et al.*, 2003), but can occur even if the vaccine is produced with non-host cells or ingredients (Wilbur *et al.*, 1994). A ts MLV was generated using chemical mutagenesis (Tikoo *et al.*, 1995a), which was safe for pregnant animals.

3.3.2. Gene deleted

Although gene mutations and deletions may occur using conventional attenuation (Kaashoek *et al.*, 1994), their design can be more controlled with genetic engineering. There are typically two goals in constructing gene-deleted live vaccines: (1) remove/reduce virulence or another undesirable disease trait; and/or (2) remove (or add) a marker detected by a companion diagnostic, usually a serologic marker, which can also be detected on a viral isolate. In the case of BHV-1, deletions in the thymidine kinase, gC, gE, gG, gI, Us9, LR, and UL49.5 genes have been made to reduce virulence (Kit *et al.*, 1985; Chowdhury, 1996; Kaashoek *et al.*, 1998), recrudescence (Kaashoek *et al.*, 1998; Inman *et al.*, 2001), and/or immunosuppression (Wei *et al.*, 2012). Viral envelope GPs have been targeted for serologic markers, including gC and gE due to the host's strong serologic responses to these non-essential proteins.

Disadvantages of gene-deleted live vaccines are under- or over-attenuation (Kaashoek *et al.*, 1998), depending on

the genes chosen. Since virulent isolates are usually the starting material for deletion work, recombination can also be an issue (reviewed in Thiry *et al.*, 2005). BHV-1 recombination *in vivo* between two gene-deleted strains was demonstrated, which led to wild-type virus (Schynts *et al.*, 2003). In addition, recombination leading to a virulent marker (gE^-) BHV-1 virus was shown (Muylkens *et al.*, 2006a, b), a situation that could confuse eradication campaigns. Such recombination of gene-deleted vaccines has been demonstrated for other αHVs (Henderson *et al.*, 1991; Lee *et al.*, 2012).

3.3.3. Live virus vectored

Vaccination using live vectors for BHV-1 GPs has elicited VN Ab, CMI responses, and/or partial protection. These have included vaccinia-vectored gB and gC (VN, van Drunen Littel-van den Hurk *et al.*, 1989), bovine adenovirus 3 expressing gD (VN and CMI, Zakhartchouk *et al.*, 1999), human adenovirus 3 or 5 expressing gC or gD (VN, Gupta *et al.*, 2001), and Newcastle disease virus-vectored gD (partial protection, Khattar *et al.*, 2010). Although an αHV chimeric veterinary vaccine has been developed (Cochran *et al.*, 2000, 2001), no chimeric BHV-1 vaccine has been reported.

3.3.4. DNA vaccines

DNA vaccines for BHV-1 have also been used in trials. DNA vaccines provide certain advantages over conventional MLV, including safety, stability, and efficacy in the presence of maternal antibodies (Donnelly *et al.*, 1997). They result in Ag presentation by both MHC I and II, similar to live vaccines (Gurunathan *et al.*, 2000), although they typically elicit a Th1 response. Although replicating, they can be made specific to one or a few Ag. A disadvantage at this time is their mode of delivery, e.g., veterinary use of the gene gun is not currently practical (Loehr *et al.*, 2001). In most reported trials, complete protection was not achieved.

BHV-1 GP (gB, gC, and gD) DNA has been administered by a variety of routes. Trials include gB, gC, and gD individually (Cox *et al.*, 1993), gD (van Drunen Littel-van den Hurk *et al.*, 1998), gC with ubiquitin (Gupta *et al.*, 2001), secreted gD (Castrucci *et al.*, 2004), a combined, secreted gB–gD, (Caselli *et al.*, 2005), gB (Huang *et al.*, 2005), and gD with CpG (van Drunen Littel-van den Hurk *et al.*, 2008).

3.3.5. BHV-1 as a vector

The use of BHV-1 as a vector of other proteins has a variety of advantages, including knowledge of the molecular biology of BHV-1, existing systems for vaccine production, and the already-widespread use of BHV-1 vaccines (so there are few or no new safety or serosurveillance concerns) (Jones and Chowdhury, 2007). The virus has been used to express IL-1β (Raggo *et al.*, 1996), IL-2, IL-4 (Kühnle *et al.*, 1996), IFN-γ (Raggo *et al.*, 2000), and to display IFN-α (Keil *et al.*, 2010). Expression of cytokines could provide an adjuvant effect for BHV-1 vaccination. Protective immunogens of other bovine viruses have been expressed in BHV-1. An FMDV VP1 epitope was inserted as the N-terminal sequence of a BHV-1 gC fusion protein, was expressed on the surface of virions and infected cells, and elicited protective levels of Ab to FMD, while protecting against BHV-1 (Kit *et al.*, 1991). The G protein of bovine respiratory syncytial virus (BRSV) was expressed in BHV-1 and the vaccine provided the same degree of protection to BHV-1 and BRSV in calves as a multivalent vaccine (Schrijver *et al.*, 1997). Bovine viral diarrhea (BVD) virus E2 protein was expressed in BHV-1 (Cochran, 1998) and the vaccine virus elicited VN Ab to BVD (Kweon *et al.*, 1999). Parainfluenza 3 fusion (F) and hemagglutinin (HN) genes were inserted into BHV-1 (Haanes and Wardley, 1997; Cochran, 1998). In addition, insertion of an influenza hemagglutinin 1 (HA1) sequence resulted in HA1 being expressed with gG as a fusion protein on the outside of virions and infected cells (Keil *et al.*, 2010). αHV have also been proposed for use with other viruses as chimeric vectors (Epstein and Manservigi, 2004) and as episomal systems for gene therapy (Macnab *et al.*, 2008).

3.4. Routes

BHV-1 infects via mucosal epithelium, so stimulating immunity for those surfaces would be desirable. However, most of the conventional vaccines are parenterally administered and may result in systemic rather than mucosal immunity. In contrast, mucosal immunization is said to induce mucosal as well as systemic immunity (Loehr *et al.*, 2000). Immunization of mucosal surfaces results in good Ag detection, and B and T cells stimulated in the mucosa home to mucosa in general and to the immunized mucosal tissue specifically (Neutra and Kozlowski, 2006). A variety of mucosal routes have been employed or suggested for viral vaccines (including αHV), such as oral, nasal, vaginal, ocular, sublingual, and anorectal (Shiau *et al.*, 2001; Czerkinsky and Holmgren, 2012; Pavot *et al.*, 2012).

A ts BHV-1 vaccine administered IN was shown to induce secretory IgA and a CMI response (Frerichs *et al.*, 1982). Israel *et al.* (1992) demonstrated mucosal immunity to BHV-1 subunit vaccine using cholera B subunit as an adjuvant and the IN route. A regime using a conventional BHV-1 IN vaccine was shown to confer rapid protection (Roth and Carter, 2000; Endsley *et al.*, 2002). Intravaginal vaccination with gD DNA (Loehr *et al.*, 2000, 2001) protected against IN BHV-1 challenge. Oral vaccination with BHV-1 *in utero* stimulated mucosal immunity (Gerdts *et al.*, 2002). A gD DNA vaccine was administered IN with reduction in challenge virus shedding (Castrucci *et al.*, 2004), and a gB DNA vaccine administered vulvovaginally elicited partial protection from genital lesions (Huang *et al.*, 2005).

3.5. Application

The ultimate goal of BHV-1 vaccination would be to prevent infections, which can in turn lead to latency/recrudescence and spread. Although this may occasionally be achieved (Israel *et al.*, 1992), it is not routinely practical.

A challenge for vaccination in cattle is immunizing stressed animals, because vaccines are often administered in association with movement and other treatments. Such stressors impact immune function (Kelley, 1980) and have been demonstrated to be associated with increased blood cortisol levels. High cortisol levels can impair phagocytic cell function, decrease CMI, and decrease Ab response to primary vaccination (Roth and Perino, 1998). Vaccinating young animals includes the difficulty of vaccinating in the face of passive immunity (Menanteau-Horta *et al.*, 1985), and young animals may mount poor Th1 responses (van Drunen Littel-van den Hurk, 2006). Use of CpG adjuvants or DNA vaccines may help with the younger animal immunization.

In the United States, BHV-1 vaccines are currently used as an aid in the prevention of disease. Between 150 and 200 million doses are produced annually (Anon, 2011b; personal communication), all of the conventional types (MLV and KV). In some countries of the EU, (gE^-) marker vaccines (live and KV) are used in eradication programs (van Oirschot *et al.*, 1996; Kahrs, 2001; Ackermann and Engels, 2006; van Drunen Littel-van den Hurk, 2006). As vaccines cannot prevent infection, vaccination must be frequent to keep recrudescence low, and culling based on DIVA serology employed. A significant issue for control and eradication is SNLC cattle that can re-excrete after a stress (Hage *et al.*, 1998). It has been shown that young animals can remain seronegative when infected while protected from disease by passive immunity, and that these infections can recrudesce at a later time, resulting in SNLC animals (Lemaire *et al.*, 1995, 2000a, b).

4. Summary/conclusions

In summary, there is a delicate balance between viral infection, host response, and viral evasive measures in BHV-1 infection and immunity in cattle. BHV-1 has a rapid life cycle and robust systems for entry, transcription, assembly and egress. The host responds with multiple tools, from infected-cell IFN to Ab-assisted infected cell killing. Like all αHV, BHV-1 has multiple evasion strategies to blunt or delay the host response, including in some cases multiple measures for the same host effector mechanism. The timing of response vs. viral replication (and spread in the animal and between animals) is therefore critical for disease outcomes. Maternal Ab provides humoral tools from the dam's immune response, and vaccination ensures the response to infection will be a rapid, strong secondary immune response that can provide the host with the advantage needed to prevent severe disease on primary infection.

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