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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

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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

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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).

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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

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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

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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).

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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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References

Ackermann M and Engels M (2006). Pro and contra IBR-eradication. *Veterinary Microbiology* **113**: 293–302.

Amadori M, Archetti IL, Verardi R and Berneri C (1995). Role of a distinct population of bovine gamma delta T cells in the immune response to viral agents. *Viral Immunology* **8**: 81–91.

Ambagala APN, Gopinath RS and Srikumaran S (2004). Peptide transport activity of the transporter associated with antigen processing (TAP) is inhibited by an early protein of equine herpesvirus-1. *Journal of General Virology* **85**: 349–353.

Anon (2011a). *Cattle death loss.* [Available online at http://www.nass.usda.gov/Publications/Todays_Reports/reports/catlos11.pdf (Last accessed March 24, 2013)].

Anon (2011b). *Veterinary biologics notice number 78. Veterinary biological products in licensed establishments produced and destroyed January 1, 2010 through December 31, 2010.* [Available online at http://www.aphis.usda.gov/animal_health/vet_biologics/publications/notice_11_78.pdf (Last accessed October 26, 2012)].

Babiuk LA, Wardley RC and Rouse BT (1975). Defense mechanisms against bovine herpesvirus: relationship of virus-host cell events to susceptibility to antibody-complement cell lysis. *Infection and Immunity* **12**: 958–963.

Babiuk LA, L'Italien J, van Drunen Littel-van den Hurk S, Zamb T, Lawman MJP, Hughes G and Gifford GA (1987). Protection of cattle from bovine herpesvirus type I (BHV-1) infection by immunization with individual viral glycoproteins. *Virology* **159**: 57–66.

Babiuk LA, van Drunen Littel-van den Hurk S and Tikoo SK (1996). Immunology of bovine herpesvirus 1 infection. *Veterinary Microbiology* **53**: 31–42.

Baldwin CL, Sathiyaseelan T, Rocchi M and McKeever D (2000). Rapid changes occur in the percentage of circulating bovine WC1($^+$)$\gamma\delta$ Th1 cells. *Research in Veterinary Science* **69**: 175–180.

Baranowski E, Keil G, Lyaku J, Rijsewijk FA, van Oirschot JT, Pastoret PP and Thiry E (1996). Structural and functional analysis of bovine herpesvirus 1 minor glycoproteins. *Veterinary Microbiology* **53**: 91–101.

Bauer D and Tampé R (2002). Herpes viral proteins blocking the transporter associated with antigen processing TAP–from

genes to function and structure. *Current Topics in Microbiology and Immunology* **269**: 87–99.

Baxter R, Craigmile SC, Haley C, Douglas AJ, Williams JL and Glass EJ (2009). BoLA-DR peptide binding pockets are fundamental for foot-and-mouth disease virus vaccine design in cattle. *Vaccine* **28**: 28–37.

Beer M (2012). Infectious bovine rhinotracheitis/infectious pustular vulvovaginitis. Chapter 2.4.13 In: Steven Edwards (ed.) *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2012*. Paris, France: World Organisation for Animal Health. [Available online at http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/ Last accessed 6 June 2012].

Belknap EB, Walters LM, Kelling C, Ayers VK, Norris J, McMillen J, Hayhow C, Cochran M, Reddy DN, Wright J and Collins JK (1999). Immunogenicity and protective efficacy of a gE, gG and US2 gene-deleted bovine herpesvirus-1 (BHV-1) vaccine. *Vaccine* **17**: 2297–2305.

Blumerman SL, Herzig CT, Rogers AN, Telfer JC and Baldwin CL (2006). Differential TCR gene usage between WC1- and WC1+ ruminant $\gamma\delta$ T cell subpopulations including those responding to bacterial antigen. *Immunogenetics* **58**: 680–692.

Bonilla FA and Oettgen HC (2010). Adaptive immunity. *Journal of Allergy and Clinical Immunology* **125** (suppl. 2): S33–S40.

Brown WC, Rice-Ficht AC and Estes DM (1998). Bovine type 1 and type 2 responses. *Veterinary Immunology and Immunopathology* **63**: 45–55.

Bryan LA, Fenton RA, Misra V and Haines DM (1994). Fatal, generalized bovine herpesvirus type-I infection associated with a modified-live infectious bovine rhinotracheitis parainfluenza-3 vaccine administered to neonatal calves. *Canadian Veterinary Journal* **35**: 223–228.

Bunnell BA and Morgan RA (1998). Gene therapy for infectious diseases. *Clinical Microbiology Reviews* **11**: 42–56.

Butler JE (1995). Antigen receptors, their imrnunomodulation and the imrnunoglobulin genes of cattle and swine. *Livestock Production Science* **42**: 105–121.

Butler JE (1997). Immunoglobulin gene organization and the mechanism of repertoire development. *Scandanavian Journal of Immunology* **45**: 455–462.

Campos M, Bielefeidt Ohmann H, Hutchings D, Rapin N and Babiuk LA (1989). Role of interferon gamma in inducing cytotoxicity of peripheral blood mononuclear leukocytes to bovine herpesvirus type 1 (BHV-l)-infected cells. *Cellular Immunology* **120**: 259–269.

Campos M, Godson DL, Hughes HPA and Babiuk LA (1994). Cytokine applications in infectious diseases. In: Goddeeris B and Morrisons I (eds) *Cell-Mediated Immunity in Ruminants*. Boca Raton, FL: CRC Press, pp. 229–240.

Caselli E, Boni M, Di Luca D, Salvatori D, Vita A and Cassai E (2005). A combined bovine herpesvirus 1 gB-gD DNA vaccine induces immune response in mice. *Comparative Immunology, Microbiology and Infectious Diseases* **28**: 155–166.

Castrucci G, Ferrari M, Marchini C, Salvatori D, Provinciali M, Tosini A, Petrini S, Sardonini Q, Lo Dico M, Frigeri F and Amici A (2004). Immunization against bovine herpesvirus-1 infection. Preliminary tests in calves with a DNA vaccine. *Comparative Immunology, Microbiology and Infectious Diseases* **27**: 171–179.

Cavignac Y and Esclatine A (2010). Herpesviruses and autophagy: catch me if you can! *Viruses* **2**: 314–333.

Chase CCL, Carter-Allen K, Lohff C and Letchworth III GJ (1990). Bovine cells expressing bovine herpesvirus 1 (BHV-1) glycoprotein IV resist infection by BHV-1, herpes simplex virus, and pseudorabies virus. *Journal of Virology* **64**: 4866–4872.

Chen C, Herzig CTA, Telfer JC and Baldwin CL (2009). Antigenic basis of diversity in the $\gamma\delta$ T cell co-receptor WC1 family. *Molecular Immunology* **46**: 2565–2575.

Chentoufi AA, Kritzer E, Tran MV, Dasgupta G, Lim CH, Yu DC, Afifi RE, Jiang X, Carpenter D, Osorio N, Hsiang C, Nesburn AB, Wechsler SL and BenMohamed L (2011). The herpes simplex virus 1 latency-associated transcript promotes functional exhaustion of virus-specific CD8+ T cells in latently infected trigeminal ganglia: a novel immune evasion mechanism. *Journal of Virology* **85**: 9127–9138.

Chowdhury SI (1996). Construction and characterization of an attenuated bovine herpesvirus type 1 (BHV-1) recombinant virus. *Veterinary Microbiology* **52**: 13–23.

Ciabattini A, Pettini E, Fiorino F, Prota G, Pozzi G and Medaglini D (2011). Distribution of primed T cells and antigen-loaded antigen presenting cells following intranasal immunization in mice. *Public Library of Science One* **6**: e19346. doi:10.1371/journal.pone.0019346.

Cochran MD (1998). Recombinant infectious bovine rhinotracheitis virus s-ibr-052 and uses thereof. European Patent 0745133 A4.

Cochran MD, Shih M-F, MacConnell WP and Macdonald RD (2000). Recombinant herpesvirus of turkeys comprising a foreign DNA inserted into a non-essential region of the herpesvirus of turkeys genome. U.S. Patent 6,121,043.

Cochran MD, Wild MA and Winslow BJ (2001). Recombinant chimeric virus and uses thereof. U.S. Patent 6,183,753.

Collen T and Morrison WI (2000). CD4_ T-cell responses to bovine viral diarrhoea virus in cattle. *Virus Research* **67**: 67–80.

Connelley T, MacHugh ND, Burrells A and Morrison WI (2008). Dissection of the clonal composition of bovine $\alpha\beta$ T cell responses using T cell receptor Vβ subfamily-specific PCR and heteroduplex analysis. *Journal of Immunological Methods* **335**: 28–40.

Coussens PM, Sipkovsky S, Murphy B, Roussey J and Colvin CJ (2012). Regulatory T cells in cattle and their potential role in bovine paratuberculosis. *Comparative Immunology, Microbiology and Infectious Diseases* **35**: 233–239.

Cox GJM, Zamb TJ and Babiuk LA (1993). Bovine herpesvirus 1: immune responses in mice and cattle injected with plasmid DNA. *Journal of Virology* **67**: 5664–5667.

Cummins JM, Hutcheson DP, Cummins MJ, Georgiades JA and Richards AB (1993). Oral therapy with human interferon alpha in calves experimentally injected with infectious bovine rhinotracheitis virus. *Archivum Immunologiae Et Therapiae Experimentalis* **41**: 193–197.

Curtsinger JM and Mescher MF (2010). Inflammatory cytokines as a third signal for T cell activation. *Current Opinion in Immunology* **22**: 333–340.

Curtsinger JM, Schmidt CS, Mondino A, Lins DC, Kedl RM, Jenkins MK and Mescher MF (1999). Inflammatory cytokines provide a third signal for activation of naive CD4+ and CD8+ T cells. *Journal of Immunology* **162**: 3256–3262.

Czerkinsky C and Holmgren J (2012). Mucosal delivery routes for optimal immunization: targeting immunity to the right tissues. *Current Topics in Microbiology and Immunology* **354**: 1–18.

Dargan DJ, Patel AH and Subak-Sharpe JH (1995). PREPs: herpes simplex virus type 1-specific particles produced by infected cells when viral DNA replication is blocked. *Journal of Virology* **69**: 4924–4932.

Davis WC and Hamilton MJ (1998). Comparison of the unique characteristics of the immune system in different species of mammals. *Veterinary Immunology and Immunopathology* **63**: 7–13.

Denis M, Slaoui M, Keil G, Babiuk LA, Ernst E, Pastoret P-P and Thiry E (1993). Identification of different target glycoproteins for bovine herpes virus type 1-specific cytotoxic T lymphocytes depending on the method of in vitro stimulation. *Immunology* **78**: 7–13.

Denis M, Splitter G, Thiry E, Pastoret PP and Babiuk LA (1994). Infectious bovine rhinotracheitis (bovine herpesvirus 1): helper T cells, cytotoxic T cells, and NK cells. In: Goddeeris BML and Morrison WI (eds) *Cell-Mediated Immunity in Ruminants*. Boca Raton, FL: CRC Press, pp. 157–172.

Denis M, Hanon E, Rijsewijk FAM, Kaashoek MJ, van Oirschot JT, Thiry E and Pastoret P-P (1996). The role of glycoproteins gC, gE, gI and gG in the induction of cell-mediated immune responses to bovine herpesvirus 1. *Veterinary Microbiology* **53**: 121–132.

Deruelle MJ and Favoreel HW (2011). Keep it in the subfamily: the conserved alphaherpesvirus US3 protein kinase. *Journal of General Virology* **92**: 18–30.

Devireddy LR and Jones CJ (1999). Activation of caspases and p53 by bovine herpesvirus 1 infection results in programmed cell death and efficient virus release. *Journal of Virology* **73**: 3778–3788.

Dingwell KS and Johnson DC (1998). The herpes simplex virus gE-gI complex facilitates cell-to-cell spread and binds to components of cell junctions. *Journal of Virology* **72**: 8933–8942.

Distelhorst K, Voyich J and Wilson E (2010). Partial characterization and distribution of the chemokines CCL25 and CCL28 in the bovine system. *Veterinary Immunology and Immunopathology* **138**: 134–138.

Donnelly JJ, Ulmer JB, Shiver JW and Liu MA (1997). DNA vaccines. *Annual Review of Immunology* **15**: 617–648.

Dubuisson J, Israel BA and Letchworth III GJ (1992). Mechanisms of bovine herpesvirus type 1 neutralization by monoclonal antibodies to glycoproteins gI, gIII and gIV. *Journal of General Virology* **73**: 2031–2039.

Duchez S, Rodrigues M, Bertrand F and Valitutti S (2011). Reciprocal polarization of T and B cells at the immunological synapse. *Journal of Immunology* **187**: 4571–4580.

Elazhary MA, Silim A and Dea S (1984). Prevalence of antibodies to bovine respiratory syncytial virus, bovine viral diarrhea virus, bovine herpesvirus-1, and bovine parainfluenza-3 virus in sheep and goats in Quebec. *American Journal of Veterinary Research* **45**: 1660–1662.

El Hussein AM, Intisar KS, Ali YH and Fadol MA (2005). Prevalence of antibodies to infectious bovine rhinotracheitis virus in Sudanese cattle. *Journal of Science and Technology* **6**: 151–157.

Ellis JA (2009). Update on viral pathogenesis in BRD. *Animal Health Research Reviews* **10**: 149–153.

Endsley JJ, Quade MJ, Terhaar B and Roth JA (2002). BHV-1-Specific CD4+, CD8+, and $\gamma\delta$ T cells in calves vaccinated with one dose of a modified live BHV-1 vaccine. *Viral Immunology* **15**: 385–393.

Engels M and Ackermann M (1996). Pathogenesis of ruminant herpesvirus infections. *Veterinary Microbiology* **53**: 3–15.

Epstein AL and Manservigi R (2004). Herpesvirus/retrovirus chimeric vectors. *Current Gene Therapy* **4**: 409–416.

Eskra L and Splitter GA (1997). Bovine herpesvirus-1 infects activated CD4 lymphocytes. *Journal of General Virology* **78**: 2159–2166.

Estes DM (2010). Regulation of IgA responses in cattle, humans and mice. *Veterinary Immunology and Immunopathology* **138**: 312–317.

Estes DM and Brown WC (2002). Type 1 and type 2 responses in regulation of Ig isotype expression in cattle. *Veterinary Immunology and Immunopathology* **90**: 1–10.

Falcone E, Cordioli P, Tarantino M, Muscillo M, Sala G, La Rosa G, Archetti IL, Marianelli C, Lombardi G and Tollis M (2003). Experimental infection of calves with bovine viral diarrhoea virus type-2 (BVDV-2) isolated from a contaminated vaccine. *Veterinary Research Communications* **27**: 577–589.

Favoreel HW, Van de Walle GR, Nauwynck HJ and Pensaert MB (2003). Virus complement evasion strategies. *Journal of General Virology* **84**: 1–15.

Favoreel HW, Van Minnebruggen G, Van de Walle GR, Ficinska J and Nauwynck HJ (2006). Herpesvirus interference with virus-specific antibodies: bridging antibodies, internalizing antibodies, and hiding from antibodies. *Veterinary Microbiology* **113**: 257–263.

Filion LG, McGuire RL and Babiuk LA (1983). Nonspecific suppressive effect of bovine herpesvirus type 1 on bovine leukocyte functions. *Infection and Immunity* **42**: 106–112.

Fitzpatrick DR, Babiuk LA and Zamb TJ (1989). Nucleotide sequence of bovine herpesvirus type 1 glycoprotein gIII, a structural model for gIII as a new member of the immunoglobulin superfamily, and implications for the homologous glycoproteins of other herpesviruses. *Virology* **173**: 46–57.

Fitzpatrick DR, Snider M, McDougall L, Beskorwayne T, Babiuk LA, Zamb TJ and Ohmann HB (1990). Molecular mimicry: a herpes virus glycoprotein antigenically related to a cell-surface glycoprotein expressed by macrophages, polymorphonuclear leucocytes, and platelets. *Immunology* **70**: 504–512.

Forman AJ, Babiuk LA, Baldwin F and Friend SC (1982). Effect of infectious bovine rhinotracheitis virus infection of calves on cell populations recovered by lung lavage. *American Journal of Veterinary Research* **43**: 1174–1179.

Freer G and Matteucci D (2009). Influence of dendritic cells on viral pathogenicity. *Public Library of Science Pathogens* **5**: e1000384. doi:10.1371/journal.ppat.1000384.

Frerichs GN, Woods SB, Lucas MH and Sands JJ (1982). Safety and efficacy of live and inactivated infectious bovine rhinotracheitis vaccines. *Veterinary Record* **111**: 116–122.

Gao Y, Wang C and Splitter GA (1999). Mapping T and B lymphocyte epitopes of bovine herpesvirus-1 glycoprotein B. *Journal of General Virology* **80**: 2699–2704.

Gerdts V, Snider M, Brownlie R, Babiuk LA and Griebel PJ (2002). Oral DNA vaccination in utero induces mucosal immunity and immune memory in the neonate. *Journal of Immunology* **168**: 1877–1885.

Gerner W, Hammer SE, Wiesmüller K-H and Saalmüller A (2009). Identification of major histocompatibility complex restriction and anchor residues of foot-and-mouth disease virus-derived bovine T-cell epitopes. *Journal of Virology* **83**: 4039–4050.

Gibbs EPJ and Rweyemamu MM (1977). Bovine herpesviruses. Part 1: bovine herpesvirus 1. *Veterinary Bulletin* **47**: 317–343.

Glass EJ (2004). Genetic variation and responses to vaccines. *Animal Health Research Reviews* **5**: 197–208.

Glass EJ, Baxter R, Leach RJ and Jann OC (2012). Genes controlling vaccine responses and disease resistance to respiratory viral pathogens in cattle. *Veterinary Immunology and Immunopathology* **148**: 90–99.

Gopinath RS, Ambagala AP, Hinkley S and Srikumaran S (2002). Effects of virion host shut-off activity of bovine herpesvirus 1 on MHC class I expression. *Viral Immunology* **15**: 595–608.

Grewal AS, Rouse BT and Babiuk LA (1977). Mechanisms of resistance to herpesviruses: Comparison cof the effectiveness of different cell types in mediating antibody-dependent cell-mediated cytotoxicity. *Infection and Immunity* **15**: 698–703.

Griebel PJ, Ohmann HB, Lawman MJP and Babiuk LA (1990). The interaction between bovine herpesvirus type 1 and activated bovine T lymphocytes. *Journal of General Virology* **71**: 369–377.

Griffin BD, Verweij MC and Wiertz EJ (2010). Herpesviruses and immunity: the art of evasion. *Veterinary Microbiology* **143**: 89–100.

Gupta PK, Saini M, Gupta LK, Rao VDP, Bandyopadhyay SK, Butchaiah G, Garg GK and Garg SK (2001). Induction of immune responses in cattle with a DNA vaccine encoding glycoprotein C of bovine herpesvirus-1. *Veterinary Microbiology* **78**: 293–305.

Gurish MF, Ben-Porat T and Nisonoff A (1988). Induction of antibodies to pseudorabies virus by immunization with antiidiotypic antibodies. *Annals of the Institute Pasteur/Immunology* **139**: 677–687.

Gurunathan S, Klinman DM and Seder RA (2000). DNA vaccines: immunology, application, and optimization. *Annual Review of Immunology* **18**: 927–974.

Guzman E, Taylor G, Charleston B, Skinner MA and Ellis SA (2008). An MHC-restricted CD8+ T-cell response is induced in cattle by foot-and-mouth disease virus (FMDV) infection and also following vaccination with inactivated FMDV. *Journal of General Virology* **89**: 667–675.

Guzman E, Price S, Poulsom H and Hope J (2012). Bovine $\gamma\delta$ T cells: cells with multiple functions and important roles in immunity. *Veterinary Immunology and Immunopathology* **148**: 161–167.

Haanes EJ and Wardley RC (1997). Expression of the bovine parainfluenza virus type 3 hemagglutinin/neuraminidase (hn) glycoprotein in two heterologous systems. European Patent 0793728 A1.

Hage JJ, Glas RD, Westra HH, Maris-Veldhuis MA, Van Oirschot JT and Rijsewijk FAM (1998). Reactivation of latent bovine herpesvirus 1 in cattle seronegative to glycoproteins gB and gE. *Veterinary Microbiology* **60**: 87–98.

Hanon E, Keil G, van Drunen Littel-van den Hurk S, Griebel P, Vanderplasschen A, Rijsewijk FAM, Babiuk L and Pastoret P-P (1999). Bovine herpesvirus 1-induced apoptotic cell death: role of glycoprotein D. *Virology* **257**: 191–197.

Haralambiev H (1976). Immunogenicity studies of an inactivated IBR vaccine administered into the nasal mucosa. *Acta Veterinaria Academiae Scientiarum Hungaricae* **26**: 215–217.

Hariharan K, Hariharan MJ, Zamb TJ, Krueger RJ and Srikumaran S (1991). Bovine monoclonal anti-idiotypes induce antibodies specific for a synthetic peptide bearing a neutralizing epitope of bovine herpesvirus 1 glycoprotein gI (gB). *Journal of Immunology* **146**: 3489–3495.

Harland RJ, Potter AA, van Drunen-Littel-van den Hurk S, Van Donkersgoed J, Parker MD, Zamb TJ and Janzen ED (1992). The effect of subunit or modified live bovine herpesvirus-1 vaccines on the efficacy of a recombinant Pasteurella haemolytica vaccine for the prevention of respiratory disease in feedlot calves. *Canadian Veterinary Journal* **33**: 734–741.

Hart J, MacHugh ND and Morrison WI (2011). Theileria annulata-transformed cell lines are efficient antigen-presenting cells for in vitro analysis of CD8 T cell responses to bovine herpesvirus-1. *Veterinary Research* **42**: 119.

Held K, Junker A, Dornmair K, Meinl E, Sinicina I, Brandt T, Theil D and Derfuss T (2011). Expression of herpes simplex virus 1-encoded microRNAs in human trigeminal ganglia and their relation to local T-cell infiltrates. *Journal of Virology* **85**: 9680–9685.

Henderson G, Zhang Y and Jones C (2005). The bovine herpesvirus 1 gene encoding infected cell protein 0 (bICP0) can inhibit interferon-dependent transcription in the absence of other viral genes. *Journal of General Virology* **86**: 2697–2702.

Henderson LM, Levings RL, Davis AJ and Sturtz DR (1991). Recombination of pseudorabies virus vaccine strains in swine. *American Journal of Veterinary Research* **52**: 820–825.

Henninger RW, Reed SM, Saville WJ, Allen GP, Hass GF, Kohn CW and Sofaly C (2007). Outbreak of neurologic disease caused by equine herpesvirus-1 at a university equestrian center. *Journal of Veterinary Internal Medicine* **21**: 157–165.

Herzig CTA and Baldwin CL (2009). Genomic organization and classification of the bovine WC1 genes and expression by peripheral blood gamma delta T cells. *BioMed Central Genomics* **10**: 191. doi:10.1186/1471-2164-10-191.

Herzig CTA, Waters RW, Baldwin CL and Telfer JC (2010). Evolution of the CD163 family and its relationship to the bovine gamma delta T cell co-receptor WC1. *BioMed Central Evolutionary Biology* **10**: 181.

Hinkley S, Hill AB and Srikumaran S (1998). Bovine herpesvirus-1 infection affects the peptide transport activity in bovine cells. *Virus Research* **53**: 91–96.

Hirano M, Das S, Guo P and Cooper MD (2011). The evolution of adaptive immunity in vertebrates. *Advances in Immunology* **109**: 125–157.

Hodgins DC, Conlon JA and Shewen PE (2002). Respiratory viruses and bacteria in cattle. Chapter 12 In: Brogden KA and Guthmiller JM (eds) *Polymicrobial Diseases*. Washington: ASM Press, pp. 213–229.

Hogg AE, Parsons K, Taylor G, Worth A, Beverley P, Christopher J, Howard CJ and Villarreal-Ramos B (2011). Characterization of age-related changes in bovine CD8+ T-cells. *Veterinary Immunology and Immunopathology* **140**: 47–54.

Huang Y, Babiuk LA and van Drunen Littel-van den Hurk S (2005). Immunization with a bovine herpesvirus 1 glycoprotein B DNA vaccine induces cytotoxic T-lymphocyte responses in mice and cattle. *Journal of General Virology* **86**: 887–898.

Hutchings DL, Campos M, Qualtiere L and Babiuk LA (1990). Inhibition of antigen-induced and interleukin-2-induced proliferation of bovine peripheral blood leukocytes by inactivated bovine herpes virus 1. *Journal of Virology* **64**: 4146–4151.

Inman M, Lovato L, Doster A and Jones C (2001). A mutation in the latency-related gene of bovine herpesvirus 1 leads to impaired ocular shedding in acutely infected calves. *Journal of Virology* **75**: 8507–8515.

Ioannou XP, Griebel P, Hecker R, Babiuk LA and van Drunen Littel-van den Hurk S (2002). The immunogenicity and protective efficacy of bovine herpesvirus 1 glycoprotein D plus emulsigen are increased by formulation with CpG oligodeoxynucleotides. *Journal of Virology* **76**: 9002–9010.

Israel BA, Herber R, Gao Y and Letchworth III GJ (1992). Induction of a mucosal barrier to bovine herpesvirus 1 replication in cattle. *Virology* **188**: 256–264.

Jaime-Ramirez AC, Mundy-Bosse BL, Kondadasula S, Jones NB, Roda JM, Mani A, Parihar R, Karpa V, Papenfuss TL, LaPerle KM, Biller E, Lehman A, Chaudhury AR, Jarjoura D, Burry RW and Carson 3rd WE (2011). IL-12 enhances the antitumor actions of trastuzumab via NK cell IFN-γ production. *Journal of Immunology* **186**: 3401–3409.

Jenssen H (2009). Therapeutic approaches using host defence peptides to tackle herpes virus infections. *Viruses* **1**: 939–964.

Jericho KWF and Langford EV (1978). Pneumonia in calves produced with aerosols of bovine herpesvirus 1 and *Pasteurella haemolytica*. *Canadian Journal of Comparative Medicine* **42**: 269–277.

Jones C (2003). Herpes simplex virus type 1 and bovine herpesvirus 1 latency. *Clinical Microbiology Reviews* **16**: 79–95.

Jones C and Chowdhury S (2007). A review of the biology of bovine herpesvirus type 1 (BHV-1), its role as a cofactor in the bovine respiratory disease complex and development of improved vaccines. *Animal Health Research Reviews* **8**: 187–205.

Juliarena MA, Poli M, Ceriani C, Sala L, Rodríguez E, Gutierrez S, Dolcini G, Odeon A and Esteban EN (2009). Antibody response against three widespread bovine viruses is not impaired in Holstein cattle carrying bovine leukocyte antigen DRB3.2 alleles associated with bovine leukemia virus resistance. *Journal of Dairy Science* **92**: 375–381.

Jutila MA, Holderness J, Graff JC and Hedges JF (2008). Antigen-independent priming: a transitional response of bovine $\gamma\delta$ T-cells to infection. *Animal Health Research Reviews* **9**: 47–57.

Kaashoek MJ, Moerman A, Madić J, Rijsewijk FA, Quak J, Gielkens AL and van Oirschot JT (1994). A conventionally attenuated glycoprotein E-negative strain of bovine herpesvirus type 1 is an efficacious and safe vaccine. *Vaccine* **12**: 439–444.

Kaashoek MJ, Moerman A, Madić J, Weerdmeester K, Maris-Veldhuis M, Rijsewijk FA and van Oirschot JT (1995). An inactivated vaccine based on a glycoprotein E-negative strain of bovine herpesvirus 1 induces protective immunity and allows serological differentiation. *Vaccine* **13**: 342–346.

Kaashoek MJ, Rijsewijk FAM and Van Oirschot JT (1996a). Persistence of antibodies against bovine herpesvirus 1 and virus reactivation two to three years after infection. *Veterinary Microbiology* **53**: 103–110.

Kaashoek MJ, van Engelenburg FAC, Moerman A, Gielkens ALJ, Rijsewijk FAM and van Oirschot JT (1996b). Virulence and immunogenicity in calves of thymidine kinase- and glycoprotein E-negative bovine herpesvirus 1 mutants. *Veterinary Microbiology* **48**: 143–153.

Kaashoek MJ, Rijsewijk FA, Ruuls RC, Keil GM, Thiry E, Pastoret PP and Van Oirschot JT (1998). Virulence, immunogenicity and reactivation of bovine herpesvirus 1 mutants with a deletion in the gC, gG, gI, gE, or in both the gI and gE gene. *Vaccine* **16**: 802–809.

Kacskovics I (2004). Fc receptors in livestock species. *Veterinary Immunology and Immunopathology* **102**: 351–362.

Kahn CM, Line S and Aiella SE (2005). *The Merck Veterinary Manual*. Whitehouse Station, NJ: Merck, Sharp and Dohme, p. 2712.

Kahrs R, Atkinson G, Baker JA, Carmichael L, Coggins L, Gillespie J, Langer P, Marshall V, Robson D and Sheffy B (1964). Serological studies on the incidence of bovine viral diarrhea, infectious bovine rhinotracheitis, bovine myxovirus parainfluenza-3, and *Leptospira Pomona* in New York state. *Cornell Veterinarian* **54**: 360–369.

Kahrs RF (2001). Infectious bovine rhinotracheitis. In: Kahrs RF (ed.) *Viral Diseases of Cattle*, 2nd edn. Ames, IA: Iowa State University Press, pp. 159–170.

Kampa J, Ståhl K, Moreno-López J, Chanlun A, Aiumlamai S and Alenius S (2004). BVDV and BHV.1 infections in dairy herds in northern and northeastern Thailand. *Acta Veterinaria Scandinavica* **45**: 181–192.

Keil GM, Klopfleisch C, Giesow K and Veits J (2010). Protein display by bovine herpesvirus type 1 glycoprotein B. *Veterinary Microbiology* **143**: 29–36.

Kelley KW (1980). Stress and immune function: a bibliographic review. *Annales de Recherches Vétérinaires* **11**: 445–478.

Kendrick JW, York CJ and McKercher DG (1957). A controlled field trial of a vaccine for infectious bovine rhinotracheitis. *Proceedings, Annual Meeting of the United States Livestock Sanitary Association* **60**: 155–158.

Kennedy RC, Adler-Storthz K, Burns Sr JW, Henkel RD and Dreesman GR (1984). Antiidiotype modulation of herpes simplex virus infection leading to increased pathogenicity. *Journal of Virology* **50**: 951–953.

Khattar SK, Collins PL and Samal SK (2010). Immunization of cattle with recombinant Newcastle disease virus expressing bovine herpesvirus-1 (BHV-1) glycoprotein D induces mucosal and serum antibody responses and provides partial protection against BHV-1. *Vaccine* **28**: 3159–3170.

Kit M, Kit S, Little SP, Di Marchi RD and Gale C (1991). Bovine herpesvirus-1 (infectious bovine rhinotracheitis virus)-based viral vector which expresses foot-and-mouth disease epitopes. *Vaccine* **9**: 564–572.

Kit S, Qavi H, Gaines JD, Billingsley P and McConnell S (1985). Thymidine kinase-negative bovine herpesvirus type 1 mutant is stable and highly attenuated in calves. *Archives of Virology* **86**: 63–83.

Klasse PJ and Sattentau QJ (2002). Occupancy and mechanism in antibody-mediated neutralization of animal viruses. *Journal of General Virology* **83**: 2091–2108.

Knittler MR, Alberts P, Deverson EV and Howard JC (1999). Nucleotide binding by TAP mediates association with peptide and release of assembled MHC class I molecules. *Current Biology* **9**: 999–1008.

Kolar JR, Shechmeister IL and Kammlade WG (1972). Use in cattle of formalin-killed polyvalent vaccine with adjuvant against infectious bovine rhinotracheitis, bovine viral diarrhea, and parainfluenza-3 viruses. *American Journal of Veterinary Research* **33**: 1415–1420.

Koppers-Lalic D (2007). Immune evasion by varicelloviruses: the identification of a new family of TAP-inhibiting proteins. Doctoral thesis, Leiden University.

Koppers-Lalic D, Rijsewijk FAM, Verschuren SBE, van Gaans-van den Brink JAM, Neisig A, Ressing ME, Neefjes J and Wiertz EJHJ (2001). The UL41-encoded virion host shutoff (vhs) protein and vhs independent mechanisms are responsible for down-regulation of MHC class I molecules by bovine herpesvirus 1. *Journal of General Virology* **82**: 2071–2081.

Koppers-Lalic D, Reits EAJ, Ressing ME, Lipinska AD, Abele R, Koch J, Rezende MM, Admiraal P, van Leeuwen D, Bienkowska-Szewczyk K, Mettenleiter TC, Rijsewijk FAM, Tampé R, Neefjes J and Wiertz EJHJ (2005). Varicelloviruses avoid T cell recognition by UL49.5-mediated inactivation of the transporter associated with antigen processing. *Proceedings of the National Academy of Sciences USA* **102**: 5144–5149.

Koppers-Lalic D, Verweij MC, Lipińska AD, Wang Y, Quinten E, Reits EA, Koch J, Loch S, Rezende MM, Daus F, Bieńkowska-Szewczyk K, Osterriede N, Mettenleiter TC, Heemskerk MHM, Tampé R, Neefjes JJ, Chowdhury SI, Ressing ME, Rijsewijk FAM and Wiertz EJHJ (2008). Varicellovirus UL49.5 proteins differentially affect the function of the transporter associated with antigen processing, TAP. *PLoS Pathog* **4**: e1000080. doi:10.1371/journal.ppat.1000080.

Kowalski J, Gilbert SA, van Drunen-Littel-van den Hurk S, van den Hurk J, Babiuk LA and Zamb TJ (1993). Heat-shock promoter-driven synthesis of secreted bovine herpesvirus glycoproteins in transfected cells. *Vaccine* **11**: 1100–1107.

Kühnle G, Collins RA, Scott JE and Keil GM (1996). Bovine inerleukins 2 and 4 expressed in recombinant bovine herpesvirus 1 are biologically active secreted glycoproteins. *Journal of General Virology* **77**: 2231–2240.

Kweon CH, Kang SW, Choi EJ and Kang YB (1999). Bovine herpes virus expressing envelope protein (E2) of bovine

viral diarrhea virus as a vaccine candidate. *Journal of Veterinary Medical Science* **61**: 395–401.

Lambotin M, Raghuraman S, Stoll-Keller F, Baumert TF and Barth H (2010). A look behind closed doors: interaction of persistent viruses with dendritic cells. *Nature Reviews Microbiology* **8**: 350–360.

Lanzavecchia A and Sallusto F (2007). Toll-like receptors and innate immunity in B-cell activation and antibody responses. *Current Opinion in Immunology* **19**: 268–274.

Lazear E, Whitbeck JC, Ponce-de-Leon M, Cairns TM, Willis SH, Zuo Y, Krummenacher C, Cohen GH and Eisenberg RJ (2012). Antibody-induced conformational changes in herpes simplex virus glycoprotein gD reveal new targets for virus neutralization. *Journal of Virology* **86**: 1563–1576.

Leary TP and Splitter GA (1990). Recombinant herpesviral proteins produced by cell-free translation provide a novel approach for the mapping of T lymphocyte epitopes. *Journal of Immunology* **145**: 718–723.

Lee S-W, Markham PF, Coppo MJC, Legione AR, Markham JF, Amir H, Noormohammadi AH, Browning GF, Ficorilli N, Hartley CA and Devlin JM (2012). Attenuated vaccines can recombine to form virulent field viruses. *Science* **227**: 188.

Lemaire M, Meyer G, Ernst E, Vanherreweghe V, Limbourg B, Pastoret P-P and Thiry E (1995). Latent bovine herpesvirus 1 infection in calves protected by colostral immunity. *Veterinary Record* **137**: 70–71.

Lemaire M, Meyer G, Baranowski E, Schynts F, Wellemans G, Kerkhofs P and Thiry E (2000a). Production of bovine herpesvirus type 1-seronegative latent carriers by administration of a live-attenuated vaccine in passively immunized calves. *Journal of Clinical Microbiology* **38**: 4233–4238.

Lemaire M, Weynants V, Godfroid J, Schynts F, Meyer G, Letesson J-J and Thiry E (2000b). Effects of bovine herpesvirus type 1 infection in calves with maternal antibodies on immune response and virus latency. *Journal of Clinical Microbiology* **38**: 1885–1894.

Levings RL and Roth JA (2013). Immunity to bovine herpesvirus 1 infections: I. Viral lifecycle and innate immunity. *Animal Health Research Reviews* **14**: doi: 10.1017/S1466252313000042.

Levings RL, Kaeberle ML and Reed DE (1984). The effect of some common inactivation procedures on the antigens of bovine herpesvirus 1. *Veterinary Microbiology* **9**: 313–328.

Liang X, Tang M, Manns B, Babiuk LA and Zamb TJ (1993). Identification and deletion mutagenesis of the bovine herpesvirus 1 dUTPase gene and a gene homologous to herpes simplex virus UL49.5. *Virology* **195**: 42–50.

Lipińska AD, Koppers-Lalic D, Rychłowski M, Admiraal P, Rijsewijk FAM, Bieńkowska-Szewczyk K and Wiertz EJHJ (2006). Bovine herpesvirus 1 UL49.5 protein inhibits the transporter associated with antigen processing despite complex formation with glycoprotein M. *Journal of Virology* **80**: 5822–5832.

Lippolis JD (2008). Immunological signaling networks: integrating the body's immune response. *Journal of Animal Science* **86** (suppl. 14): E53–E63.

Loch S, Klauschies F, Schölz C, Verweij MC, Wiertz EJHJ, Koch J and Tampé R (2008). Signaling of a varicelloviral factor across the endoplasmic reticulum membrane induces destruction of the peptide-loading complex and immune evasion. *Journal of Biological Chemistry* **283**: 13428–13436.

Loehr BI, Willson P, Babiuk LA and van Drunen Littel-van den Hurk S (2000). Gene gun-mediated DNA immunization primes development of mucosal immunity against bovine herpesvirus 1 in cattle. *Journal of Virology* **74**: 6077–6086.

Loehr BI, Rankin R, Pontarollo R, King T, Willson P, Babiuk LA and van Drunen Littel-van den Hurk S (2001). Suppository-mediated DNA immunization induces mucosal immunity against bovine herpesvirus-1 in cattle. *Virology* **289**: 327–333.

Lubinski JM, Lazear HM, Awasthi S, Wang F and Friedman HM (2011). The herpes simplex virus 1 IgG Fc receptor blocks antibody-mediated complement activation and antibody-dependent cellular cytotoxicity in vivo. *Journal of Virology* **85**: 3239–3249.

Lupton HW and Reed DE (1980). Evaluation of experimental subunit vaccines for infectious bovine rhinotracheitis. *American Journal of Veterinary Research* **41**: 383–390.

MacHugh ND, Mburu JK, Carol MJ, Wyatt CR, Orden JA and Davis WC (1997). Identification of two distinct subsets of bovine $\gamma\delta$ T cells with unique cell surface phenotype and tissue distribution. *Immunology* **92**: 340–345.

Macnab S, White R, Hiscox J and Whitehouse A (2008). Production of an infectious Herpesvirus saimiri-based episomally maintained amplicon system. *Journal of Biotechnology* **134**: 287–296.

Marnila P and Korhonen H (2011). Milk proteins – immunoglobulins. In: Fuquay JW, Fox PF and McSweeney PLH (eds) *Encyclopedia of Dairy Sciences*. Salt Lake City, UT: Academic Press, pp. 807–815.

Marshall RL and Letchworth III GJ (1988). Passively administered neutralizing monoclonal antibodies do not protect calves against bovine herpesvirus 1 infection. *Vaccine* **6**: 343–348.

Martin SW, Meek AH, Davis DG, Thomson RG, Johnson JA, Lopez A, Stephens L, Curtis RA, Prescott JF, Rosendol S, Savon M, Zuboidy AJ and Bolton MR (1980). Factors associated with mortality in feedlot cattle: the Bruce county beef cattle project. *Canadian Journal of Comparative Medicine* **44**: 1–10.

McGuire RL and Babiuk LA (1984). Evidence for defective neutrophil function in lungs of calves exposed to infectious bovine rhinotracheitis virus. *Veterinary Immunology and Immunopathology* **5**: 259–271.

Meckes Jr DG and Raab-Traub N (2011). Microvesicles and viral infection. *Journal of Virololgy* **85**: 12844–12854.

Meeusen ENT, Walker J, Peters A, Pastoret P-P and Jungersen G (2007). Current status of veterinary vaccines. *Clinical Microbiology Reviews* **20**: 489–510.

Meissner N, Radke J, Hedges JF, White M, Behnke M, Bertolino S, Abrahamsen M and Jutila MA (2003). Serial analysis of gene expression in circulating $\gamma\delta$ T cell subsets defines distinct immunoregulatory phenotypes and unexpected gene expression profiles. *Journal of Immunology* **170**: 356–364.

Menanteau-Horta AM, Ames TR, Johnson DW and Meiske JC (1985). Effect of maternal antibody upon vaccination with infectious bovine rhinotracheitis and bovine virus diarrhea vaccines. *Canadian Journal of Comparative Medicine* **49**: 10–14.

Metzler AE, Matile H, Gassmann U, Engels M and Wyler R (1985). European isolates of bovine herpesvirus 1: a comparison of restriction endonuclease sites, polypeptides, and reactivity with monoclonal antibodies. *Archives of Virology* **85**: 57–69.

Meyer A, Parng CL, Hansal SA, Osborne BA and Goldsby RA (1997). Immunoglobulin gene diversification in cattle. *International Reviews of Immunology* **15**: 165–183.

Mühlbach H, Mohr CA, Ruzsics Z and Koszinowski UH (2009). Dominant-negative proteins in herpesviruses – From assigning gene function to intracellular immunization. *Viruses* **1**: 420–440.

Murphy K, Travers P and Walport M (2008). *Janeway's Immunobiology*. New York, NY: Garland Science, p. 887.

Muylkens B, Meurens F, Schynts F, de Fays K, Pourchet A, Thiry J, Vanderplasschen A, Antoine N and Thiry E

(2006a). Biological characterization of bovine herpesvirus 1 recombinants possessing the vaccine glycoprotein E negative phenotype. *Veterinary Microbiology* **113**: 283–291.

Muylkens B, Meurens F, Schynts F, Farnir F, Pourchet A, Bardiau M, Gogev S, Thiry J, Cuisenaire A, Vanderplasschen A and Thiry E (2006b). Intraspecific bovine herpesvirus 1 recombinants carrying glycoprotein E deletion as a vaccine marker are virulent in cattle. *Journal of General Virology* **87**: 2149–2154.

Muylkens B, Thiry J, Kirten P, Schynts F and Thiry E (2007). Bovine herpesvirus 1 infection and infectious bovine rhinotracheitis. *Veterinary Research* **38**: 181–209.

Nace G, Evankovich J, Eid R and Tsung A (2012). Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. *Journal of Innate Immunity* **4**: 6–15.

Nandi S, Kumar M, Manohar M and Chauhan RS (2009). Bovine herpes virus infections in cattle. *Animal Health Research Reviews* **10**: 85–98.

Nataraj C and Srikumaran S (1994). Bovine x murine T-cell hybridomas specific for bovine herpesvirus 1 (BHV-1) glycoproteins. *Viral Immunology* **7**: 11–23.

Neefjes JJ, Momburg F and Hämmerling GJ (1993). Selective and ATP-dependent translocation of peptides by the MHC-encoded transporter. *Science* **261**: 769–771.

Neutra MR and Kozlowski PA (2006). Mucosal vaccines: the promise and the challenge. *Nature Reviews Immunology* **6**: 148–158.

Nguyen ML and Blaho JA (2009). Cellular players in the herpes simplex virus dependent apoptosis balancing Act. *Viruses* **1**: 965–978.

Niku M, Liljavirta J, Durkin K, Schroderus E and Iivanainen A (2012). The bovine genomic DNA sequence data reveal three IGHV subgroups, only one of which is functionally expressed. *Developmental and Comparative Immunology* **37**: 457–461.

Ohmann HB and Babiuk LA (1985). Viral-bacterial pneumonia in calves: effect of bovine herpesvirus-1 on immunologic functions. *Journal of Infectious Diseases* **151**: 937–947.

Ohmann HB and Babiuk LA (1986). Alteration of alveolar macrophage functions after aerosol infection with bovine herpesvirus type 1. *Infection and Immunity* **51**: 344–347.

Orten DJ, Reddy PG, Reddy DN, Xue W, AbdelMagid OY, Blecha F and Minocha HC (1991). Induction of immune response to bovine herpesvirus-1 with anti-idiotypic antibodies. *Viral Immunology* **4**: 111–122.

Orten DJ, Xue W, van Drunen Littel-van den Hurk S, AbdelMagid OY, Reddy DN, Campos M, Babiuk LA, Blecha F and Minocha HC (1993). Comparison of bovine immune responses to affinity-purified bovine herpesvirus-1 antiidiotypes and glycoproteins. *Viral Immunology* **6**: 109–117.

O'Toole D, Miller MM, Cavender JL and Cornish TE (2012). Pathology in practice. *Journal of the American Veterinary Medical Association* **241**: 189–191.

Pasman Y, Saini SS, Smith E and Kaushik AK (2010). Organization and genomic complexity of bovine lambda-light chain gene locus. *Veterinary Immunology and Immunopathology* **135**: 306–313.

Pastoret P-P, Aguilar-Setién A, Burtonboy G, Mager J, Jetteur P and Schoenaers F (1979). The effect of repeated treatment with dexamethasone on the re-excretion pattern of infectious bovine rhinotracheitis virus and humoral immune response. *Veterinary Microbiology* **4**: 149–155.

Pastoret PP, Babiuk LA, Misra V and Griebel P (1980). Reactivation of temperature-sensitive and non-temperature-sensitive infectious bovine rhinotracheitis vaccine virus with dexamethasone. *Infection and Immunity* **29**: 483–488.

Pavot V, Rochereau N, Genin C, Verrier B and Paul S (2012). New insights in mucosal vaccine development. *Vaccine* **30**: 142–154.

Ploegh HL (1998). Viral strategies of immune evasion. *Science* **280**: 248–253.

Quinlivan M, Breuer J and Schmid DS (2011). Molecular studies of the Oka varicella vaccine. *Expert Review of Vaccines* **10**: 1321–1336.

Raggo C, Fitzpatrick DR, Babiuk LA and Liang X (1996). Expression of bovine interleukin-1 beta in a bovine herpesvirus-1 vector: in vitro analysis. *Virology* **221**: 78–86.

Raggo C, Habermehl M, Babiuk LA and Griebel P (2000). The in vivo effects of recombinant bovine herpesvirus-1 expressing bovine interferon-gamma. *Journal of General Virology* **81**: 2665–2673.

Ratcliffe MJH and Mitchison NA (1984). Function of Ig receptors in B-cell triggering. *Annales D Immunologie* **135D**: 73–79.

Reading SA and Dimmock NJ (2007). Neutralization of animal virus infectivity by antibody. *Archives of Virology* **152**: 1047–1059.

Reinink P and Van Rhijn I (2009). The bovine T cell receptor alpha/delta locus contains over 400 V genes and encodes V genes without CDR2. *Immunogenetics* **61**: 541–549.

Reizis B, Bunin A, Ghosh HS, Lewis KL and Sisirak V (2011). Plasmacytoid dendritic cells: recent progress and open questions. *Annual Review of Immunology* **29**: 163–183.

Renjifo X, Letellier C, Keil GM, Ismail J, Vanderplasschen A, Michel P, Godfroid J, Walravens K, Charlier G, Pastoret P-P, Urbain J, Denis M, Moser M and Kerkhofs P (1999). Susceptibility of bovine antigen-presenting cells to infection by bovine herpesvirus 1 and in vitro presentation to T vells: two independent events. *Journal of Virology* **73**: 4840–4846.

Rogers AN, VanBuren DG, Hedblom EE, Tilahun ME, Telfer JC and Baldwin CL (2005). $\gamma\delta$ T cell function varies with the expressed WC1 coreceptor. *Journal of Immunology* **174**: 3386–3393.

Roizman B and Taddeo B (2007). The strategy of herpes simplex virus replication and takeover of the host cell. Chapter 13 In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R and Yamanishi K (eds) *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press, pp. 163–173.

Roizman B, Knipe DM and Whitley RJ (2007). Herpes simplex viruses. Chapter 67 In: Knipe DM and Howley PM (eds) *Fields Virology*. Philadelphia: Wolters Kluwer, pp. 2501–2601.

Rollinson EA, White G, Thiry E, Dubuisson J and Pastoret PP (1988). Therapy of Aujeszky's disease (pseudorabies) in naturally infected and artificially inoculated piglets using BW B759U (9-[1,3-dihydroxy-2-propoxymethyl] guanine). *Research in Veterinary Science* **45**: 54–61.

Roth JA and Carter DP (2000). Comparison of bovine herpesvirus 1 vaccines for rapid induction of immunity. *Veterinary Therapeutics* **1**: 220–228.

Roth JA and Perino LJ (1998). Immunology and prevention of infection in feedlot cattle. *Veterinary Clinics of North America, Food Animal Practice* **14**: 233–256.

Rouse BT and Babiuk LA (1977). The direct antiviral cytotoxicity by bovine lymphocytes is not restricted by genetic incompatibility of lymphocytes and target cells. *Journal of Immunology* **118**: 618–624.

Rouse BT and Babiuk LA (1978). Mechanisms of recovery from herpesvirus infections – a review. *Canadian Journal of Comparative Medicine* **42**: 414–427.

Rouse BT, Wardley RC and Babiuk LA (1976). Antibody-dependent cell-mediated cytotoxicity in cows: comparison of effector cell activity against heterologous erythrocyte and herpesvirus-infected bovine target cells. *Infection and Immunity* **13**: 1433–1441.

Ruprecht CR and Lanzavecchia A (2006). Toll-like receptor stimulation as a third signal required for activation of human naive B cells. *European Journal of Immunology* **36**: 810–816.

Saini SS, Hein WR and Kaushik A (1997). A single predominantly expressed polymorphic immunoglobulin VH gene family, related to mammalian group I, clan II, is identified in cattle. *Molecular Immunology* **34**: 641–651.

Salak-Johnson JL and McGlone JJ (2007). Making sense of apparently conflicting data: stress and immunity in swine and cattle. *Journal of Animal Science* **85**: E81–88.

Schmitt J and Keil GM (1998). Characterization of the bovine herpesvirus 1 UL8 gene and gene products. *Journal of General Virology* **79**: 133–141.

Schoenborn JR and Wilson CB (2007). Regulation of interferon-gamma during innate and adaptive immune responses. *Advances in Immunology* **96**: 41–101.

Schrijver RS, Langedijk JP, Keil GM, Middel WG, Maris-Veldhuis M, Van Oirschot JT and Rijsewijk FA (1997). Immunization of cattle with a BHV-1 vector vaccine or a DNA vaccine both coding for the G protein of BRSV. *Vaccine* **15**: 1908–1916.

Schuster P, Boscheinen JB, Tennert K and Schmidt B (2011). The role of plasmacytoid dendritic cells in innate and adaptive immune responses against alpha herpes virus infections. *Advances in Virology* Article ID 679271 **2011**: 12. doi:10.1155/2011/679271.

Schwyzer M and Ackermann M (1996). Molecular virology of ruminant herpesviruses. *Veterinary Microbiology* **53**: 17–29.

Schynts F, Meurens F, Detry B, Vanderplasschen A and Thiry E (2003). Rise and survival of bovine herpesvirus 1 recombinants after primary infection and reactivation from latency. *Journal of Virology* **77**: 12535–12542.

Shah AC, Parker JN, Shimamura M and Cassady KA (2009). Spontaneous and engineered compensatory HSV mutants that counteract the host antiviral PKR response. *Viruses* **1**: 510–522.

Shiau A-L, Chen Y-L, Liao C-Y, Huang Y-S and Wu C-L (2001). Prothymosin α enhances protective immune responses induced by oral DNA vaccination against pseudorabies delivered by Salmonella choleraesuis. *Vaccine* **19**: 3947–3956.

Shojaei F, Saini SS and Kaushik AK (2003). Unusually long germline DH genes contribute to large sized CDR3H in bovine antibodies. *Molecular Immunology* **40**: 61–67.

Sinclair MC, Gilchrist J and Aitken R (1995). Molecular characterization of bovine Vh regions. *Journal of Immunology* **155**: 3068–3078.

Singer A, Adoro S and Park J-H (2008). Lineage fate and intense debate: myths, models and mechanisms of CD4- versus CD8-lineage choice. *Nature Reviews Immunology* **8**: 788–801.

Singh R and Cresswell P (2010). Defective cross-presentation of viral antigens in GILT-free mice. *Science* **328**: 1394–1398.

Smith GA, Young PL and Reed KC (1995). Emergence of a new bovine herpesvirus 1 strain in Australian feedlots. *Archives of Virology* **140**: 599–603.

Spickler AR and Roth JA (2003). Adjuvants in Veterinary Vaccines: modes of Action and Adverse Effects. *Journal of Veterinary Internal Medicine* **17**: 273–281.

Splitter GA, Eskra L and Abruzzini AF (1988). Cloned bovine cytolytic T cells recognize bovine herpes virus-1 in a genetically restricted, antigen-specific manner. *Immunology* **63**: 145–150.

Srikumaran S, Onisk DV, Borca MV, Nataraj C and Zamb TJ (1990). Anti-idiotypic antibodies induce neutralizing antibodies to bovine herpesvirus 1. *Immunology* **70**: 284–289.

Srikumaran S, Kelling CL and Ambagala A (2007). Immune evasion by pathogens of bovine respiratory disease complex. *Animal Health Research Reviews* **8**: 215–229.

Steinman RM and Hemmi H (2006). Dendritic cells: translating innate to adaptive immunity. *Current Topics in Microbiology and Immunology* **311**: 17–58.

St. George TD, Snowdon WA, Parsonson IM and French EL (1967). A serological survey of mucosal disease and infectious bovine rhinotracheitis in cattle in Australia and New Guinea. *Australian Veterinary Journal* **43**: 549–557.

Straub OC (1990). Infectious bovine rhinotracheitis virus.. In: Dinter Z, Morein B (eds) *Virus Infections of Ruminants*. Chap 11, Vol. **3**. *Virus infections of Vertebrates*. New York, NY: Elsevier Science, pp. 71–108.

Strube W, Auer S, Block W, Heinen E, Kretzdom D, Rodenbach C and Schmeer N (1996). A gE deleted infectious bovine rhinotracheitis marker vaccine for use in improved bovine herpesvirus 1 control programs. *Veterinary Microbiology* **53**: 181–189.

Taylor GS, Mautner J and Münz C (2011). Autophagy in herpesvirus immune control and immune escape. *Herpesviridae* **2**: 2.

Taylor J, Meignier B, Tartaglia J, Languet B, VanderHoeven J, Franchini G, Trimarchi C and Paoletti E (1995). Biological and immunogenic properties of a canarypox-rabies recombinant, ALVAGRk (vCP65) in non-avian species. *Vaccine* **13**: 539–549.

Teng G and Papavasiliou FN (2007). Immunoglobulin somatic hypermutation. *Annual Review of Genetics* **41**: 107–120.

The Bovine Genome Sequencing and Analysis Consortium, Elsik CG, Tellam RL and Worley KC (2009). The genome sequence of taurine cattle: a window to ruminant biology and evolution. *Science* **324**: 522–528.

Theil D, Derfuss T, Paripovic I, Herberger S, Meinl E, Schueler O, Strupp M, Arbusow V and Brandt T (2003). Latent herpesvirus infection in human trigeminal ganglia causes chronic immune response. *American Journal of Pathology* **163**: 2179–2184.

Theil KW, Mohanty SB and Hetrick FM (1971). Effect of poly I:C on infectious bovine rhinotracheitis virus infection in calves. *Proceedings, Society Experimental Biology and Medicine* **137**: 1176–1179.

Thiry E, Meurens F, Muylkens B, McVoy M, Gogev S, Thiry J, Vanderplasschen A, Epstein A, Keil G and Schynts F (2005). Recombination in alphaherpesviruses. *Review of Medical Virology* **15**: 89–103.

Tikoo SK, Campos M and Babiuk LA (1995a). Bovine herpesvirus 1 (BHV-1): biology, pathogenesis, and control. *Advances in Virus Research* **45**: 191–222.

Tikoo SK, Campos M, Popowych YI, van Drunen Littel-van den Hurk S and Babiuk LA (1995b). Lymphocyte proliferative responses to recombinant bovine herpes virus type 1 (BHV-1) glycoprotein gD (gIV) in immune cattle: identification of a T cell epitope. *Viral Immunology* **8**: 19–25.

Toka FN, Kenney MA and Golde WT (2011). Rapid and transient activation of $\gamma\delta$ T cells to IFN-g production, NK cell-like killing, and antigen processing during acute virus infection. *Journal of Immunology* **186**: 4853–4861.

Trudel M, Boulay G, Séguin C, Nadon F and Lussier G (1988). Control of infectious bovine rhinotracheitis in calves with a BHV-1 subunit-ISCOM vaccine. *Vaccine* **6**: 525–529.

Tsuda T, Onodera T, Sugimura T, Murakami Y (1992). Induction of protective immunity and neutralizing antibodies to pseudorabies virus by immunization of anti-idiotypic antibodies. *Archives of Virology* **124**: 291–300.

Turin L, Russo S and Poli G (1999). BHV-1: new molecular approaches to control a common and widespread infection. *Molecular Medicine* **5**: 261–284.

van der Meulen K, Garré B, Croubels S and Nauwynck H (2006). In vitro comparison of antiviral drugs against feline herpesvirus 1. *BioMed Central Veterinary Research* **2**: 13. doi:10.1186/1746-6148-2-13.

Vander Veen RL, Harris DLH and Kamrud KI (2012). Alphavirus replicon vaccines. *Animal Health Research Reviews* **13**: 1–9.

van Drunen Littel-van den Hurk S (2006). Rationale and perspectives on the success of vaccination against bovine herpesvirus-1. *Veterinary Microbiology* **113**: 275–282.

van Drunen Littel-van den Hurk S (2007). Cell-mediated immune responses induced by BHV-1: rational vaccine design. *Expert Review of Vaccines* **6**: 369–380.

van Drunen Littel-van den Hurk S, Zamb T and Babiuk LA (1989). Synthesis, cellular location, and immunogenicity of bovine herpesvirus 1 glycoproteins gI and gIII expressed by recombinant vaccinia virus. *Journal of Virology* **63**: 2159–2168.

van Drunen Littel-van den Hurk S, Parker MD, Massie B, van den Hurk JV, Harland R, Babiuk LA and Zamb TJ (1993). Protection of cattle from BHV-1 infection by immunization with recombinant glycoprotein gIV. *Vaccine* **11**: 25–35.

van Drunen Littel-van den Hurk S, Van Donkersgoed J, Kowalski J, van den Hurk JV, Harland R, Babiuk LA and Zamb TJ (1994). A subunit gIV vaccine, produced by transfected mammalian cells in culture, induces mucosal immunity against bovine herpesvirus-1 in cattle. *Vaccine* **12**: 1295–1302.

van Drunen Littel-van den Hurk S, Braun RP, Lewis PJ, Karvonen BC, Baca-Estrada ME, Snider M, McCartney D, Watts T and Babiuk LA (1998). Intradermal immunization with a bovine herpesvirus-1 DNA vaccine induces protective immunity in cattle. *Journal of General Virology* **79**: 831–839.

van Drunen Littel-van den Hurk S, Snider M, Thompson P, Latimer L and Babiuk LA (2008). Strategies for induction of protective immunity to bovine herpesvirus-1 in newborn calves with maternal antibodies. *Vaccine* **26**: 3103–3111.

van Oirschot JT (1999). Diva vaccines that reduce virus transmission. *Journal of Biotechnology* **73**: 195–205.

van Oirschot JT, Kaashoek MJ and Rijsewijk FAM (1996). Advances in the development and evaluation of bovine herpesvirus 1 vaccines. *Veterinary Microbiology* **53**: 43–54.

van Oirschot JT, Kaashoek MJ, Maris-Veldhuis MA and Rijsewijk FAM (1999). Strains of bovine herpesvirus 1 that do not express an epitope on glycoprotein E in cell culture still induce antibodies that can be detected in a gE-blocking ELISA. *Veterinary Microbiology* **65**: 103–113.

Verweij MC, Koppers-Lalic D, Loch S, Klauschies F, de la Salle H, Quinten E, Lehner PJ, Mulder A, Knittler MR, Tampé R, Koch J, Ressing ME and Wiertz EJHJ (2008). The varicellovirus UL49.5 protein blocks the transporter associated with antigen processing (TAP) by inhibiting essential conformational transitions in the 6+6 transmembrane TAP core complex. *Journal of Immunology* **181**: 4894–4907.

Vesosky B, Turner OC, Turner J and Orme IM (2003). Activation marker expression on bovine peripheral blood gamma-delta T cells during post-natal development and following vaccination with a commercial polyvalent viral vaccine. *Developmental and Comparative Immunology* **27**: 439–447.

Wang C and Splitter GA (1998). CD41 cytotoxic T-lymphocyte activity against macrophages pulsed with bovine herpesvirus 1 polypeptides. *Journal of Virology* **72**: 7040–7047.

Wei H, Wang Y and Chowdhury SI (2011). Bovine herpesvirus type 1 (BHV-1) UL49.5 luminal domain residues 30 to 32 are critical for MHC-I down-regulation in virus-infected cells. *PLoS ONE* **6**: e25742. doi:10.1371/journal.pone.0025742.

Wei H, He J, Paulsen DB and Chowdhury SI (2012). Bovine herpesvirus type 1 (BHV-1) mutant lacking UL49.5 luminal domain residues 30–32 and cytoplasmic tail residues 80–96 induces more rapid onset of virus neutralizing antibody and cellular immune responses in calves than the wild-type strain Cooper. *Veterinary Immunology and Immunopathology* **147**: 223–229.

Wessman SJ and Levings RL (1999). Benefits and risks due to animal serum used in cell culture production. *Developments in Biological Standardization* **99**: 3–8.

Whetstone CA, Wheeler JG and Reed DE (1986). Investigation of possible vaccine-induced epizootics of infectious bovine rhinotracheitis, using restriction endonuclease analysis of viral DNA. *American Journal of Veterinary Research* **47**: 1789–1795.

Whitbeck JC, Knapp AC, Enquist LW, Lawrence WC and Bello LJ (1996). Synthesis, processing, and oligomerization of bovine herpesvirus 1 gE and gI membrane proteins. *Journal of Virology* **70**: 7878–7884.

Wilbur LA, Evermann JF, Levings RL, Stoll IR, Starling DE, Spillers CA, Gustafson GA and McKeirnan AJ (1994). Abortion and death in pregnant bitches associated with a canine vaccine contaminated with bluetongue virus. *Journal of the American Veterinary Medical Association* **204**: 1762–1765.

Wilkins PA, Henninger R, Reed SM and Del Piero F (2003). Acyclovir as treatment for EHV-1 myeloencephalopathy. *American Association of Equine Practitioners Proceedings* **49**: 394–396.

Wilson E, Hedges JF, Butcher EC, Briskin M and Jutila MA (2002). Bovine $\gamma\delta$ T cell subsets express distinct patterns of chemokine responsiveness and adhesion molecules: a mechanism for tissue-specific $\gamma\delta$ T cell subset accumulation. *Journal of Immunology* **169**: 4970–4975.

Winkler MTC, Doster A and Jones C (1999). Bovine herpesvirus 1 can infect CD4+ T lymphocytes and induce programmed cell death during acute infection of cattle. *Journal of Virology* **73**: 8657–8668.

Wuyckhuise L, Van Bosch J, Franken P, Hage J, Verhoeff J and Zimmer G (1994). The prevalence of infectious bovine rhinotracheitis (IBR) in the Netherlands. In: *18th World Buiatrics Congress*, Bologna, Italy, pp. 1439–1442.

Wyler R, Engels M and Schwyzer M (1989). Infectious bovine rhinotracheitis/vulvovaginitis (BHV-1). In: Wittmann G (ed.) *Herpesvirus Diseases of Cattle, Horses and Pigs*. Boston, MA: Kluwer Academic, pp. 1–72.

Yan BF, Chao YJ, Chen Z, Tian KG, Wang CB, Lin XM, Chen HC and Guo AZ (2008). Serological survey of bovine herpesvirus type 1 infection in China. *Veterinary Microbiology* **127**: 136–141.

Zakhartchouk AN, Pyne C, Mutwiri GK, Papp Z, Baca-Estrada ME, Griebel P, Babiuk LA and Tikoo SK (1999).

Mucosal immunization of calves with recombinant bovine adenovirus-3: induction of protective immunity to bovine herpesvirus-1. *Journal of General Virology* **80**: 1263–1269.

Zhao X and Xi J (2011). The vaccines for bovine herpesvirus type 1: a review. *African Journal of Biotechnology* **10**: 10072–10075.

Zhao Y, Kacskovics I, Rabbani H and Hammarström L (2003). Physical mapping of the bovine immunoglobulin heavy chain constant region gene locus. *Journal of Biological Chemistry* **278**: 35024–35032.

Zhou EM and Afshar A (1995). Comparison of Freund's adjuvant and TiterMax in inducing anti-idiotype to idiotypic antibodies against pseudorabies virus antigens. *Veterinary Immunology and Immunopathology* **48**: 113–122.

Zimin AV, Delcher AL, Florea L, Kelley DR, Schatz MC, Puiu D, Hanrahan F, Pertea G, Van Tassell CP, Sonstegard TS, Marçais G, Roberts M, Subramanian P, Yorke JA and Salzberg SL (2009). A whole-genome assembly of the domestic cow, *Bos Taurus*. *Genome Biology* **10**: R42. doi:10.1186/gb-2009-10-4-r42b.