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Vaccine 26 (2008) 6508–6528

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Antigen delivery systems for veterinary vaccine development Viral-vector based delivery systems

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ARTICLE INFO

Article history:
Received 12 July 2008
Received in revised form 21 August 2008
Accepted 16 September 2008
Available online 7 October 2008

Keywords:
Antigen delivery systems
Veterinary vaccines
Modified live virus
Viral vectors
Poxvirus vectors
Herpesvirus vectors
Adenovirus vectors
Baculovirus vectors
Positive strand RNA virus vectors
Negative strand RNA virus vectors

ABSTRACT

The recent advances in molecular genetics, pathogenesis and immunology have provided an optimal framework for developing novel approaches in the rational design of vaccines effective against viral epizootic diseases. This paper reviews most of the viral-vector based antigen delivery systems (ADSs) recently developed for vaccine testing in veterinary species, including attenuated virus and DNA and RNA viral vectors. Besides their usefulness in vaccinology, these ADSs constitute invaluable tools to researchers for understanding the nature of protective responses in different species, opening the possibility of modulating or potentiating relevant immune mechanisms involved in protection.

Contents

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doi:10.1016/j.vaccine.2008.09.044

1. Introduction

Vaccination, besides early detection and warning systems, remains the most cost-effective means to prevent the spread of viral infectious diseases. For many years considerable scientific effort has been directed towards the development of novel vaccine technologies, mainly aimed at improving the performance and safety of classical vaccines, either inactivated or based on modified live virus. Many delivery systems provide powerful platforms to check the immunogenicity or to trigger specific immune responses against target antigens, as well as to unveil the immune mechanisms involved in protection against disease. The current knowledge in viral DNA and RNA vectors as carriers of foreign antigens, illustrates many of the potential approaches for antigen delivery and development of veterinary vaccines. Considerations for development of veterinary vaccines differ from those for humans in some respects. One of the most important of these is the cost since, depending on the species vaccinated, high cost may preclude the use of certain types of vaccine. The requirement for vaccine boosts of course contributes greatly to the cost. Of increasing importance in design of veterinary vaccines is the ability to distinguish between infected and vaccinated animals (DIVA). This is particularly important in eradication campaigns since it enables countries to gain a disease free status more readily. Other considerations, particularly for disease outbreaks, are the time taken to induce protection and the potential for environmental spread of the vaccine including in non-target species. Particular challenges for development of veterinary vaccines are the limited fundamental knowledge and reagents to study protective immune responses in veterinary species.

Interestingly, the first vaccine ever used became one of the most widely used systems for vaccine antigen delivery, the poxvirus vectors. Since then, many other DNA viruses, including adenoviruses, herpesviruses and baculoviruses, have proven very useful in development of vaccination approaches. More recently, the refinement of reverse genetics technologies allowed the rescue of attenuated RNA viruses and their use as potential expression or delivery vectors.

This paper reviews those delivery systems based on viral vectors that are commonly used for basic and applied veterinary vaccine research.

2. Modified virus as antigen delivery systems

Live attenuated vaccines were the first form of vaccine and these have been successfully used for many years. These have targeted not only a number of the most economically important animal diseases but also companion animal diseases. The advances in molecular biology in recent years have allowed some of the problems and concerns encountered in developing and using live attenuated vaccines to be addressed.

A live attenuated virus vaccine is a live virus that has lost its virulence while maintaining its ability to induce protective immunity against the virulent virus. They have many advantages over inactivated/killed virus or component vaccines and these include the fact that most if not all of the virus proteins are expressed, presenting a broad spectrum of epitopes to the immune system. Moreover, since these virus proteins are expressed inside the cell, they are presented in association with MHC Class I molecules and stimulate a cytotoxic T cell response. In addition they can be administrated through the natural route of infection, such as via nasal mucosa (e.g. influenza) and mimic the infection at a local site. They are able to induce effective and long lasting, appropriate, humoral and cell-mediated immune responses [1,2], as well as inducing innate immune responses. Other advantages of live attenuated virus vaccines include their low reactivity, the induction of a systemic response, which leads to enhanced protection against disease, their induction of a mucosal response and, importantly for the pharmaceutical companies, they have relatively low manufacturing costs as they require only minimal downstream processing and require no adjuvants in the formulation. However, given all these advantages live attenuated vaccines cannot be considered an ideal vaccine due to their overall safety profiles [3] such as being potentially genetically unstable, and they may cause problems in immunocompromised hosts or in pregnancy (e.g. Rubella). A recent example was the use of monovalent BTV16 vaccine in Italy, in 2004, which caused undesirable effects, attributed to inadequate attenuation to European sheep [4].

Live attenuated virus vaccines are prepared either from a naturally occurring virus from another species (e.g. Jenner's cowpox) or are artificially attenuated. The traditional methodology for producing a live attenuated vaccine often involved the blind serial passage of a virulent isolate in heterologous tissues (cell culture, eggs or laboratory animals) until an attenuated mutant is produced. Other methods for producing an attenuated virus are the generation of mutants either by chemical treatment, heating or spontaneous mutagenesis (and subsequent clonal selection). The problem with mutational attenuation, in this way, is that it is an uncontrollable and random process, and often the induced mutation is not mapped at the genomic level [5]. It is therefore very difficult to control the level of attenuation while maintaining the antigenicity. Although live attenuated vaccines are the most successful form of vaccine, reversion to virulence or differences in virulence in different hosts is always the single greatest risk associated with their use.

The first successful use of an attenuated vaccine was in 1796 when Edward Jenner inoculated an 8-year-old boy with cowpox which subsequently protected the boy when he was challenged with Smallpox. The first artificially created attenuated vaccine was against rabies, produced by Louis Pasteur in 1884, and a recent report [6] summarises the benefit to both humans and dogs of the mass rabies vaccination program to domestic dogs in different parts of the world.

One of the most successfully applied attenuated vaccines was the Plowright vaccine strain used to combat rinderpest, a highly pathogenic and often fatal (up to 90% mortality) disease of cattle and buffalo [7]. This vaccine strain was derived by 90 serial passages in cell culture of the highly pathogenic Kabete 'O' strain of rinderpest virus. The Plowright vaccine has been instrumental in the near eradication of rinderpest. This particular attenuated vaccine meets many of the requirements of a good vaccine. It stimulates a strong

immune response which confers lifelong immunity from a single inoculation. It is also highly unlikely to revert to a virulent form as the attenuation is generated by several small changes located throughout the genome [8].

Less successful attenuated vaccines have been used against Rift Valley fever, African horse sickness and African swine fever, to name a few. Rift Valley fever is an insect borne, multi-species zoonotic viral disease of livestock caused by Rift Valley fever virus. The attenuated vaccine is based on the Smithburn isolate which was derived from mosquitoes in 1944 and passaged 79–85 times by intracerebral inoculation of mice. This resulted in the loss of hepatotropism and the acquisition of neurotropism. This vaccine, when administered parenterally can immunise sheep [9], and millions of doses have been widely used in Africa [10]. However, vaccines based on the Smithburn isolate can induce abortions, teratology in the foetuses of vaccinated animals, hydrops amnii and prolonged gestation in a proportion of vaccinated dams [11]. Research is ongoing into finding a safer attenuated vaccine. One possible replacement named Clone 13 has been shown in trials to be highly efficacious in both sheep and cattle and does not induce abortions in sheep [12].

Problems due to insufficient attenuation of vaccine strains were also encountered with African horse sickness (AHS), a vector borne viral disease of all equidae, which results in a high mortality in susceptible horses [5] and with African swine fever virus, an acutely fatal haemorrhagic fever of domestic pigs [13].

The failure to develop effective live attenuated vaccines in the above mentioned examples is mainly due to the conventional methodology employed. In addition to this an increasing stringency from regulatory bodies has driven vaccine development to incorporate the latest advances in molecular biology, cell biology and immunology. The use of reverse genetics and recombination technology has allowed vaccines to be more carefully designed. It is now possible to have fully defined attenuating mutations clearly mapped on the virus genome. This logical design of vaccine strains can help ensure that the risk arising from a reversion to virulence is greatly minimised. The logical design of vaccines can also allow for immunomodulatory genes to be removed from an attenuated virus, while ensuring that protective antigens are not accidentally removed, hence increasing its efficacy in stimulating the immune system of the vaccinated animal. A great advantage of a designed vaccine is the ability to include their use in conjunction with epidemiological surveillance systems. In many cases, where a disease is not endemic, vaccination has not been considered as a control option due to the inability to differentiate between an infected animal and one which has been vaccinated. The development of vaccines which allow differentiation between infected and vaccinated animals (DIVA) enables virus free status to be more rapidly granted to countries which have suffered disease incursion.

With the introduction of exciting new vaccine technologies such as peptides/recombinant antigens, DNA and viral vectors, attenuated live vaccines have been out of fashion for awhile. However, the development of new molecular biological techniques is seeing the return of attenuated vaccines to the forefront of disease control. For example reverse genetics is being used to develop the latest vaccines against H5N1 avian influenza virus and these have the potential to be used in both the avian host and humans [14]. The use of this technology has allowed the identification of virulence determinants in the three envelope glycoproteins of classical swine fever virus (CSFV) [15–19]. Several of the live attenuated CSFV mutants generated conferred complete protection to swine challenged with rescued virulent virus as early as 3 days post-vaccination [16–19]. Similar success has been experienced using molecular tools to design vaccines for disease caused by DNA viruses. Pseudorabies (Aujeszky's disease) has been combated successfully using recombinant, gene deleted, attenuated vaccines. The first commercially available gene deleted live vaccine was a glycoprotein E (gE) deleted vaccine used in the eradication programmes in both Europe and America. More recently a new generation of gE-gG-TK-gene deleted vaccines has been developed [20]

3. Viral-based vectors as antigen delivery systems

3.1. DNA virus vectors

3.1.1. Poxviruses

Poxviruses provide a number of advantages as antigen delivery systems. They are large viruses containing a DNA genome ranging in size between 130 and 300 kb pairs. They can accommodate large amounts (over 25 kb) of extra DNA [21] thus several transgenes can be expressed simultaneously providing a multi-valent vaccine approach [22–24]. Importantly, poxviruses replicate within the cytoplasm of infected cells and do not integrate into the host genome, thus eliminating the potential for insertional mutagenesis. Poxviruses have been used in two different approaches as vaccines. The first approach relies on productive replication of an attenuated strain in a permissive host. The second approach relies on the fact that poxviruses may enter cells of non-permissive hosts and express most of the proteins encoded, including inserted transgenes, but do not produce infectious virus. These replication-deficient viruses provide advantages in terms of their safety although a disadvantage is that more than one inoculation may be required to induce a protective immune response. These approaches have been used both with vaccinia virus (VV), which has a very wide host tropism and with different poxviruses with more restricted host tropisms.

Replicating poxvirus vectors can induce a long-lasting immunity after a single injection and can activate both humoral and cellular immunity depending upon the promoter controlling the expression of the immunogen. The possibility of using poxviruses as vectors for foreign gene expression was initially demonstrated in 1982 with VV [25,26]. The first recombinant VV to be used in the field was the Copenhagen strain expressing the rabies virus surface glycoprotein [27]. A commercial version of this strain embedded in baits (RABORAL V-RG®) was used in the eradication of fox rabies in several Western Europe countries [28,29]. Since then numerous strains of VV have been engineered to express a variety of antigens from a number of pathogens in various animal species (Table 1).

Wild type VV strains may produce undesirable effects in humans and therefore two highly attenuated vaccinia virus vectors were developed. Both modified vaccinia Ankara (MVA) and NYVAC strains undergo very limited or no productive replication in mammalian cells [30,31] although most of the virus proteins are produced including inserted transgenes. Therefore both humoral and cellular immunity can be induced against the transgene product. The MVA strain has lost about 15% of the genome including host range and virulence genes, during passage in chick embryo fibroblasts [32]. The NYVAC strain was developed more recently from the Copenhagen VV vaccine strain by the targeted deletion of 18 genes [31]. Both strains have been used successfully to induce protection against animal pathogens (Table 1).

Other animal poxviruses have been attenuated and used as replicating recombinant vaccines in permissive host species. Among them, capripoxviruses were selected because they have a restricted host range [33,34]. The attenuated KS1 strain was used as vector to express both the H or F genes of rinderpest virus and these recombinant viruses conferred protection of cattle against both rinderpest and lumpy skin disease [35,36]. KS1 vaccine expressing either the H or F genes of peste des petits ruminants (PPR) protected

Table 1
Examples of viral antigens expressed in different poxvirus vectors.

VV vectors	Antigen	Pathogen	Species	Commercially available	References
Vaccinia virus	H protein	RPV	Cattle		[295–298]
	H + F proteins				
	F, G, N	BRSV	Cattle		[299]
	G	BEV	Cattle		[300]
	P67	*T. parva*	Cattle		[301]
	VP2, VP5	BTV	Sheep		[302]
	Envelope protein	BLV	Sheep		[303,304]
	Env	CA-EV	Goat		[305]
	EO, E2	CSFV	Pigs		[306,307]
	H5	AIV	Chicken		[308]
MVA strain	F, G	BRSV	Cattle		[309]
	HA, NP	Equine influenza	Ponies		[310]
	Ag85A	*M. tub*	Cattle		[311]
NYVAC strain	H, F	CDV	Ferrets		[62]
	prM, E, NS1	JEV	Pigs		[312]
	gB, gD	ADV	Pigs		[313,314]
ALVAC strain	gB, gC, gD	EHV-I	Horses		[63]
	Glycoprotein G	NiV	Pigs		[315]
	Fusion protein F				
	VP2 and VP5	BTV	Sheep		[66]
	H5	AIV	Cats		[57]
	F and H	CDV	Dogs and ferrets	RECOMBITEK CDV PUREVAX FDV	[61,62]
	Env, gaga	FeLV	Cats	PUREVAX FeLV	[65,316,317]
	prM and E	WNV	Horses	RECOMBITEK equine WNV	[318–320]
	H3	Influenza H3N8	Foals	PROTEQ-FLU™	[321]
Myxoma virus	Capsid gene (F9 strain)	FCV	Cats		[322]
	Influenza hemaglutinin	AIV	Rabbits		[44]
	Vp60	RHDV	Rabbits		[45,46,323]
Swinepox	Gp50 and gp63	ADV	Pigs		[47,48]
Capripoxvirus	H and F (KS1 strain)	RPV	Cattle		[35,36,324–326]
	H and F (KS1 strain)	PPRV	Goats		[37,67]
	VP7 (KS1 strain)	BTV	Sheep		[38,39]
	VP2, VP7, NS1 and NS3 (serotype 2)				
	G glycoprotein (LSDV Neethling)	RV	Cattle		[40]
	G1 and G2 (LSDV Neethling)	RVFV	Mice		[42]
Avipoxvirus	H5 or H7 (+N1 gene)	AIV	Chickens Turkeys	TROVAC™-AIV-H5	[327–330]
	HN, ±F	NDV	Chickens		[331–334]
	gB	MDV	Chickens		[335]
	env	SNV	Chickens		[336]
	VP2	IBDV	Chickens		[337]
	F gene	TRTPV	Turkeys		[338]
	F gene (Pigeonpox)	NDV	Chickens		[43]

Abbreviations: ADV: Aujezsky disease virus, AIV: Avian influenza virus, BEV: Bovine ephemeral virus, BHV-1: bovine herpesvirus 1, BHV-4: bovine herpesvirus 4, BLV: bovine leukaemia virus, BRSV: bovine respiratory syncytial virus, BTV: bluetongue virus, BVDV: bovine viral diarrhoea virus, CDV: canine distemper virus, CHV: canine herpesvirus, CSFV: classical swine fever virus, EHV-1: equine herpesvirus 1, FCV: feline calicivirus, FeLV: feline leukemia virus, FHV-1: feline herpesvirus 1, FMDV: foot-and-mouth disease virus, IBDV: infectious bursal disease virus, JEV: Japanese encephalitis virus, LSDV: lumpy skin disease virus, *M. tub*: *Mycobacterium tuberculosis*, MDV: Marek's disease virus, NDV: Newcastle disease virus, NiV: Nipah virus, PPV: porcine parvovirus, PPRV: peste des petit ruminants virus, PRRSV: porcine reproductive and respiratory syndrome virus, PRV: pseudorabies virus, RHDV: rabbit hemorraghic disease virus, RPV: rinderpest virus, RV: rabies virus, RVFV: Rift Valley fever virus, SNV: spleen necrosis virus, *T. parva*: *Theileria parva*, WNV: West Nile virus, TRTPV: turkey rhinotracheitis pneumovirus.

goats against goatpox and PPR [37]. The KS1 vaccine strain was also used to express several antigens of bluetongue virus in sheep and this provided partial to full protection against challenge with a virulent strain [38,39]. Another attenuated capripoxvirus, the LSDV Neethling vaccine strain, has been used as a vector to deliver antigens. A LSDV recombinant expressing the rabies virus glycoprotein elicited both humoral and cell-mediated immune responses in cattle [40]. Interestingly, the same recombinant LSDV strain did not replicate in mice and rabbits but still induced protective immune responses against rabies [41]. Another LSDV recombinant expressing the G1 and G2 glycoproteins of Rift Valley fever virus also induced protection against Rift Valley fever in mice [42].

Numerous recombinant avipoxviruses have been developed to control avian diseases. Some examples of fowlpox recombinant are also listed on Table 1. A pigeonpox virus expressing the F gene of Newcastle disease virus was also safe and efficient in chickens [43].

Rabbits injected with an attenuated myxoma virus expressing the influenza virus haemagglutinin developed a specific antibody response to the foreign antigen, thus suggesting this myxoma virus could be an efficient antigen delivery system for rabbits [44]. Shortly after, recombinant myxoma viruses were produced to protect against both myxomatosis and rabbit viral haemorrhagic disease [45,46]. In pigs, a recombinant swinepox virus was developed to protect against a virulent challenge with Aujezsky's disease virus [47,48].

These examples illustrate the use of replicating poxviruses in permissive host species for vaccination strategies. However, while very promising, to our knowledge only one recombinant, the attenuated fowlpox virus expressing the H5 gene of avian influenza virus

(TROVAC™-AIV-H5) has been used commercially [49]. This limited use reflects the fact that these recombinants are genetically modified organisms that replicate in their natural host species, thus causing biosafety concerns. In addition, interfering pre-immunity resulting from a previous "natural" infection or the transfer of maternal antibodies in the young may reduce the capacity of the vector to replicate and, thus, induce less effective immunity [50,51].

Poxviruses are known to generate a nearly lifelong immunity in their natural host species after the initial contact. This is an advantage when poxvirus vectors are to be used in naive animals but certainly a major constraint for repeated use in immune animals. However, recent work has opened new possibilities to circumvent the problem of pre-existing immunity. The B5 protein is the primary target for the antibodies that neutralize the extracellular form of VV. Mice primed with a replicating VV and then boosted with a recombinant VV lacking the ectodomain of this B5 protein had a stronger antibody response against the transgene product compared to mice boosted with the wild type recombinant VV [52]. A similar strategy could be envisaged for other poxviruses used as vectors in permissive host species.

An alternative strategy is the use of replication-deficient poxvirus vectors in non-permissive host species. Indeed, it has been shown in mice, that pre-existing immunity against the non-replicating MVA is not strong enough to block a boosting vaccination with the same virus [53]. The poxvirus vectors most studied so far for antigen delivery in non-permissive host species are the avipoxviruses used in mammals. Avipoxviruses replicate only in avian cells or birds. In mammalian cells or mammals, they initiate an abortive infection but can express antigens and stimulate both humoral and cell-mediated immune responses against the transgene product [54,55]. Recombinant fowlpox viruses have been successfully used to express antigens in guinea pigs [56], in cats [57] and in pigs [58]. Recombinant canarypox vectors are about 100 times more efficient than comparable fowlpox vectors in inducing protective immunity [59]. The most studied avipoxvirus for antigen delivery in mammals is the ALVAC canarypox strain. This strain has been used to induce protection against diverse pathogens in various species. Despite this extensive use in research, commercial applications are presently available only for companion animals and horses. ALVAC strains were developed to protect dogs and ferrets against rabies [60] or canine distemper virus [61,62]. Licensed canarypox based vaccines are also listed in Table 1.

Non-replicative recombinant poxviruses offer several advantages including added safety since they do not spread between animals. They also induce low immunity against the vector virus used, thus permitting repeated administrations, they can be used for priming young animals with maternal antibodies when conventional attenuated live vaccines failed [63,64] and they can also boost the immune response engendered by a killed virus vaccine [65]. However, compared to replicating poxviruses used in permissive host species, they generally require the administration of high titres with a boosting injection to achieve sufficient protection. For example, the immunisation of sheep against bluetongue virus with a canarypox virus vaccine required two injections of 6.3×10^8 particles 3 weeks apart [66], only one dose of 10–100 particles of recombinant capripox virus was enough to protect goats against peste des petits ruminants [37,67]. Finally, both replicating and replication-deficient recombinant poxvirus vaccines offer the possibility to differentiate naturally infected from vaccinated animals since the recombinants express a single or a couple of antigens of the pathogens and other antigens remain available for immunological testing [49].

The virus type species *Orf Virus* (ORFV) from the genus *Parapoxviridae* (*PPV*) has been proposed as a candidate for novel marker vector vaccines [68]. The ORFV has a very restricted host range *in vivo* and *in vitro* (sheep and goats and occasionally man), a restricted skin tropism and an absence of systemic infection [69]. Among different ORFV vaccine strains, only the D1701 is a highly attenuated strain with a markedly reduced pathogenicity after subcutaneous application. This strain presents several advantages for use as a viral vector including its ability to be propagated on a cell line and its ability to induce a strong immune-stimulating and regulating response in non-permissive hosts such as mice and swine [70,71]. An additional benefit of this vector is that only a short-term vector specific immunity, without the formation of neutralizing antibodies against PPV, is induced even in the natural host sheep, thus avoiding immune interference following repeated inoculations. This is mainly linked to the action of the virus immunomodulatory proteins interfering with the host immune response to avoid virus elimination [72,73]. In addition, the observed adjuvant properties of ORFV, promote ORFV as a new safe poxvirus vector [69,74,75]. Several *in vivo* studies reported that a prophylactic administration of the inactivated D1701 (Baypamun, Bayer AG, Leverkusen, Germany) reduced the susceptibility of different animal species to infectious diseases such as IBR virus in cattle [76], and Aujezsky's disease in swine [77]. More recently, the immunostimulatory properties of the D1701 was shown following immunisation with CSFV glycoprotein E2 subunit vaccine in swine [78,79].

Studies on the genome of the highly attenuated ORFV strain D1701 led to the identification of some viral genes non-essential for virus replication but with an influence on viral pathogenesis, virulence and host immunity [80]. Thus, deletion of the vegf-e (mammalian vascular endothelial growth factor homologue) locus permits foreign genes to be expressed *in vitro*, even in the absence of productive virus replication in non-permissive cells, leading to the induction of a specific immune response in the non-permissive host [81]. Several reports on the protective capacity following inoculation of different recombinant ORFV (strain D1701) are summarised in Table 2. In conclusion, although more studies are needed to understand the immunostimulatory properties of ORFV, the capability of ORFV recombinants to induce antigen specific memory immune responses and to control acute or persistent infections requiring different immune mechanisms demonstrates their potential as a promising new poxvirus delivery system

3.1.2. Herpesvirus

The family *Herpesviridae* encompasses the subfamilies *Alpha-*, *Beta-*, and *Gammaherpesvirinae* each of which contains several genera [82]. The large genome size, which can be extended, presence of virulence genes not essential for productive viral replication *in vitro* and *in vivo*, and the availability of efficient methods to manipulate herpesviral genomes are significant advantages for using herpesviruses as vaccine vectors. Several herpesviruses which cause diseases in pets or in animal husbandry, resulting in high economic losses, have been engineered to serve as vaccine vectors (Table 3). With the exception of BHV-4, all of them are alphaherpesviruses which reflects that members of this subfamily cause the majority of herpesviral infections of significant veterinary relevance.

The first herpesviruses of farm animals engineered to express heterologous antigens were bovine herpesvirus type 1 (BHV-1) which causes infectious bovine rhinotracheitis/infectious pustular balanoposthitis and pseudorabies virus (PRV), the cause of Aujeszky's disease. In 1991 a BHV-1 virion surface display approach used a fusion protein between foot-and-mouth disease virus (FMDV) VP1 epitopes linked to the N-terminus of BHV-1 glycoprotein C. Calves immunized with the hybrid BHV-1 recombinant were protected from challenge with pathogenic BHV-1 and developed a protective antibody response against FMDV [83,84]. However, no follow-up studies using a similar display approach were published. Further developments with BHV-1 as a vector used genomic

Table 2
ORF virus (strain D1701L) as a vector for veterinary vaccine antigens.

Antigen	Pathogen	Species	Immunological consequences	Reference
gC or gD	ADV	Mouse	Strong anti-gC humoral response after single dose	[339]
p40	BVDV	Rats	Induction of B-cells, plasma cells and T cells	[340]
gC+gD	ADV	Pigs	Balanced Th1/Th2 ratio following DNA priming	[341]
E2	CSFV	Pigs	Higher antibody titres and enhancement of frequency of IFN-gamma producing PBMCs	[79]

integration of expression cassettes coding for structural proteins of bovine respiratory syncytial virus (BRSV), bovine viral diarrhoea virus (BVDV), PRV, and *Cryptosporidium parvum*, a parasite which causes cryptosporidiosis, a zoonotic disease [85–93]. Integration of the expression cassettes into the BHV-1 genome resulted in replacement or inactivation of pathogenicity-associated genes like the thymidine kinase gene [88–92] or genes encoding glycoproteins gC [92], gG [92,93], gE [86], or gI [85,87]. Analyses of the immunogenic properties of the BHV-1 recombinants expressing PRV glycoproteins in mice revealed induction of a protective immune response against a lethal challenge with PRV. Thus, these recombinants might be beneficial in situations where maternal antibodies interfere with immunization of piglets with PRV-based vaccines [91,92]. Recombinant herpesviruses expressing *C. parvum* p23 and BVDV E2 were inocculated into rabbits [93] or guinea pigs [89] and a specific antibody response against the appropriate pathogens was induced. To our knowledge, the only vaccination/challenge experiment in cattle was reported for the BRSV attachment protein G expressing BHV-1 vector which demonstrated that vaccinated calves were resistant to BRSV infection. However, in comparison to the control infection, virulence of the BRSV G expressing recombinant for calves was increased [86]. The suitability of canine herpesvirus as a vector for immunization purposes was evaluated using recombinants expressing the rabies virus G protein [94] or the *Neospora caninum* surface protein NcSRS2 [95]. Both vaccine candidates elicited specific antibodies against the respective target antigens. Vaccination/challenge experiments, however, await publication.

Two studies reported vaccination against feline leukemia virus (FLV) using recombinant feline herpesvirus 1 (FHV-1). Efficient vaccination was achieved by immunization of cats with an FHV-1 recombinant expressing only the env protein [96] whereas a previous vaccination/challenge experiment was only successful after immunization with FHV-1 recombinants expressing env and gag followed by a booster immunization with baculovirus expressed env and gag [97]. The differences in vaccine efficacy might have been due to the intrinsic characteristics of each recombinant of the recombinants such as the insertion locus (ORF2 and TK locus,

Table 3
Examples of veterinary herpesvirus vectors for antigen delivery.

Vector	Target pathogen	Expressed target antigen	References
BHV-1	BRSV	BRSV attachment protein G	[4,5,85,86]
	BVDV	Glycoprotein E2	[6–8,87–89]
	C. parvum	Surface protein p23	[12,93]
	FMDV	VP1	[2,3,83,84]
	PRV	Glycoproteins gB, gC, gD, gE, gI	[9–11,90–92]
BHV-4	BVDV	Glycoprotein E2	[43,122]
	BHV-1	Glycoprotein D	[44,123]
CHV	Rabies virus	Glycoprotein	[13,94]
	N. caninum	Surface protein NcSRS2	[14,95]
EHV-1	BVDV	Structural proteins C, E^{rns}, E1, E2	[41,120]
	WNV	Proteins E and prM	[42,121]
FHV-1	FeLV	env, gag,	[15,16,96,97]
	T. gondii	ROP2 antigen	[17,98]
FCV	FIV	Capsid protein	[18,99]
		gag, env	[19,20,100,101]
HVT	IBDV and MDV	IBDV VP2	[23–25,104–106]
ILTV	AIV	Haemagglutinin H5 and H7	[26,27,107,342]
MDV	NDV	Fusion protein F	[21,102]
	IBDV	VP2	[22,103]
PRV	CSFV	Glycoprotein E2	[28,29,108,343]
	JEV	NS1 protein	[30,109]
	FMDV	VP1	[31,110]
	PRRSV	GP5	[32–34,111–113]
	TGEV	S1 protein	[35,114]
	PCV2	Capsid protein	[36,115]
	FMDV + PPV	P1-2A (FMDV) + VP2 (PPV)	[37,116]
	Rabies virus	Glycoprotein	[38,117]
	Swine Flu virus	Haemagglutinin H3	[39,118]

Abbreviations: BHV-1: bovine herpesvirus 1, BHV-4: bovine herpesvirus 4, BRSV: bovine respiratory syncytial virus, BVDV: bovine viral diarrhoea virus, CHV: canine herpesvirus, *C. Parvum*: *Cryptosporidium parvum*, CSFV: classical swine fever virus, EHV-1: equine herpesvirus 1, FCV: feline calicivirus, FeLV: feline leukemia virus, FHV-1: feline herpesvirus 1, FIV: feline immunodeficiency virus, FMDV: foot-and-mouth disease virus, HVT: herpesvirus of turkeys, IBDV: infectious bursal disease virus, ILTV: infectious laryngotracheitis virus, JEV: Japanese encephalitis virus, MDV: Marek's disease virus, NDV: Newcastle disease virus, *N. caninum*: *Neospora caninum*, PPV: porcine parvovirus, PRRSV: porcine reproductive and respiratory syndrome virus, PRV: pseudorabies virus, Swine Flu virus: Swine influenza virus, TGEV: transmissible gastroenteritis virus, *T. gondii*: *Toxoplasma gondii*, WNV: West Nile virus.

respectively) or the promoters used to direct transcription (Rous sarcoma LTR promoter versus human cytomegalovirus immediate early promoter). Induction of a protective immune response was also reported for recombinant FHV-1 expressing the ROP2 protein of *Toxoplasma gondii*. Immunization of cats with the recombinant followed by a challenge infection with the parasite reduced the parasite load in the brain and serum antibodies inhibited the in vitro invasion of tachyzoites [98]. Feline calicivirus neutralizing antibodies were induced in cats by a FVH-1 recombinant expressing the capsid protein of feline calicivirus [99]. Only *in-vitro* expression analyses have been reported so far for FVH-1 vectors containing gene cassettes for gag or env proteins from feline immunodeficiency virus [100,101]. These studies suggested that the resulting recombinants might be suitable vaccine candidates.

Marek's disease virus (MDV), which causes a highly contagious neoplastic disease in chickens, has been engineered to develop polyvalent vaccines against Marek's disease (MD) and Newcastle disease [102] or MD and infectious bursal disease (IBD) [103]. Vaccination challenge experiments revealed good protection against both diseases targeted by the respective MDV recombinants which was also achieved in the presence of maternal antibodies against MDV [103]. Herpesvirus of turkey (HVT) is apathogenic in chickens and has been used for a long time in vaccines for protection against MD. Bivalent vaccines against both MD and IBD based on HVT vectors expressing VP2 of IBDV were shown to be efficacious and safe. They can be inoculated into embryonated eggs and 1-day chickens and are effective in the presence of high titres of maternally derived antibodies [104–106]. Remarkably, the resulting vaccine Vaxxitex^{R}HVT + IBD is so far the only licensed and commercialised animal herpesvirus vector based product.

Further developments of vectored bivalent vaccines against poultry diseases include expression of haemagglutinin genes encoding H5 and H7 of highly pathogenic avian influenza viruses by deletion mutants of infectious laryngotracheitis virus [107]. As mentioned above, PRV was one of the first animal herpesvirus suggested to be suitable as bivalent vaccine vector. Proof of concept was achieved by showing that attenuated PRV expressing envelope glycoprotein E2 of classical swine fever virus constitutes an efficacious, safe and non-transmissible vaccine against both Aujeszky's disease and classical swine fever [108]. Despite the promising results, this vaccine was never commercialised. The main reason may have been that use of a PRV-based vector vaccine was not favoured by producers due to the concurrently initiated eradication programs for PRV. Consequently, development of PRV-based vector vaccines was only recently resumed. Publications originate mainly from research institutes in China and report PRV recombinants expressing antigens from Japanese encephalitis virus (JEV) [109], FMDV [110] porcine reproductive and respiratory syndrome virus (PRRSV) [111–113], transmissible gastroenteritis virus (TGEV) [114], porcine circovirus 2 (PCV2) [115], FMDV plus porcine parvovirus (PPV) [116], rabies virus [117] and H3N2 swine influenza virus [118]. Data on vaccination/challenge experiments of these potential vaccine candidates are available for the recombinants expressing NS1 of JEV [109] VP1 of FMDV [110], GP5 of PRRSV [111–113], and haemagglutinin H3 of swine influenza virus [118]. They all induced specific immune responses against PRV and the target pathogens which, however, in all cases need to be improved. It will be interesting to see which of these PRV vector constructs will find the way into field applications.

The recombinant herpesviruses described above were all generated using the classical recombination in cultured cells of mammalian or avian origin. In the last years, cloning and maintaining of entire, infectious herpesviral genomes in *Escherichia coli*, so-called bacterial artificial chromosomes (BAC), and development of techniques to manipulate these genomes in bacteria significantly eased construction and recovery of recombinants [119]. The BAC technique was applied for generation of equine herpesvirus 1 (EHV-1) recombinants expressing BVDV structural proteins [120] or West Nile virus (WNV) prM and E proteins. The latter induced WNV neutralizing antibodies after immunization of horses [121]. Vaccination of cattle with the EHV-1/BVDV recombinant resulted in BVDV-specific, neutralizing antibodies and reduction of viraemia levels and nasal virus shedding after a BVDV challenge infection. This shows that EHV-1 vectors are suitable for vaccination of cattle and may find application in cases where existing antibodies preclude use of live vector vaccines derived from bovine viruses, like the recombinant BHV-4 viruses reported recently which express BVDV glycoprotein E2 or BHV-1 gD [122,123]. Inoculation of the recombinants into rabbits or sheep induced neutralizing antibodies against the respective target pathogens. However, vaccination/challenge experiments in cattle are needed to elucidate whether BHV-4, a gammaherpesvirus which is regarded as apathogenic or of low pathogenicity in cattle, may become a suitable live vector for vaccination against bovine diseases.

With regard to commercialisation, animal herpesvirus vector vaccines are far from being a success story. However their development and testing in animal models and target animal species significantly contributed to the understanding of the biology of relevant veterinary diseases and will help in the rationale design of future developments to improve efficacy which might include coexpression of immunostimulatory proteins like cytokines or chemokines and/or ligands for activation of specific signal transduction pathways. These approaches will be facilitated by the BAC technology.

3.1.3. Adenovirus

Adenoviruses (Ad) have been isolated from humans and many animals, including bovine, ovine, porcine, canine and avian species. Human Ad are by far the best characterised, and the vast majority of gene transfer studies involving Ad, whether for therapeutic or vaccinal purposes, have been carried out with vectors derived from serotype 5 of Ad (Ad5). Adenovirus-based vectors are very attractive candidates for vaccine development, as in mammalian hosts they elicit potent humoral and cell-mediated immune responses (IR), both systemically and at local sites, against the antigens encoded by the inserted foreign genes [124]. Different strategies of construction have been employed, depending upon whether the aim was to obtain replicative vectors (Ad-R^{+}), capable of multiplying in natural or permissive hosts, or rather non-replicative vectors, incapable of multiplying in the host (Ad-R^{-}). Numerous vaccination trials have been conducted using Ad-R^{+} or Ad-R^{-} vectors, and have led to the conclusion that Ad-R^{+} are quantitatively (diminution of the required dose) and qualitatively (induction of mucosal immunity) more effective. Nevertheless, Ad-R^{+} vectors present a major drawback; that is, their use in permissive hosts gives rise to the production of infectious particles that can be released into the environment. In view of the legislation governing the use of genetically modified organisms, the use of Ad-R^{+} is in practice only conceivable for strains of Ad whose innocuity has been firmly established.

When different vectors expressing the same heterologous antigen have been compared, Ad5-based vectors have proven particularly immunogenic, and notably as regards induction of antigen-specific CD8+ T cells [125,126]. The qualities of Ad5 that underpin such immunogenicity are not as yet fully elucidated, but include its capacity to elicit strong innate immunity [127]. Parenteral administration of Ad5 in mice induces an intense inflammatory response, characterised by the secretion of high levels of proinflammatory cytokines and the induction of a maturation process in immature dendritic cells. Cytokine secretion does not

Table 4
Examples of animal adenovirus (Ad) vectors used in veterinary species.

Vector	Target pathogen	Expressed antigen	Species	Reference
Porcine Adenovirus	CSFV	gp55	Pigs	[149,167]
Porcine Adenovirus	PRV	gD	Pigs	[151]
Ovine Adenovirus	MHV	NS3	Mouse	[152]
Bovine Adenovirus	BHV1	gD	Cattle	[153]
Canine Ad serotype 2 (Cav2)	Rabies virus	Glycoprotein	Mouse, dogs, cats	[154–156]
Cav2	Feline panleukopenia virus	VP2	Cats	[157]
Cav2	FMDV	VP1	Pigs	[158]
CELO virus (avian adenovirus)	IBDV	VP2	Chickens/*in ovo*	[160]
Porcine Adenovirus	TGEV	Spike protein	Swine	[169]
Fowl adenovirus	Avian infectious bronchitis virus	Spike subunit	Chickens	[171]

initially require viral gene expression, but rather, is induced by the viral particles themselves [128–131]. Indeed, one viral structural protein, the hexon, has been described to behave as an intrinsic adjuvant [132]. The presence of high levels of proinflammatory cytokines and mature dendritic cells is presumed to create conditions conducive to the induction of antigen-specific adaptive immunity.

As regards adaptive immunity, the memory response elicited by Ad5 has been observed to be protracted, both in murine and simian studies, in relation to what is typical of acute viral infections [133–135]. In particular, the antigen-specific CD8+ T-cell population elicited by Ad5 has been observed to maintain an effector phenotype for a prolonged period of time [136]. The protracted memory response may be related to prolonged exposure to antigen, as recent studies have shown that while high level antigen expression was maintained for only 1 week after parenteral administration [136,137], antigen remained available to prime naïve T cells for at least 30 days after immunisation [137]. Long-term low level antigen presentation has been linked to the persistence of low levels of transcriptionally active Ad5 genomes at the site of inoculation, in liver and lymphatic tissues [138].

Vectors derived from human Ad have been extensively evaluated as vaccines in murine and nonhuman primate models [139–141]. Less data are generally available for veterinary species [142] although a remarkable success have been achieved in protection of swine and cattle against FMDV by means of a single inoculation of an Ad5-vectored subunit vaccine [143,144]. Data are currently being accumulated for nonhuman Ad, not only in murine and nonhuman primate species, but also in target animal species, whether they represent natural hosts or not [145,146]. If necessary, pre-existing immunity against one adenovirus can be circumvented by the use of another adenovirus [147,148]. The review focused on nonhuman Ad, except vaccination by the oral route, for which data obtained with human Ad is highly instructive.

Vectors derived from several animal adenoviruses have been evaluated as vaccines delivered by parenteral routes (Table 4). Vectors derived from porcine Ad (Pav) have been used to vaccinate swine against CSFV and pseudorabies virus. In one study, a single dose of Pav expressing the gp55 (Pav-gp55) of CSFV induced protection against virulent challenge [149]. In a second study, Pav-gp55 was administered after DNA priming and improved protection as regards two doses of DNA or a single dose of Pav-gp55 [150]. Likewise, administration of a Pav vector expressing the glycoprotein D of pseudorabies virus protected pigs against disease after virulent challenge [151]. Vectors derived from ovine Ad (Oav) have been evaluated in murine models and one such vector expressing the non-structural protein 3 (NS3) of the hepatitis virus was shown to elicit NS3-specific IFN-γ secreting T cells in mice [152]. Vectors derived from bovine Ad (Bav) expressing the glycoprotein gD of bovine herpesvirus-1 (BHV1) induced protective immune responses in calves [153]. Regarding vectors derived from canine Ad serotype 2 (Cav2), a single administration by intramuscular or intranasal routes of a Cav2 vector expressing the glycoprotein of rabies virus (Cav2-G) induced protective immunity in mice [154]. In dogs, subcutaneous inoculation of replication-competent Cav2-G elicited antibodies neutralising infectivity of rabies virus and protected against lethal challenge [155]. Similarly, intramuscular inoculation of Cav2-G in cats elicited rabies–virus-specific neutralising antibodies (NA) and protection [156]. Administration of a Cav2-derived vector expressing the VP2 protein of the feline panleukopenia virus elicited neutralising antibodies (NA) in all cats and protected from infection and disease [157]. A Cav2 vector expressing the VP1 protein of foot-and-mouth disease virus gave rise to a humoral response, including the induction of NA, in pigs [158]. Subcutaneous vaccination with Cav2 vectors expressing canine distemper virus (CDV) antigens afforded solid protective immunity in puppies born to CDV and Cav2 immune dams. Administration with Cav2 vectors may thus be an efficient strategy for overcoming maternal-derived immunity [159]. Vectors derived from CELO virus (avian adenovirus) have been evaluated in chickens, and a CELO vector expressing the VP2 antigen of the infectious bursal disease virus induced protection upon injection in chickens or *in ovo* [160].

Orally delivered vaccines against animal diseases are sought for their ease of administration. They represent the only means of immunising wildlife, whose major role as a reservoir of pathogenic agents was underscored in an in-depth analysis of the origin of emerging human diseases [161]. Just as importantly, oral vaccination holds the promise of eliciting immune responses not only systemically, but also at mucosal surfaces, which represent the major sites of pathogen entry. Such responses are poorly elicited by most injected vaccines. Certain observations suggest that effective oral vaccines might well be derived from Ad. In particular, an orally delivered Ad-based vaccine against acute respiratory disease (ARD) of adenoviral origin was administered to military personnel in the USA over a period of 25 years, beginning in the 1970s. This vaccine, composed of replication-competent Ad4 and Ad7 in the form of enteric coated tablets, was well-tolerated and afforded a significant level of protection against ARD [162–164]. While vaccine production was discontinued in 1996, a similar Ad-derived vaccine against ARD is in the process of being relicensed [165].

Regarding oral delivery of human Ad expressing a heterologous antigen, many experimental vaccines have been evaluated in diverse species. Upon oral administration of an Ad5-based vector expressing the glycoprotein of the rabies virus in foxes, most vaccinees developed NA against the rabies virus, while in dogs immune responses were not detected after oral administration and even after endoscopic deposition in the small intestine [166]. As regards oral delivery of Ad of non-primate origin, antigen-specific immune responses have been elicited against the transgene product in rodent models as well as in veterinary species, including pigs and dogs. Upon oral delivery of Pav-gp55, 60% of pigs were protected after oral challenge, although antibodies that neutralised

CSFV infectivity had not been detected [167]. Pigs that received two oral doses, but not one, of Pav-gp55 were protected against disease after contact challenge [168], despite the absence of serum NA. While a similar percentage of pigs that had been vaccinated by the subcutaneous route were protected, CSFV antigen was found in the spleens of surviving orally-vaccinated but not subcutaneously-vaccinated pigs. Oral administration of a Pav vector expressing the transmissible gastroenteritis virus (TGEV) spike protein induced TGEV-specific virus-neutralising antibodies in swine. Moreover, coronavirus-specific secretory IgA was detected in the small intestine and lungs of immunised animals [169]. Bav-derived vectors have been shown to elicit mucosal immunity and induce protection against BHV1 in a natural host (cattle), even in animals with pre-existing antibodies to the vector [170]. A Cav-2 vector expressing the glycoprotein of the rabies virus (Cav-2-G) was administered to cats by parenteral and local routes: intramuscular but neither intranasal nor oral administration elicited NA and afforded protection against lethal challenge [156]. By contrast, oral vaccination of dogs with baits containing Cav2-G elicited virus NA and afforded long-lasting protection against fatal disease upon challenge with rabies virus [156]. Chickens were protected against challenge following oral vaccination with a Fowl adenovirus expressing the spike subunit of the avian infectious bronchitis virus [171].

In order to develop effective orally-delivered vaccines, several objectives must be met. These include stability in the highly degradative gastrointestinal milieu, efficacy of antigen delivery across mucosal barriers to gut-associated immune-inductive tissue, and induction of immunity despite a local immunological context biased towards immunological tolerance. Given these inherent obstacles to oral administration, it is perhaps not surprising that at present oral delivery of Ad has not proven entirely satisfactory. Antigen-specific immune responses have been elicited in rodent [172] and primate models [173], as well as in feral and veterinary species, including foxes, dogs, cats and pigs. Nevertheless, immune responses have been considered to be weak, particularly in large animals [174]. When different routes of infection have been compared, higher doses have been required in general to achieve detectable systemic humoral responses and protection by oral administration [175]. At present, the relative contribution of the various obstacles to oral vaccination is unknown, but must be appreciated to improve upon current Ad vectors and oral delivery strategies. Suboptimal transduction secondary to inefficient breaching is likely to be a major factor. Indeed low amounts of genomic Ad DNA were detected in stomach, small intestine and Peyer's patches as compared with high amounts in the oral cavity [176]. Whether such low level expression is due to inactivation of Ad vector in the gastrointestinal milieu or to mucosal barriers is not unknown. It is unlikely, however, that gastric inactivation represents the only obstacle, as when the stomach has been bypassed by direct enteric administration in sheep or endoscopic deposition in the small intestine of dogs, adaptive immune responses were weak [177] or undetectable [166], respectively. Nevertheless, gastro-protection of Ad-based vaccines is being actively explored [173,178]. Finally, poor immunological context in the gastrointestinal milieu would seem to be a factor, as oral adjuvants, and in particular double stranded RNA or its analogs), gave rise to improved adaptive IR [179]. Not only the magnitude but also the quality of immune responses generated by oral administration of Ad has come under scrutiny. In particular, oral delivery of Ad in mice gives rise to systemic rather than intestinal cell-mediated immunity [180,181]. Upon oral delivery of hAd in mice, strong immune responses were elicited against the transgene product in CD8+ T lymphocytes in the spleen, but only extremely limited immune responses in Peyer's patches [181]. Similarly, after oral delivery of Ad of chimpanzee origin in mice, weak responses were elicited in CD8+ T lymphocytes in the spleen, but not in Peyer's patches and mesenteric lymph nodes [180]. At present it is unclear why oral delivery of Ad should elicit local humoral but not local cell-mediated immune responses, despite eliciting systemic, albeit weak, cell-mediated immune responses.

Nevertheless, in view of the powerful proof of principle provided by the Ad4/Ad7 vaccine, it is likely that solutions will be found to optimise adenoviral vaccines for oral administration.

3.1.4. Baculovirus

Baculoviruses, members of the family *Baculoviridae* with the genera *Granulovirus* and *Nucleopolyhedrovirus*, are large enveloped viruses with double-stranded, circular DNA genomes of about 80–180 kbp in size. So far, baculoviruses were found only in arthropods [182] and their restricted host range made some baculoviruses attractive as biological agents for insect pest control [183]. The best studied baculovirus is *Autographa californica multicapsid nucleopolyhedrovirus* (AcMNPV). The ~134 kbp AcMNPV genomic DNA which is infectious, is packaged in a rod-shaped nucleocapsid whose length is proportional to the genome size [182] enabling insertion of large foreign DNA segments.

AcMNPV has been extensively used for production of recombinant proteins in insect cells since the early 1980s [184]. Since that time the methods for generation and isolation of recombinant baculoviruses were continuously improved. In the mid-1990s Hofmann et al. [185,186] and Boyce and Bucher [187] demonstrated that AcMNPV recombinants carrying mammalian cell-active expression cassettes, so-called BacMam viruses [188] were suitable vectors for gene delivery into hepatic cells. Successful transduction not only of a large number of primary mammalian cells and established cell lines by BacMam virus has now been reported (for examples see Kost and Condrey [189] but also efficient gene transfer into cells of avian [190,191] and piscine origin [192,193] has been demonstrated. Thus, it appears that uptake of AcMNPV by vertebrate cells is a common event. It has been shown that the viral envelope glycoprotein gp64 is essential for virus attachment and subsequent release of the nucleocapsids from endosomes [194]. The exact mechanism of entry into non-insect cells, however, needs to be clarified.

During the last years an increasing number of BacMam virus applications have been published confirming that advantages of the BacMam technology for gene delivery into vertebrate cells are:(1) BacMam viruses are easy to generate, (2) they have a broad cell type range, (3) there is no detectable gene expression driven by AcMNPV promoters and they do not replicate in vertebrate cells, (4) there is little to no microscopically observable cytopathic effect in transduced cell cultures, (5) they are applicable for transient and stable expression and (6) their application is cost-effective in comparison to chemical transfection procedures [195].

Initially, *in vivo* transduction was negative for transgene expression due to inactivation of the virus in presence of native serum and it was shown that the complement system mediated neutralization by both the classical and alternative pathways [186,196,197]. To overcome this problem, complement resistant viruses were generated by displaying the human decay accelerating factor on the viral envelope [197]. This modification resulted in enhanced gene transfer efficiency in neonatal rats. As an alternative, BacMam viruses were pseudotyped with the G protein of vesicular stomatitis virus (VSV-G) and it was demonstrated that the resulting viruses were more resistant to inactivation by animal sera than unmodified BacMam viruses [198]. Recombinants displaying VSV-G proteins on their envelope proved to be suitable for *in vivo* gene transfer into the cerebral cortex and testis of mice [198], mouse skeletal muscle [199], rat brain and rabbit muscle [200].

So far reports dealing with the application of the BacMam technology for induction of immune responses against viral pathogens

Table 5
Negative sense RNA viruses rescued using reverse genetics technology[a].

Family	Subfamily	Genus	Species	Abbreviation
Rhabdoviridae		Vesiculovirus	Vesicular stomatitis virus	VSV
		Lyssavirus	Rabies virus	RV
Paramyxoviridae	Paramyxovirinae	Morbillivirus	Measles virus	MeV
			Rinderpest virus	RPV
			Canine distemper virus	CDV
		Respirovirus	Sendai virus	SeV
			Human parainfuenza virus type 3	hPIV3
		Rubulavirus	Bovine parainfuenza virus type 3	bPIV3
			Simian virus type 5	SV5/PIV5
			Mumps virus	MuV
			Human parainfuenza virus type 2	hPIV2
			Newcastle disease virus	NDV
		Henipavirus	Nipah virus	NiV
	Pneumovirinae	Pneumovirus	Human respiratory syncytial virus	hRSV
			Bovine respiratory syncytial virus	bRSV
Filoviridae		Ebola-like viruses	Ebola virus	EboV
Bunyaviridae		Bunyavirus	Bunyamwera virus	BUNV
			LaCrosse virus	LACV
		Phlebovirus	Rift Valley fever virus	RVFV
Orthomyxoviridae		Influenzavirus	Influenza A virus	
		Thogotovirus	Thogoto virus	

[a] Adapted from Neumann et al. (2002) J. Gen. Virol. 83, 2635–2662.

are limited. Aoki et al. [201] inoculated mice intramuscularly or intranasally with an AcMNPV recombinant expressing pseudorabies virus glycoprotein B (gB). Intramuscular inoculation yielded higher gB-specific antibody titres in sera but mucosal antibodies were only found after intranasal inoculation. Strauss et al. [202] injected mice intramuscularly with a series of AcMNPV recombinants which displayed the *Plasmodium falciparum* circumsporozoite (CS) protein in the viral envelope or contained a mammalian cell-active CS protein expression cassette or displayed and expressed the CS protein. The latter induced higher CS protein-specific antibody titres and a greater amount of antigen specific interferon-γ producing T cells than the viruses which only displayed or expressed the CS protein. The CS display/expression BacMam virus also performed better in inducing CS protein-specific CD4+ and CD8+ T-cell responses *in vitro*. This study also revealed that splenocytes from AcMNPV infected mice produced a number of non-specific IFN-γ producing cells, leading to the assumption that the vector itself induced a generalized activation of lymphocytes. This interpretation is in line with previous reports which showed that AcMNPV induced antiviral activity in mammalian cells and conferred protection against lethal encephalomyocarditis virus [203] and influenza virus infections [204] in mice. In addition, a recent study [205] demonstrated that AcMNPV is a strong adjuvant also for adaptive immune responses in mice where effective humoral and T-cell adaptive responses against coinjected antigens were induced.

As mentioned above, pseudotyping BacMam viruses with VSV-G improved *in vivo* gene transfer by conferring resistance to complement-mediated neutralization. Improvement in induction of antigen-specific immune responses by pseudotyped viruses was addressed by Facciabene et al. [206] who compared the immunogenic properties of conventional and VSV-G displaying BacMam viruses expressing the hepatitis C virus E2 glycoprotein. In contrast to the E2-specific antibody response which was comparable for the different viruses, 10-fold less pseudotyped virus was needed as minimal dose for induction of a specific cellular immune response. Nevertheless, both viruses induced $CD8^+$ cells with antigen specific effector function. Pseudotyped BacMam virus was also used to compare induction of PRRSV neutralizing antibodies in mice after inoculation of a recombinant virus coexpressing the PRRSV GP5 and M proteins, or DNA immunization with purified DNA encoding the same antigens [207]. This study showed that PRRSV neutralizing antibodies were raised in a dose dependant manner and, astonishingly, twofold inoculation of 10^8 plaque forming units of the BacMam virus elicited significantly higher neutralizing antibody titres than dual injection of 100 μg purified plasmid DNA.

The field and examples for application for BacMam viruses are rapidly growing and the development of next generation BacMam vectors for vaccination purposes. Improvements to enhance the transduction efficacies *in vivo* include display of specific ligands on the surface of BacMam virions [208–212] and augmentation of transgene expression by vertebrate cell-active transcriptional and post-transcriptional regulatory elements [213].

3.2. RNA virus vectors

3.2.1. Paramyxovirus

Viruses classified in the family *Paramyxoviridae* [214] are enveloped, single-stranded, negative-sense RNA viruses that include highly prevalent human pathogens, such as respiratory syncytial virus (RSV) and measles virus (MV), as well as viruses that have major economic impacts on the poultry and livestock industries [e.g. Newcastle Disease virus (NDV), rinderpest virus (RPV) and peste des petits ruminants (PPRV)]. Extraordinary progress has been made in the past 10 years in the genetic engineering of these RNA viruses and this has provided an opportunity which allows the design of new vaccines expressing foreign epitopes with the potential to combat these and other pathogens. This major breakthrough occurred when reverse genetics systems, the ability to rescue an RNA virus from a complete DNA copy of its genome, were established for the negative-sense RNA viruses. The first such virus to be rescued from a copy of its genome was rabies virus in 1994 [215]. This was quickly followed by the rescue of other negative sense RNA viruses [216–219] (Table 5). The ability to specifically alter the genome at any chosen site has led to a better understanding of virus protein functions and interactions and has enabled the development of live attenuated virus vaccines; in particular marker vaccines. These, when used in association with companion diagnos-

tic tests, can be used to identify vaccinated as opposed to naturally infected animals. Another application is the use of these virus vaccines as vectors to deliver immunogens from other pathogenic agents

The family *Paramyxoviridae* is divided into two subfamilies, *Paramyxovirinae* (containing the *morbillivirus, respirovirus, rubulavirus* and two new genera, *henipavirus* and *avulavirus*) and *Pneumovirinae* (containing the *pneumovirus* and *metapneumovirus* genera) [220,221]. Paramyxoviruses have non-segmented negative-sense RNA genomes of between 15 and 19 kb in length [222]. One characteristic of this virus family, and other negative-strand RNA viruses, is that naked RNA when transfected into cells is not infectious in contrast to the full-length genome RNAs of positive-sense RNA viruses. The minimum protein requirement for RNA transcription and initiation of infection is the association of the nucleoprotein (N), the phosphoprotein (P), and the polymerase (L) with the RNA genome which are the components of the functionally active ribonucleoprotein complex (RNP). The current technique for the recovery of virus from an infectious clone by reverse genetics involves co-transfection into permissive eukaryotic cells of plasmids expressing the mRNAs of the viral RNP proteins and a full-length genome RNA. The expression of these RNAs is generally controlled by phage T7 promoters and the T7 polymerase is supplied to the cell by prior infection with a recombinant poxvirus expressing this protein.

Live attenuated strains of these viruses are extraordinarily good inducers of humoral immune responses and cellular immunity. Most importantly, in the case of NDV, MV and PPRV or RPV vaccines, individuals are completely protected from homologous virus challenges and display no virus shedding or signs of disease. They also induce a life-long protection after either a single or two-dose administration. Moreover, they can be produced in large scale in most countries and can be distributed at low cost. NDV vaccines are administered through drinking water or spraying flocks, making feasible the vaccination of large populations of poultry in the field at very low cost. Paramyxovirus genomes can accommodate additional genetic information, enabling the expression of at least one foreign antigen, and the inserted genes are stably maintained during serial passage in cell culture. Because of these desirable characteristics, *Paramyxoviridae* vaccines are being engineered to develop recombinant vector vaccines able to express high levels of foreign proteins which can then be used to immunise against infections by both the homologous virus and other infectious agents.

To explore the potential of the *Paramyxoviridae* as vaccine vectors, a number of investigators have generated recombinants of viruses of major scientific, human and veterinary importance. The feasibility of this approach was first demonstrated by introducing reporter genes into the genomes of the human RSV, the prototype member of the genus *pneumovirus* [223], and the Sendai virus [224]. Subsequently a number of research groups used other paramyxoviruses to express foreign proteins. These include the foot-and-mouth disease virus polymerase ($3D^{pol}$) and part of the capsid protein from the RPV vaccine strain [225]; the green fluorescent protein (GFP) from SV5 [226,227]; the G glycoprotein from VSV substituting for the reading frames both envelope glycoproteins (haemagglutinin (H) and fusion (F)) of MV [228] proteins from West Nile virus and other flaviviruses from the MV vaccine strain cDNA [229].

Development of maker vaccines for DIVA strategies is very important for veterinary vaccines [230]. For example, vaccination with the live attenuated vaccine to combat Newcastle disease is highly effective but vaccinated poultry cannot be distinguished from those infected by wild-type virus, thus making it difficult to detect wild type viruses that may be circulating. In order to overcome this problem, a recombinant virus was generated that expressed the NDV F protein and a chimeric haemagglutinin (HN) protein whose immunogenic globular head was replaced by that of avian paramyxovirus type 4 (APMV4) [231]. Protective neutralizing antibodies against the NDV F protein are produced on vaccination, while those produced against the APMV4 HN protein allow a serological distinction of vaccines from wild-type NDV infections [231]. In another study deletion of a B-cell immunodominant epitope in the C-terminal region of the N protein from NDV generated an efficient negative-marker vaccine [232]. This successful result indicated that it is possible to find a sequence in the N protein that is highly immunogenic but dispensable for virus growth. The deletion of this sequence does not affect the efficacy of the recovered NDV vaccine since an N-specific immune response is not absolutely required for the protection of poultry against a lethal challenge [233,234].

The pandemic spread of highly pathogenic avian influenza virus (HPAIV) is of special importance since it poses a significant threat to both animal and human health. A number of studies have explored the possibility of creating safe recombinant viruses expressing the protective proteins of the H5N1 strain. This would overcome the safety limitations that hinder the production and widespread use of the current influenza vaccines in the field. Haemagglutinin (HA) of the H5 subtype HPAIV was expressed from recombinant vaccine strains of NDV and this virus has been used successfully to vaccinate large numbers of animals. In a recent study [235] both a wild-type and a mutated HA open reading frame of an HPAIV derived from a wild bird isolate, were inserted into the intergenic region between the P and matrix (M) genes of the LaSota NDV vaccine strain. A single dose of the recombinant viruses in chickens induced both NDV- and AIV H5-specific antibodies and completely protected chickens from challenge with a lethal dose of both velogenic NDV and homologous and heterologous H5N1 HPAIV.

In an approach similar to that of the NDV B-cell epitope deletion, the N protein gene of rinderpest was replaced by that of PPRV. This exchange deletes rinderpest-specific epitopes in the N protein and this chimeric virus can act as an effective marker vaccine for RPV [236]. Another promising approach to marker vaccine development is the exchange of glycoproteins between members of related *Paramyxoviridae*. Since these proteins are immunogenic and protective, their replacement with the corresponding gene(s), or part of a gene, from another virus can give rise to a new and viable chimeric virus [237,238]. Glycoproteins were exchanged between *respirovirus* and *pneumovirus* genera [239] as a first step on the way to developing an attenuated bivalent live vaccine against the two most important viral pathogens in the bovine respiratory tract, BRSV and BPIV-3. BRSV gycoproteins (G and F) were replaced by the HN and F proteins of bovine PIV3 (bPIV3). Similarly, the envelope proteins have been exchanged within the *morbillivirus* genus. The M, the F and H protein genes of rinderpest virus were replaced by those of PPRV using the RPV vaccine as the backbone. Goats were protected against virulent PPR challenge with the resulting chimeric PPR marker vaccine [240]. The widespread use of such vaccines, along with the diagnostic tests to identify their serological signature, would greatly improve the surveillance capabilities for disease preparedness and emergency prevention procedures.

3.2.2. *Rhabdovirus*

Among the *Rhabdoviridae* family are the causative agents of three very different and important diseases: rabies, bovine ephemeral fever, and vesicular stomatitis. In particular, rabies virus (RV) and vesicular stomatitis virus (VS) have been used as viral vectors and as vaccine vehicles [241]. Employing reverse genetics, the viral non-segmented negative stranded RNA genomes became accessible to genetic manipulation [242–244].

RV and VSV accept additional transcriptional units and maintain an unexpected genetic stability of the modified genome [245–247]. Due to the life cycle of members of *Rhabdoviridae*, recombination, reversion, and integration of viral genome into the host genome does not occur. Many foreign genes have been inserted into and expressed by rhabdovirus-based vectors [248,249]. While VSV expresses foreign proteins at a high level and is highly cytopathogenic to infected cells, RV is non-cytopathic to infected cells and expresses modest to high levels of foreign proteins. Both viruses and viral vectors derived from these viruses are highly immunogenic and elicit humoral, cellular, and innate immune effector pathways. Additionally, other mechanisms such as viral interference [248] and efficiency of viral-vector spread [250] might contribute to successful vaccination using rhabdoviral vectors. Application of this kind of vectors is further eased due to almost complete absence of seropositivity in humans and animals.

As for all biological vectors, safety concerns exist and have been addressed. For both viruses attenuated strains have been generated through molecular and virological manipulations [251]. A major focus of attenuation is the viral glycoprotein, which can be modified, substituted with other glycoproteins, or deleted. Other viral gene products contributing to virulence such as the phophosprotein have also been targeted for modifications. Another method to achieve attenuation of RV and VSV was rearranging the gene order within the genome [252]. This approach appears to shift the balance between viral gene expression and viral replication more towards expression.

3.2.3. Bunyavirus

The *Bunyaviridae* family is the largest known family of animal RNA viruses, representing important human and animal arthropod and rodent-borne pathogens. The *Bunyaviridae* are tri-segmented negative sense RNA viruses. Reverse genetics systems have been described for some members of the genus Bunyavirus [253,254]. Very recently foreign gene expression has been demonstrated for the first time in any bunyavirus by means of a Rift Valley fever virus, T7-RNApol driven, reverse genetic system [255]. Deletion of the viral interferon antagonist gene NSs highly attenuates the virus and provides room for insertion of foreign sequences. The attenuated virus can still be propagated in type I-IFN-deficient cell lines and remain highly immunogenic, eliciting very efficient neutralizing antibody responses. The ability of bunyavirus to infect many vertebrate cells makes them attractive candidates for future developments as viral vectors.

3.2.4. Alphavirus

Other viral vectors and potential antigen delivery strategies in veterinary species can be found in studies dealing with human pathogens. Good examples are expression strategies relying on the use of replication-deficient alphavirus, modified for expressing foreign antigens. These have been used as candidate vaccines, and in anti-cancer and gene therapy strategies. Alphaviruses belong to the *Togaviridae* family and contain a 12 kb ssRNA(+) genome with two ORFs, the first one encoding 4 non-structural proteins and the second one encoding 4 structural proteins controlled by a subgenomic promoter. The three prototype viruses are Sindbis (SIN), Semliki Forest Virus (SFV) and Venezuelan equine encephalitis virus (VEE). Three types of vector systems have being engineered, replication-deficient viral particles (replicon particles), replication-competent viral particles and DNA/RNA-based vectors. Most vaccine studies have been addressed in mouse models [256] with a few examples related with animal diseases. VEE replicon vectors expressing the two major envelope proteins (GP5 and M) of equine arteritis virus (EAV) have been used for horse vaccination against a virulent EAV challenge [257]. This study, together with others in human pathogens, demonstrates the ability of alphaviruses to induce protective mucosal responses in horses after intranasal or intrauterine EAV challenge. Therefore, an interesting aspect of the alphavirus replicon particle is the potential ability to induce mucosal immunity as also shown for SIN [258] and SFV [259]. In addition the ability of VEE and SIN glycoprotein E2 to target dendritic cells has been reported in mice [260] and humans [261]. The use of self-replicating alphavirus DNA vectors containing RNApol II promoters may provide an alternative to increase the immune stimulation. At least in mice, antigen specific immune responses can be obtained with lower DNA doses with compared to conventional plasmids [262,263]. SIN-based DNA vectors were used to prime immune responses against Aujezsky's disease in pigs [264] or to decrease strongly the quantity of plasmids needed [265].

3.2.5. Coronavirus

Coronavirus based-vectors are emerging with high potential for vaccine development. Coronaviruses (CoVs) have several advantages as viral vectors: (i) CoVs are single-stranded, positive-sense RNA viruses that replicate in the cytoplasm without a DNA intermediary, making integration of the virus genome into the host cell genome unlikely [266]; (ii) these viruses have the largest RNA virus genome and, in principle, have room for the insertion of large foreign genes [267]; (iii) a pleiotropic secretory immune response is best induced by the stimulation of gut-associated lymphoid tissues. Since CoVs, in general, infect the mucosal surfaces (both respiratory and enteric), CoVs may be used to target the antigen to the enteric and respiratory areas to induce a strong secretory immune response; (iv) the tropism of CoVs may be engineered by modifying the S gene [268]; (v) non-pathogenic CoVs strains infecting most species of interest (human, porcine, bovine, canine, feline, and avian) are available and therefore suitable to develop safe virus vectors; and (vi) infectious CoV cDNA clones are available to design expression systems.

Reverse genetics for CoVs was first achieved by targeted recombination [269]. Soon after, the first CoV infectious cDNA clones were constructed for transmissible gastroenteritis CoV (TGEV) [270,271]. These achievements were followed by the development of infectious cDNA clones for human coronavirus (HCoV) 229E [272] and HCoV-OC43 [273], severe and acute respiratory syndrome coronavirus (SARS-CoV) [274], mouse hepatitis virus (MHV) [275], and for avian coronavirus [276].

Using the TGEV infectious cDNA maintained as a BAC, the green fluorescent protein (GFP) gene was successfully expressed by replacing the non-essential 3a and 3b genes by sequences encoding GFP. The engineered genome was very stable (>30 passages in cultured cells) and led to the production of high protein levels (50 μg/10^6cells) [277]. Using this vector the bicistronic expression of two surface proteins of porcine respiratory and reproductive syndrome virus (PRRSV) virus (Gp5 and M proteins) has been shown. After more than ten passages in tissue culture 80% and 100% of virus infected cells expressed Gp5 and M proteins, respectively (L. Enjuanes, personal communication). This vector was also used for bicistronic expression of rotavirus VP2 and VP6. These viral proteins self aggregated leading to the formation of rotavirus like particles (VLPs) in the cytoplasm of infected cells (J. Ceriani, J. Buesa, L. Enjuanes, Javier Ortego, unpublished results). Therefore, expression levels using these vectors are similar to those described with vectors derived from other positive strand RNA viruses such as Sindbis virus [278]. Using TGEV-derived vectors expressing GFP, the induction of lactogenic immunity has been demonstrated [277]. Recombinant TGEVs have also been assembled by *in vitro* junction of six cDNA fragments encoding a full-length genome. Using these systems, GFP gene replaced ORF3a, leading to the production of a TGEV that grew to titres of 10^8 pfu/ml and expressed GFP in a high

proportion of cells [279]. Finally, CoV-derived virus vectors have been engineered for infectious bronchitis virus (IBV). GFP protein was expressed replacing the non-essential gene 5a. The recombinant virus grew to a titre 10-fold lower than that of the wild type virus, and GFP expression was lost at a very early passage [280].

Propagation-deficient CoV-derived vectors have also been generated based on replicons derived from TGEV and HCoV-229E. The advantages of these systems are; (i) an increased room for the insertion of foreign genes when compared with full-length infectious cDNAs, as the structural genes were deleted, (ii) the possibility of engineering multigene expression vectors due to the transcriptional strategy of CoVs and, (iii) an increased level of safety as the replicons are non-infectious. TGEV-derived replicons have been generated from the infectious cDNA. GFP protein was successfully expressed from these replicons, with high expression levels in 80% of the transfected cells [281]. Replicons derived from HCoV-229E expressing GFP were also generated (0.1% of cells) [282]. These levels were increased up to 3% by co-transfection of N protein mRNA [283]. A multigene vector based on HCoV-229E replicon has also been constructed that expressed GFP, chloranphenicol acetyltransferase (CAT), and firefly luciferase (LUC). Heterologous gene expression levels were up to 3% GFP-positive cells, CAT levels of 0.46 ng/10^6 cells, and LUC activity of around 25.0 relative light units/10^6 cells [284]. Human CoV-based vector RNA can be packed into propagation-deficient pseudovirions that, in turn, can be used to transduce immature and mature human dendritic cells.

Safe replication-competent propagation-deficient virus vectors, based on TGEV genomes deficient in the essential gene E (obtained by using E^+ packaging cell lines), have also been developed [285]. Two types of cell lines were constructed, expressing transiently or stably the E protein from TGEV. Virus titres were directly related to E protein expression levels that were higher in the transiently expressing cell lines. In the absence of E protein immature TGEV particles of a size slightly larger than the mature viruses were formed. These particles were not released to the supernatants of infected cultures, whereas infectious viruses were assembled in packaging cell lines providing the E protein in trans [286]. The ability to generate TGEV-ΔE mutants that are replication-competent but propagation-deficient by complementation in packaging cell lines, supports the potential use of coronavirus as vaccine vectors.

3.2.6. Retrovirus

Among the *Retroviridae* family, the foamy viruses (subfamily *spumavirinae*) and Lentiviruses (subfamily *lentivirinae*) constitute potential delivery ssRNA(+) viral vectors. Lentiviral vectors can be considered promising vaccination vectors since they are good inducers of protective CTL responses [287,288] and efficiently transduce dendritic cells [289], therefore ensuring the induction of Th cell responses and correct development of antibody responses. Among the common advantages of lentiviral vectors are genetic stability and the expression of the vaccine antigen over a period of time, favouring the triggering of immune responses. More recently a lentiviral vector (TRIP/sEWNV) expressing a soluble form of the WNV glycoprotein E (strain IS-98-ST1) induced a strong and long-lasting neutralizing antibody response after a single i.p. dose in 129 mice [290]. This antibody response correlated with the full protec-

Table 6
Advantages and disadvantages of different antigen delivery systems.

Delivery system	Advantages	Disadvantages
Modified live vaccines (MLV)	Strong cellular and humoral immune responses; lifelong protection	Reversion to virulence; teratogenicity in pregnant animals
DNA viral vectors	Large capacity for extra genes; multivalent vaccines	
Poxvirus	Replicative poxvirus: cytoplasm replication; long-lasting immunity after single injection; activation of cell and humoral immune responses; easy to produce; low cost; thermo resistance; immunogenic by various routes Non-replicative poxvirus: limited spread; low immunity against the vector; priming young animals with maternal Abs; boost the IR after vaccination; require high doses; DIVA	Immunity against the vector after repeated use (pre-existing immunity)
Herpesvirus	Large genome size; availability of methods to manipulate the genome	Reversion to virulence; integration in the host genome
Adenovirus	Potent humoral and cell-mediated immune responses; intrinsic adjuvant properties, long-term low level antigen presentation; effective oral vaccines	Potential release as GMOs Limited capacity of adenovirus for insertion of foreign genetic material
Baculovirus	Insertion of large foreing DNA fragments; transduction of many cell lines and primary cells; do not replicate in vertebrate cells; no cpe in transduced cells; adjuvant properties	Virus inactivated by complement proteins; few data/studies on immunization
RNA(−) viral vectors	RNA not infectious; stability after serial passages	
Paramyxo	Good humoral and cellular immune induction; complete and lifelong protection without virus shedding, low cost vaccination procedures; chimeric marker vaccines possible	GMO release
Rhabdovirus	Genetic stability; high level expression of foreing proteins; highly immunogenic (humoral, cellular and innate effector mechanisms activated); complete absence of preexisting immunity in animals/humans	GMO release
RNA(+) viral vectors		
Alphavirus	Inductors of mucosal immunity Target dendritic cells (E2); replicons allow high level expression	GMO release
Coronavirus	High capacity among RNA vectors (Coronavirus); secretory immune response; modifiable tropism; non-pathogenic infect most species of interest	Preexisting immunity against the vector
Retrovirus	Good inducers of protective CTL responses; transduction of dendritic cells; genetic stability; long-lasting expression of antigens;	Integration in host's genome
Flaviviruses	Possible interchanging of genes, generating chimeras	GMO release

tion observed in the mice after lethal WNV challenge. In addition to this, the potential of replication-competent feline foamy virus (FFV) based vaccine vectors for vaccination purposes has been investigated [291]. FFV vectors expressing neutralizing epitopes from feline calicivirus (FCV) capsid protein induced humoral responses against both the vector proteins and the heterologous capsid antigen. After challenge of cats with homologous FCV virus shedding and disease specific clinical signs were significantly reduced. Other vectors derived from the bovine lentivirus Jembrana disease virus (JDV) have been developed [292] by means of the generation of bicistronic transfer vectors. The JDV-based vector could be pseudotyped with VSV-G protein and exhibited a broad tropism, useful for further vaccine developments.

3.2.7. *Flavivirus*

New emerging vectors may also provide opportunities for the generation of novel delivery systems. Novel viral-vectors based in the prototype of a live attenuated vaccine for yellow fever (YF17D) are being used as a vector system in developing vaccines against other flaviviruses including West Nile virus [293]. The approach of interchanging of genes encoding coat proteins of YF with those corresponding to the other flaviviruses, generating chimeric viruses, has been also used successfully for the generation of chimeric viruses as novel vaccines for pestiviruses [294]. As for YF based vectors, the possibility of using CSFV attenuated vectors for expression of heterologous genes in swine should be explored further.

4. Conclusions

A large number of different strategies for vaccine antigen delivery are available, many of them offering considerable advantages over classical vaccines (Table 6). However we cannot yet predict the most appropriate delivery technology to make an effective vaccine. We still do not know why certain antigens appear to work better than others using the same delivery system. The reductionistic vaccine approach seeks to look for a single antigen or antigenic determinant to be delivered by itself or using a heterologous expression system. This may have clear advantages including safety and ease of production but may compromise the immunogenicity and therefore the vaccine efficiency. A non-reductionistic vaccine approach aims to find ways to rationally attenuate the virulence of each specific pathogen. Based on the examples found in the literature this approach renders the most effective vaccines however raising more safety concerns. Between these extremes is a plethora of different strategies which provide a good compromise between safety and efficiency but as yet lack data regarding field performance. Whether a vaccine is to be applied for livestock species, the pet industry or to avoid the spread of a pathogen in a non-endemic location will depend more on biosafety considerations than on the experimental data. In spite of all the advances in the field, few strategies reach final validation for field use. Animal health policy requirements for improved vaccines usually delays or precludes their implementation in the field. In contrast, the experimental vaccines have shed more light to understand the immune mechanisms elicited in the host that are able to confer protection against disease. From this point of view, delivery systems are essential tools for vaccine development.

Acknowledgement

This work was supported by the EU Network of Excellence, EPIZONE (Contract No. FOOD-CT-2006-016236).

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