Chapter 3
Vaccines and Vaccination

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Abstract Livestock vaccines aim to increase livestock product and improve the health and welfare of livestock animals in a cost-efficient manner and prevent disease transmission. Successful livestock vaccines have been generated for pathogens including bacterial, viral, protozoan, and multicellular pathogens. These livestock vaccines have a significant effect on animal health and products and on human health through growing safe food procurement and preventing zoonotic diseases. There are successful production of biotechnological-based animal vaccines licensed for use that include virus-like particle vaccines, gene-deleted marker vaccines, subunit vaccines, DIVA vaccines, and DNA vaccines.

Keywords Vaccines · Livestock · DIVA · Marker vaccines · DNA vaccines · Subunit vaccine · VLPs · Gene-deleted vaccines · Virus-like particles

The vaccine against rinderpest is considered a milestone in the history of veterinary vaccine production (van Gelder and Makoschey 2012). In 2011, Rinderpest, a deadly animal disease, was eradicated from the world. There is only one similar example for eradicated disease, that is smallpox in humans. The World Organization for Animal Health (OIE), is currently working on strategies to control other terrible infections including peste des petits ruminants (PPR), foot-and-mouth disease (FMD), and rabies. The global eradication of rinderpest has been a remarkable achievement for veterinary science. With the eradication of rinderpest in live animals livestock production in the world has become safer and livestock industries are less at risk (World Organization for Animal Health [OIE]).

Currently, there are no vaccines for several globally significant infections. The main problem is the complexity of correlates of protection. The other is difficulty in constructing the correct presentation of antigens for many of these lacking vaccines. Luckily, molecular technology has offered many new tools for developing vaccines (Plotkin 2008). Modern vaccines are based on the scientific progress in virology,

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cell biology, and immunology (van Gelder and Makoschey 2012). These molecular equipment and knowledges may enable the scientist to make more use of cellular and humoral immune responses to antigens that are the main features for achievement of vaccines now (Plotkin 2008).

There are successful production of biotechnological-based vaccines used in protection against diseases, produced for use. These are virus-like particle, gene-deleted marker, subunit, DIVA, and DNA vaccines.

This chapter reviews the literature concerning the usefulness of livestock vaccination against and biotechnologies in vaccine development.

3.1 DNA Vaccines

DNA vaccination presents a new simple concept in vaccination strategy. It is an antigen-encoding bacterial plasmid that produces an immune response when inoculated into a suitable host (Garmory et al. 2003; Josefsberg and Barry 2012). Potential applications of plasmid DNA and other gene therapy approaches have been a matter of debate for a long time (Wolff et al. 1990). DNA vaccination elicits neutralizing antibodies and induces T helper cell response of Th1 phenotype and cytotoxic T-lymphocyte response (Donnelly et al. 1997).

Immunization is carried out via ingestion of purified plasmid in the host cells and T cell recognition of antigen-presenting cells (APC) depends on their expression of a spectrum of peptides bound to class I and II major histocompatibility complex (MHC) molecules. Subsequent protein expression results in the presentation of normal or modified forms of the protein to the immune system (World Organization for Animal Health [OIE]).

DNA vaccines have more advantages than other vaccines. The first advantage is that DNA vaccines promote humoral immune response and cell-mediated immune response. These two responses are so critical that also known DNA vaccines can induce long-term immunity in many diseases. This has become a requirement for vaccine efficacy. DNA vaccines are easy to produce and purify, and this has enabled the production and evaluation of new DNA vaccines in animal models within months. Another advantage is the long shelf life of DNA vaccines and the capability to transport (no need to cold chain). Various studies, including on humans, show the reliability of DNA vaccines (Bagarazzi et al. 1998; Kim et al. 2001). DNA vaccinations have proved in rodents as efficient. Studies on DNA vaccination are continued even in outbred species (Carvalho et al. 2009; Redding and Weiner 2009). Currently, four DNA vaccines have been licensed for veterinary use. One is for swine in Australia, for growth of hormone releasing hormone, the other is against infectious hematopoietic necrosis virus for salmon in Canada, and the others are against west nile virus (WNV) for horses and melanoma for dogs in the USA (Kutzler and Weiner 2008).

Optimization at various levels is required in large animal species to succeed for higher influence. These include vector modifications, DNA submission paths and

procedure, addition of adjuvants, and antigen targeting to APC. Inadequate benefit of DNA vaccines in large animals is likely caused by ineffective transfection of the administered plasmids. The inefficiency of the vaccine interferes with sufficient induction of development of the immunity (Rao et al. 2009).

Protective immunity has been accomplished with DNA vaccines with Pestivirus glycoprotein E2, which is the major protective antigen for bovine viral diarrhea virus (BVDV) in cattle, and classical swine fever virus (CSFV) in pigs. In poultry, the possiblity of DNA vaccination against flu using plasmids coding for hemagglutinin (HA), the main target for neutralizing antibodies, alone or in mixture with nucleoprotein (NP), the primary target of the cytotoxic lymphocyte (CTL) response, has been established by several studies (Brun et al. 2011). Vaccines induce immunogenicity and enable protection with plasmid DNA against BHV in mice (Cox et al. 1993), malaria in mice (Mor et al. 1995; Sedegah et al. 1994), hepatitis B in chimpanzees (Davis et al. 1996), human immunodeficiency virus in rhesus monkeys (Lekutis et al. 1997), influenza A virus in ferrets (Donnelly et al. 1995), *Mycobacterium tuberculosis* in mice (Lowrie et al. 1994; Lynch et al. 2011), and genital herpes simplex virus in guinea pigs (Bourne et al. 1996).

Apart from these trials, recently, DNA vaccines have entered phase I human clinical trials for protection against HIV, malaria, and influenza.

DNA vaccines against many diseases are evaluated in experimental studies and animal models.

Real-time PCR and histopathological examination confirmed that only low viral DNA loads and mild histopathological lesions appeared in pORF2-immunized mice following virus challenge to show protective immunity against porcine circovirus 2 by vaccination with ORF2-based DNA and subunit vaccines in mice (Shen et al. 2008).

Bovine leukemia virus (BLV) envelope gene encoding extracellular and transmembrane glycoprotein gp51 and gp30 was cloned into vector under Human cytomegalovirus (CMV) intermediate early promoter for DNA vaccine construction. Cellular immune response was promoted when the intramuscular administration of this plasmid vector was done (Brillowska et al. 1999). In another study, BLV transactivator Tax cloned into Mammalian cell expression plasmid pME18-Neo showed that Th1 type immune response induced by Tax DNA vaccine inhibited BLV propagation in vaccinated sheep at the early phase of infection (Usui et al. 2003).

Gogev et al. (2002) showed the efficacy of Bovine herpesvirus 1 DNA vaccine in cattle. In the study Bovine herpesvirus 1 glycoprotein C was used as antigen. In calves, the administration of recombinants Ad5CMVgD and/or Ad5CMVgC, or a composition of them, increase Bovine herpesvirus 1 neutralizing antibody responses and presented protection against challenge with BHV-1 Iowa strain (Gogev et al. 2002).

Another research made on Bovine herpesvirus 1 DNA vaccine using Vector pBISIA88 expressed glycoprotein D (gD) (Pontarollo et al. 2002) and Vector pMASIA expressed full-length BHV-1 gB (Huang et al. 2005).

Schrijver et al. (1997) prepared a DNA vaccine by which the gE gene was changed by a gene encoding the G protein of Bovine Respiratory Syncytial Virus (BRSV) in a bovine herpesvirus 1 vector. As a result of the study the G protein of BRSV can stimulate considerable protection for BRSV infection in cattle, and the BHV1/BRSV-G vaccine protects powerfully against a subsequent BRSV and Bovine herpesvirus 1 infection (Schrijver et al. 1997).

Vaccination and also poultry flock management are very important. Vaccine research and currently available commercial vaccine numbers are increasing day-by-day.

Sakaguchi et al. (1996) generated a plasmid vector expressing the Newcastle disease virus F protein (NDV-F) under the control of the human cytomegalovirus immediate early enhancer and chicken beta-actin gene promoter. Their results exhibit that the DNA vaccine is useful against the Newcastle disease (Sakaguchi et al. 1996).

Park et al. (2006) generated a chimeric Avian Influenza Virus (AIV). This virus expressed the ectodomain of the hemagglutinin-neuraminidase gene in place of the neuraminidase protein of the H5N1 AIV. A single vaccination of chickens with this improved vaccine prototype virus induced strong immunity against H7N7, highly pathogenic AIV, and against Newcastle disease Virus (Park et al. 2006). Park et al. (2006) proposed that chimeric constructs should be developed for convenient, inexpensive, and effective immunization against Newcastle disease and avian influenza in poultry (Park et al. 2006).

DNA vaccines are evaluated not only for protection against viral or bacterial diseases but also against protozoan diseases that are associated with abortions in cattle.

Various experimental studies exist for protozoan diseases, one of which is recombinant DNA vaccine with NcSAG1 and NcSRS2 proteins against *Neospora caninum* for C57BL/6 mice (Cannas et al. 2003).

Results suggested highly significant protective effect with combined DNA (based on NcSAG1)/recombinant antigen vaccine (based on NcSRS2) in cerebral neosporosis in mice (Cannas et al. 2003).

3.2 Gene-Deleted Vaccines

The availability of recombinant DNA technology and the knowledge of specific virulence factors of the pathogens have further facilitated the use of gene-deleted pathogens as vaccines. In gene-deleted pathogens, the pathogenicity and virulence are decreased without affecting immunogenicity. Gene-deleted agents cannot cause disease; however, immunogenic features are the same as in wild-type. Such agents must be genetically stable, easily reproducible, and easy to manipulate organisms. Vaccine strains of bacterial pathogens have been created that provide better protection than inactivated or killed vaccines. Gene-deleted vaccine technology is also used in marker vaccines that are used to differentiate between infected animals from

vaccinated animals. Gene-deleted Salmonella enterica serovar typhimurium and serovar enteritidis have been licensed for use in poultry (Babu et al. 2004; Meeusen et al. 2007).

In pigs, pseudorabies virus marker vaccine generated a double gene (gE and TK) deleted virus (Ferrari et al. 2000; Meeusen et al. 2007). Also in cattle, BHV-1 virus marker vaccine produced gE deleted (Meeusen et al. 2007; van Oirschot et al. 1996). Another gene-deleted vaacine is against to Streptococcus equi. In horses, Streptococcus equi vaccine generated aroA gene deleted has been licensed (Jakobs et al. 2000; Meeusen et al. 2007).

Widjojoatmodjo et al. (2000) showed the possibility of generating deletion mutant viruses lacking the entire E2 or E^{rns} for CSFV. These mutants have the ability to develop in competent cell lines. So, they are safe vaccines. The mutant viruses stimulated powerful immuno response. The immune response comprise without generating new viral progeny (Widjojoatmodjo et al. 2000). Related strategies have been used to build up several chimaeras by exchanging the E2 or the E^{rns} proteins from the attenuated C strain of CSFV with those from antigenically related pestiviruses (Van Gennip et al. 2000).

The use of conventional vaccines against infectious bovine rhinotracheitis (IBR) does not seem to have consequenced in decrease of the prevalence of the disease. BHV1 marker vaccines comprise mutant in deletion of glycoproteins included genes which is nonessential. These marker vaccines can be used as diagnostic tests to separate cattle infected or vaccinated with marker vaccine (van Oirschot et al. 1996). One of them is the Bovilis IBR Marker for cattle distributed by Intervet.

3.3 Virus-like Particles

Virus-like particles (VLPs) involve one or more recombinant proteins. They have supramolecular structures. These particles are 20–100 nm in size. They have icosahedral or rod-like structure (Jennings and Bachmann 2008). VLPs are vaccine antigens and increase immunogenicity of the vaccine via their particulate structure. This offers an advantage for VPLs (Brun et al. 2011). VLPs can be used as a vaccine or as a carrier for genetically modified antigens and have been studied for more than two decades. Hepatitis B virus (Zuckerman 2006) and human papillomavirus (Stanley 2008) vaccines are commercially presented. Studies are underway to develop vaccines against bluetongue virus, Rotavirus, and Parvovirus for veterinary application. VLPs have many advantages as a vaccine. They have high safety profile feature. Also, they have similarity to bacterial and viral structures and capability for large-scale production. The other advantage is the possibility of combining with other vaccine adjuvants.

VLPs induce strong and rapid antibody response. Induction of T-independent IgM responses activated by B cell activation via B cell receptor activation via vaccine antigens cross links (Bachmann and Zinkernagel 1996; Brun et al. 2011; Thyagarajan et al. 2003).

VLPs are also processed as if they are exogenous antigens and presented by MHC class II molecules for helper T cell activation (Pejawar-Gaddy et al. 2010; Win et al. 2011).

Thus, the complement system activates and results in elevated phagocytosis. Strong immune response is further enhanced by the uptake of the particulate structure of VLPs by APC.

It was demonstrated that particulated antigens are much efficient than soluble antigens in inducing immune response (Lenz et al. 2001).

CpG ODN and single-stranded RNA can be successfully combined with VLPs as a molecular adjuvant. Dendritic cells Stimulated by certain VLPs directly, for example, papillomavirus VLPs.

Bovine rotavirus virus has VLPs and they are highly immunogenic and has elicited protection against infections (Redmond et al. 1993).

Other examples of vaccinations with VLPs include hepatitis B surface antigen VLPs (HBsAg-VLP), HIV 1, DV (dengue virus), Norovirus, and influenza A VLPs.

Many animal virus VLPs have been derived as an immunogenic. Examples for these VLPs include NDV, Porcine parvovirus (PPV), Rift Valley fever virus (RVFV) VLPs, Porcine circovirus VLPs, AIV, and bluetongue virus (BTV) VLPs (Jeoung et al. 2011; Lynch et al. 2011).

Many of these VLPs induce neutralizing antibodies and are protective in animal models.

Roy (2004) showed the immune protective effects of high immunogenic VLPs produced against bluetongue virus in sheep (Roy 2004). Stewart et al. (2010) demonstrated that bluetongue virus VLPs were to be safe, highly effective, immunogens in sheep, reducing post-challenge viraemia to level below the threshold molecular detection limits (Stewart et al. 2010).

VLPs vaccines currently are not available in veterinary field. It is anticipated that VLP vaccines are to be developed for use in this field in the near future.

3.4 Subunit Vaccines

Two technologies used in vaccine production offer useful antigenic structures for the induction of satisfactory immune response. These include live-attenuated and inactivated or subunit vaccines. Live-attenuated vaccines are effective; however, they always possess some risks. The major advantage of inactivated and subunit vaccines are that they are safe to use (Day and Schultz 2011). Despite this advantage, limited efficacy and limited immunization limit the use of such vaccines. DNA vaccines offer a new and strong approach over subunit vaccines (den Hurk et al. 2000).

Subunit vaccines consist of semi-pure or purified proteins. Subunit vaccines have been produced by recombinant DNA technology since the 1990s and commercially available since the 1980s (Cohen 1993; Rhodes et al. 1994; Ulmer et al. 1993, 1995). Since the first bacterial genome was sequenced in 1995, genome

sequences were obtained for a number of bacterial, viral, and parasite genomes. However, the development of the bioinformatics resources and tools required to analyze these genomes allowed identification of surface exposed antigens, specific B, and T cell epitopes.

Subunit antigen productions can be obtained by both biochemical and DNA technologies. Biochemical techniques used in the production of subunit vaccines are useful where recombinant expression is not appropriate. This can be shown in fimbria of the bacteria. *Campylobacter jejuni* glycosylates many surface proteins and, therefore, they are best produced in *C. jejuni* rather than heterologous expression systems. This also applies for *Escherichia coli* that shows similar features (Wacker et al. 2002).

Escherichia coli K99 vaccine for calf scours could be one of the best examples of subunit vaccines (Acres et al. 1979).

Another example is the baculovirus used vaccine to porcine circovirus type 2 (Fachinger et al. 2008).

Subunit vaccines offer some advantages. First, they stimulate strong humoral and cell-mediated immune response. They are considerably safe. They can be combined with other subunit vaccines.

In some occasions, subunit vaccines require adjuvants to induce a better immune response. Some glycoprotein production is costly with subunit vaccines. Subunit vaccines compatible with DIVA strategies. In bovine herpes virus, glycoprotein gD has been successfully used in subunit vaccine. Although immunization with gD has proven to be partially effective, it has not reduced the prevalence of the virus in the field, thus limiting its use (Harland et al. 1992; van Drunen Littel-van den Hurk et al. 1997).

Another research for Bovine Herpes virus 1 vaccination showed the subunit gD- and tgD-vaccinated calves shed significantly lower amounts of virus than the placebo or killed virus-immunized groups throughout the follow-up period. In the gD and tgD subunit vaccine vaccinated groups only one out of eight animals shed virus (van Drunen Littel-van den Hurk et al. 1997).

A licensed porcine circovirus 2 vaccine is reported as a characteristic in inactivated baculovirus expressed PCV2 ORF2 protein in pigs by Intervet as a brand name Porcilis-PCV2 (Blanchard et al. 2003). Another licensed porcine circovirus 2 vaccine is Suvaxyn PCV2 by Fort Dodge using the Inactivated PCV1-2 chimera (Fenaux et al. 2004). Licensed vaccine against Pseudorabies virus for pigs is Suvaxyn Aujeszky distributed by Fort Dodge. The characteristic of vaccine is being a IgE- and thymidine kinase-deleted marker vaccine (Ferrari et al. 2000). CSFV infection continues to be a subject in the studies exploring successful and effective vaccines. Vaccines are commercially available. The first one is Intervet and the other is Bayer. Baculovirus recombinant E2 protein has been used in the vaccines of both companies (van Aarle 2003).

Many subunit vaccines have been tested all of which are not commercially available. These include vaccines against respiratory and enteric viruses, BVDV, BRSV, PI3, rotavirus, and coronavirus. Success of bacterial subunit vaccines over viral subunit vaccines results from recombinant and conventional production costs.

Recombinant vaccines prepared against respiratory system pathogens are commercially available. These include vaccines against *Mannheimia haemolytica* and *Actinobacillus pleuropneumoniae*. These vaccines have been formulated from leucotoxins and transferrin-binding proteins of these bacteria. Vaccine prepared for atrophic rhinitis has been formulated with nontoxic *Pasteurella multocida* dermonecrotic toxin. This toxin has been produced together with genetically modified *E. coli* strain and conventional *B. bronchiseptica* bacterin (Shewen and Wilkie 1982).

Live-attenuated vaccines for classical swine flu (CSF) have a rapid onset of immunity and are effective at preventing transmission of infection (Van Oirschot 2003). The only disadvantage is that vaccinated pigs cannot be differentiated from infected pigs. Vaccine studies following DIVA are ongoing for classical swine flu (CSF).

3.5 DIVA Vaccines (Marker Vaccines)

Vaccines have been developed for many viral diseases occurring in farm animals. However, these vaccines interfere with the surveillance of the disease in serological tests and the individual country may lose its "free from infection" status. The most prominent example is the FMD that occurs in cattle. Many vaccines are available for use against FMD. These vaccines are used in disease control (Doel 2003); however, they are not used in FMD free countries.

Marker vaccines have been developed for use in diagnostic tests by deleting a certain gene of pathogen (DIVA-differentiating infected from vaccinated animals). Antibody is not produced against the deleted gene of the pathogen. Therefore, it is possible to differentiate vaccinated from infected animals (van Oirschot 1999). Many DIVA vaccines and diagnostic test kits for these vaccines have been developed. DIVA vaccines are used and developed against many diseases important for farm animals such as IBR, pseudorabies, classical swine fever (CSF), and FMD.

Originally this term was applied to gene-deleted marker vaccines for large DNA viruses when used with their vaccine specific serological tests, but it can also apply to subunit vaccines, heterologous vaccines, or some killed whole pathogen vaccines such as the highly purified FMD vaccine, which is used in conjunction with nonstructural protein-based serological tests (Ahrens et al. 2000; Capua et al. 2003; de Smit et al. 2001; Sorensen et al. 1998).

Numerous strategies have been used to develop DIVA vaccines against CSFV, with variable achievement regarding their capacity to reduce viral replication in animals or to avoid transplacental transmission of the virus. These vaccines include full-length CSFV E2 glycoprotein or fractions, mainly (Hammond et al. 2000, 2001).

Glycoprotein E (gE)-deleted DIVA vaccine for IBR has been developed with European conventional methodology (van Oirschot et al. 1996). gE protein gene is not required for viral replication of IBR. However, this gene plays an important role

to spread across the host cells. ELISA technique and PCR amplification have been developed for diagnostic tests of gE-deleted DIVA vaccine (Perrin et al. 1996; Schynts et al. 1999). DIVA strategy developed by deletion of gE gene is also used for Aujeszky's disease (Pensaert et al. 2004).

DIVA vaccine developed for classical swine flu (CSF) has been produced in viral envelope glycoprotein E2 protein baculovirus/insect cell system and formulated with adjuvant. ELISA diagnostic kit has also been produced for this DIVA vaccine (Moormann et al. 2000; van Aarle 2003). As usual, DIVA vaccines have some disadvantages compared to conventional live or attenuated vaccines (Beer et al. 2007).

The host body must be exposed to more than one epitope of the pathogen in order to induce a strong immune response. With this purpose, studies have focused to develop vaccines combining capsid proteins (Grubman 2005).

In many diseases, DIVA vaccine is needed for surveillance or epidemiological data. These particularly include peste des petits ruminants virus, bluetongue virus in cattle, NDV and AIV in poultry, and bovine viral diarrhea virus.

References

Acres SD, Isaacson RE, Babiuk LA, Kapitany RA (1979) Immunization of calves against enterotoxigeniccolibacillosis by vaccinating dams with purified K99 antigen and whole cell bacterins. Infect Immun 25:121–126

Ahrens U, Kaden V, Drexler C, Visser N (2000) Efficacy of the classical swine fever (CSF) marker vaccine PorcilisPesti in pregnant sows. Vet Microbiol 77:83–97

Babu U, Dalloul RA, Okamura M, Lillehoj HS, Xie H, Raybourne RB, Gaines D, Heckert R (2004) Salmonella enteritidis clearance and immune responses in chickens following Salmonella vaccination and challenge. Vet Immunol Immunopathol 101:251–257

Bachmann MF, Zinkernagel RM (1996) The influence of virus structure on antibody responses and virus serotype formation. Immunol Today 17:553–558

Bagarazzi ML, Boyer JD, Ugen KE, Javadian MA, Chattergoon M, Shah A, Bennett M, Ciccarelli R,Carrano R, Coney L, Weiner DB (1998) Safety and immunogenicity of HIV-1 DNA constructs in chimpanzees. Vaccine 16:1836–1841

Beer M, Reimann I, Hoffmann B, Depner K (2007) Novel marker vaccines against classical swine fever. Vaccine 25(30):5665–5670

Blanchard P, Mahe D, Cariolet R, Keranflec'h A, Baudouard MA, Cordioli P, Albina E, Jestin A (2003) Protection of swine against postweaning multisystemic wasting syndrome (PMWS) by porcine circovirus type 2 (PCV2) proteins. Vaccine 21:4565–4575

Bourne N, Stanberry LR, Bernstein DI, Lew D (1996) DNA immunization against experimental genital herpes simplex virus infection. J Infect Dis 173:800–807

Brillowska A, Dabrowski S, Rułka J, Kubiś P, Buzała E, Kur J (1999) Protection of cattle against bovine leukemia virus (BLV) infection could be attained by DNA vaccination. Acta Biochimica Polonica 46(4): 971–976

Brun A, Barcena J, Blanco E, Borrego B, Dory D, Escribano JM, Le Gall-Recule G, Ortego J, Dixon LK (2011) Current strategies for subunit and genetic viral veterinary vaccine development. Virus Res 157:1–12

Cannas A, Naguleswaran A, Müller N, Eperon S, Gottstein B, Hemphill A (2003) Vaccination of mice against experimental *Neosporacaninum* infection using NcSAG1- and NcSRS2-based recombinant antigens and DNA vaccines. Parasitol 126:303–312

Capua I, Terregino C, Cattoli G, Mutinelli F, Rodriguez JF (2003) Development of a DIVA (differentiating infected from vaccinated animals) strategy using a vaccine containing a heterologous neuraminidase for the control of avian influenza. Avian Pathol 32:47–55

Carvalho JA, Prazeres DM, Monteiro GA (2009) Bringing DNA vaccines closer to commercial use. IDrugs 12:642–647

Cohen J (1993) Naked DNA points way to vaccines. Science 259:1745–1749

Cox G, Zamb TJ, Babiuk LA (1993) Bovine herpes virus-1 immune responses in mice and cattle injected with plasmid DNA. J Virol 67:5664–5667

Davis HL, McCluskie MJ, Gerin JL, Purcell RH (1996) DNA vaccine for hepatitis B: evidence for immunogenicity in chimpanzees and comparison with other vaccines. Proc Natl Acad Sci 93:7213–7218

Day MJ, Schultz RD (2011) Veterinary immunology: principles and practice. Manson Publishing, London, pp 192–196

de Smit AJ, Bouma A, de Kluijver EP, Terpstra C, Moormann RJ (2001) Duration of the protection of an E2 subunit marker vaccine against classical swine fever after a single vaccination. Vet Microbiol 78:307–317

den Hurk SDL, Braun RP, Babiuk LA (2000) Veterinary DNA vaccines, methods in molecular medicine, vol 29. In: Lowrie DB, Whalen RG (eds) DNA vaccines: methods and protocols. Humana Press Inc., Totowa

Doel TR (2003) FMD vaccines. Virus Res 91:81–99

Donnelly JJ, Friedman A, Martinez D, Montgomery DL, Shiver JW, Motzel S, UlmerJB Liu MA (1995) Preclinical efficacy of a prototype DNA vaccine: enhanced protection against antigenic drift in influenza virus. Nat Med 1:583–587

Donnelly JJ, Ulmer JB, Shiver JW, Liu MA (1997) DNA vaccines. Annu Rev Immunol 15:617–648

Fachinger V, Bischoff R, Jedidia SB, Saalmüller A, Elbers K (2008) The effect of vaccination against porcine circovirus type 2 in pigs suffering from porcine respiratory disease complex. Vaccine 26:1488–1499

Fenaux M, Opriessnig T, Halbur PG, Meng XJ (2004) A chimeric porcine circovirus (PCV) with the immunogenic capsid gene of the pathogenic PCV type 2 (PCV2) cloned into the genomic backbone of the nonpathogenic PCV1 induces protective immunity against PCV2 infection in pigs. J Virol 78:6297–6303

Ferrari M, Brack A, Romanelli MG, Mettenleiter TC, Corradi A, Dal Mas N, Losio MN, Silini R, Pinoni C, Pratelli A (2000) A study of the ability of a TK-negative and gI/gE-negative pseudorabies virus (PRV) mutant inoculated by different routes to protect pigs against PRV infection. J Vet Med B, Infect Dis Vet Public Health 47:753–762

Garmory HS, Brown KA, Titball RW (2003) DNA vaccines: improving expression of antigens. Genet Vaccines Ther 1(1):2

Gogev S, Vanderheijden N, Lemaire M, Schynts F, D'Offay J, Deprez I, Adam M, Eloit M, Thiry E (2002) Induction of protective immunity to bovine herpesvirus type 1 in cattle by intranasal administration of replication-defective human adenovirus type 5 expressing glycoprotein gC or gD. Vaccine 20:1451–1465

Grubman MJ (2005) Development of novel strategies to control foot and mouth disease: marker vaccines and antivirals. Biologicals 33:227–234

Hammond JM, Jansen ES, Morrissy CJ, Goff WV, Meehan GC, Williamson MM, Lenghaus C, Sproat KW, Andrew ME, Coupar BE, Johnson MA (2001) A prime-boost vaccination strategy using naked DNA followed by recombinant porcine adenovirus protects pigs from classical swine fever. Vet Microbiol 80:101–119

Hammond JM, McCoy RJ, Jansen ES, Morrissy CJ, Hodgson AL, Johnson MA (2000) Vaccination with a single dose of a recombinant porcine adenovirus expressing the classical swine fever virus gp55 (E2) gene protects pigs against classical swine fever. Vaccine 18:1040–1050

Harland RJ, Potter AA, van Drunen Littel-van Den Hurk S, Van Donkersgoed J, Parker MD, Zamb TJ, 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. Can Vet J 33:734–741
Huang Y, Babiuk LA, 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. J Gen Virol 86: 887–898
Jakobs AA, Goovaerts D, Nuijten PJ, Theelan RP, Hartford OM, Foster TJ (2000) Investigation towards an efficacious and safe strangles vaccine: submucosal vaccination with a live attenuated Streptococcus equi. Vet Rec 147:563–567
Jennings GT, Bachmann MF (2008) The coming of age of virus-like particle vaccines. Biol Chem 389:521–536
Jeoung HY, Lee WH, Jeong W, Shin BH, Choi HW, Lee HS, An DJ (2011) Immunogenicity and safety of the virus-like particle of the porcine encephalomyocarditis virus in pig. Virology J 8:170
Josefsberg JO, Barry B (2012) Vaccine process technology. Biotechnol Bioeng Spec Issue: CHO Cell Genomics Special Sect 109:1443–1460
Kim JJ, Yang JS, Nottingham LK, Tang W, Dang K, Manson KH, Wyand MS, Wilson DM, Weiner DB (2001) Induction of immune responses and safety profiles in rhesus macaques immunized with a DNA vaccine expressing human prostate specific antigen. Oncogene 20:4497–4506
Kutzler MA, Weiner DB (2008) DNA vaccines: ready for prime time? Nat Rev Genet 9:776–788
Lekutis C, Shiver JW, Liu MA, Letvin NL (1997) HIV-1 env DNA vaccine administered to rhesus monkeys elicits MHC class II-restricted CD4+ T helper cells that secrete IFN-gamma and TNF-alpha. J Immunol 158:4471–4477
Lenz P, Day PM, Pang YY, Frye SA, Jensen PN, Lowy DR, Schiller JT (2001) Papillomavirus-like particles induce acute activation of dendritic cells. J Immunol 166:5346–5355
Lowrie DB, Tascon RE, Colston MJ, Silva CL (1994) Towards a DNA vaccine against tuberculosis. Vaccine 12:1537–1540
Lynch SE, Gilkerson JR, Symes SJ, Huang JA, Tatarczuch L, Hartley CA (2011) Equine rhinitis A virus-like particle expressing DNA vaccine induces a virus neutralising immune response in mice. Virus Res 158:294–297
Meeusen EN, Walker J, Peters A, Pastoret PP, Jungersen G (2007) Current status of veterinary vaccines. Clin Microbiol Rev 20:489–510
Moormann RJ, Bouma A, Kramps JA, Terpstra C, De Smit HJ (2000) Development of a classical swine fever subunit marker vaccine and companion diagnostic test. Vet Microbiol 73:209–219
Mor G, Klinman DM, Shapiro S, Hagiwara E, Sedegah M, Norman JA, Hoffman SL, Steinberg AD (1995) Complexity of the cytokine and antibody response elicited by immunizing mice with *plasmodium yoelii* circumsporozoite protein plasmid DNA. J Immunol 155:2039–2046
Park MS, Steel J, Garcia-Sastre A, Swayne D, Palese P (2006) Engineered viral vaccine constructs with dual specificity: avian influenza and Newcastle disease. Proc Natl Acad Sci USA 103:8203–8208
Pejawar-Gaddy S, Rajawat Y, Hilioti Z, Xue J, Gaddy DF, Finn OJ, Viscidi RP, Bossis I (2010) Generation of a tumor vaccine candidate based on conjugation of a MUC1 peptide to polyionic papillomavirus virus-like particles. Cancer Immunol Immunother 59:1685–1696
Pensaert M, Labarque G, Favoreel H, Nauwynck H (2004) Aujeszky's disease vaccination and differentiation of vaccinated from infected pigs. Dev Biol (Basel) 119:243–254
Perrin B, Perrin M, Moussa A, Coudert M (1996) Evaluation of a commercial gE blocking ELISA test for detection of antibodies to infectious bovine rhinotracheitis virus. Vet Rec 138:520
Plotkin SA (2008) Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis 47:401–409
Pontarollo RA, Babiuk LA, Hecker R, van Drunen Littel-van Den Hurk S (2002) Augmentation of cellular immune responses to bovine herpesvirus-1 glycoprotein D by vaccination with CpG-enhanced plasmid vectors. J Gen Virol 83: 2973–2981
Rao SS, Styles D, Kong W, Andrews C, Gorres JP, Nabel GJ (2009) A gene-based avian influenza vaccine in poultry. Poult Sci 88:860–866
Redding L, Weiner DB (2009) DNA vaccines in veterinary use. Exp Rev Vaccines 8:1251–1276

Redmond MJ, Ijaz MK, Parker MD, Sabara MI, Dent D, Gibbons E, Babiuk LA (1993) Assembly of recombinant rotavirus proteins into virus-like particles and assessment of vaccine potential. Vaccine 11:273–281

Rhodes GH, Abai AM, Margalith M, Kuwahara-Rundell A, Morrow J, Parker SE, Dwarki VJ (1994) Characterization of humoral immunity after DNA injection. Dev Biol Stand 82:229–236

Roy P (2004) Genetically engineered structure-based vaccine for bluetongue disease. Veterinaria Italiana 40:594–600

Sakaguchi M, Nakamura H, Sonoda K, Hamada F, Hirai K (1996) Protection of chickens from Newcastle disease by vaccination with a linear plasmid DNA expressing the F protein of Newcastle disease virus. Vaccine 14:747–752

Schrijver RS, Langedijk JP, Keil GM, Middel WG, Maris-Veldhuis M, Van Oirschot JT, Rijsewijk FA (1997) Immunization of cattle with a BHV1 vector vaccine or a DNA vaccine both coding for the G protein of BRSV. Vaccine 15:1908–1916

Schynts F, Baranowski E, Lemaire M, Thiry E (1999) A specific PCR to differentiate between gE negative vaccine and wildtype bovine herpesvirus type 1 strains. Vet Microbiol 66:187–195

Sedegah M, Hedstrom R, Hobart P, Hoffman, SL (1994) Protection against malaria by immunization with plasmid DNA encoding circumsporozoite protein. Proc Natl Acad Sci 91:9866–9870

Shen HG, Zhou JY, Huang ZY, Guo JQ, Xing G, He JL, Yan Y, Gong LY (2008) Protective immunity against porcine circovirus 2 by vaccination with ORF2-based DNA and subunit vaccines in mice. J Gen Virol 89: 1857–1865

Shewen PE, Wilkie BN (1982) Cytotoxin of Pasteurella haemolytica acting on bovine leukocytes. Infect Immun 35:91–94

Sorensen KJ, Madsen KG, Madsen ES, Salt JS, Nqindi J, Mackay DKJ (1998) Differentiation of infection from vaccination in foot and mouth disease by the detection of antibodies to the non-structural proteins 3D, 3AB and 3ABC in ELISA using antigens expressed in baculovirus. Arch Virol 143:1–16

Stanley M (2008) HPV vaccines: are they the answer? Br Med Bull 88:59–74

Stewart M, Bhatia Y, Athmaran TN, Noad R, Gastaldi C, Dubois E, Russo P, Thiery R, Sailleau C, Breard E, Zientara S, Roy P (2010) Validation of a novel approach for the rapid production of immunogenic virus-like particles for bluetongue virus. Vaccine 28:3047–3054

Thyagarajan R, Arunkumar N, Song W (2003) Polyvalent antigens stabilize B cell antigen receptor surface signaling microdomains. J Immunol 170:6099–6106

Ulmer JB, Donnelly JJ, Deck RR, Dewitt CM, Liu MA (1995) Immunization against viral proteins with naked DNA. Ann NY Acad Sci 772:117–125

Ulmer JB, Donnelly JJ, Parker SE, Felgner PL, Rhodes GH, Dwarki VJ, Gromkowski SH, Deck RR, Dewitt CM, Friedman A et al (1993) Heterologous protection against influenza by injection of DNA encoding a viral protein. Science 259:1691–1692

Usui T, Konnai S, Tajima S, Watarai S, Aida Y, Ohashi K, Onuma M (2003) Protective effects of vaccination with bovine leukemia virus (BLV) Tax DNA against BLV infection in sheep. J Vet Med Sci/Japan Soc Vet Sci 65:1201–1205

van Aarle P (2003) Suitability of an E2 subunit vaccine of classical swine fever in combination with the E(rns)-marker-test for eradication through vaccination. Dev Biol (Basel) 114:193–200

van Drunen Littel-van den Hurk S, Tikoo SK, van den Hurk JV, Babiuk LA, Van Donkersgoed J (1997) Protective immunity in cattle following vaccination with conventional and marker bovine herpesvirus-1 (BHV1) vaccines. Vaccine 15:36–44

Van Gelder P, Makoschey B (2012) Berliner und Munchener Tierarztliche Wochenschrift, Production of viral vaccines for veterinary use

Van Gennip HG, Van Rijn PA, Widjojoatmodjo MN, De Smit AJ, Moormann RJ (2000) Chimeric classical swine fever viruses containing envelope protein E(RNS) or E2 of bovine viral diarrhoea virus protect pigs against challenge with CSFV and induce a distinguishable antibody response. Vaccine 19:447–459

van Oirschot JT (1999) DIVA, vaccines that reduce virus transmission. Biotechnol 73:195–205

Van Oirschot JT (2003) Vaccinology of classical swine fever: from lab to field. Vet Microbiol 96:367–384

van Oirschot JT, Kaashoek MJ, Rijsewijk FA (1996) Advances in the development and evaluation of bovine herpesvirus 1 vaccines. Vet Microbiol 53:43–54

Wacker M, Linton D, Hitchen PG, Nita-Lazar M, Haslam SM, North SJ, Panico M, Morris HR, Dell A, Wren BW, Aebi M (2002) N-linked glycosylation in Campylobacter jejuni and its functional transfer into E. coli. Science 298:1790–1793

Widjojoatmodjo MN, van Gennip HG, Bouma A, van Rijn PA, Moormann RJ (2000) Classical swine fever virus Erns deletion mutants: trans-complementation and potential use as nontransmissible, modified, live-attenuated marker vaccines. J Virol 74:2973–2980

Win SJ, Ward VK, Dunbar PR, Young SL, Baird MA (2011) Cross-presentation of epitopes on virus-like particles via the MHC I receptor recycling pathway. Immunol Cell Biol 89:681–688

Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, Felgner PL (1990) Direct gene transfer into mouse muscle in vivo. Science 247:1465–1468

World Organization for Animal Health (OIE) Available at: http://www.oie.int/en/for-the-media/press-releases/detail/article/no-more-deaths-from-rinderpest/

Zuckerman JN (2006) Vaccination against hepatitis A and B: developments, deployment and delusions. Curr Opin Infect Dis 19:456–459