



Review Article

Better Understanding of Important Aspects Associated with Vaccines Development for Controlling Viral Diseases in Animals

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Abstract

Multiple production sectors including the dairy one depend on having animal wealth free of diseases. Vaccination is the best approach to control most of animal diseases and epidemics. Most of the available vaccines are produced by the classical technology (inactivated and attenuated vaccines) which in some conditions may not be ideally used in relation to safety or inappropriate application in the disease free areas. Another step forward is required to develop and improve vaccines production by the use of recent generation vaccine technologies previously assessed in experimental work. The great advances in genomic sequencing of viruses nucleic acids and the use of comparative genomic and transcriptome analysis greatly enabled in exploring a new generation of vaccines including, recombinant subunit vaccines, virus-like particles, DNA vaccine, vector-vehicle vaccines, reassorted vaccines and concept of marker vaccines. The development of animal viral vaccines also relies on the appropriate selection of the effective strain and the choosing of proper antigen(s). At the same time, the attention should also be directed towards selecting the appropriate adjuvants. Understanding of the external factors around the process of vaccination as the strategy of disease eradication, animal age, vaccination time and the national regulation of vaccine licensing is so important in vaccine improvement. It is recommended to continuously update the strains used in the preparation of traditional vaccines according to the field circulating virus strains, adding to the establishment of new approaches to formulate new vaccine preparations with novel adjuvants and application of marker vaccines in eradication programs.

Key words: Vaccine technology, development aspects, vaccines types, antigen selection, adjuvant, marker vaccines

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INTRODUCTION

Most of the animal outbreaks are due to viral infections which cause severe economic losses adding to the zoonotic importance¹. Viral vaccines are biological formulations prepared by inactivation or attenuation of viruses that induce specific and adaptive immunity against the objective virus. Vaccines should not cause any disease signs but trigger animal immunity. Controlling of farm animals diseases using vaccines leads to improve their productivity and effectiveness for food chain purposes².

Controlling of viral diseases through using effective vaccines is the best economically effective approaches not only to control outbreaks³, but also to establish a status of complete disease free areas as in the case of using the live-attenuated vaccine to eradicate cattle plague virus⁴. Moreover, vaccination against zoonotic diseases in farm animals would be anticipated to decrease and prevent the hazard of spread of such affections to the human in addition to protection of farm animals⁵.

The vaccine production industry has gradually grown due to the increased needs for novel and improved vaccines to counteract the several re-emerging virus outbreaks in production herds⁶. Usage of vaccines to eradicate viral diseases would be an appropriate policy comparing with the other antiviral preparations. Although an overabundance of vaccines is produced, some viral vaccines are incapable to counteract most of the prevalent viruses⁷. Consequently, novel vaccines should be continuously prepared from the recently evolved isolates. Generally, vaccines are produced by several different methods either classically including, inactivation or attenuation of the virus. While the second group is the modern developed methods (genetically engineered), subunit protein, recombinant or vectored vaccines and production of virus like particle (VLP)⁸.

The present review will focus on the different types of vaccines for controlling of viral diseases in animals, passing through the classical and recent developed vaccine methodologies. Furthermore, the different factors related to vaccines development will be highlighted.

HISTORY OF VACCINE DEVELOPMENT

Historically, the first trial of Edward Jenner to immunize human by smallpox at 1796 proved that injection of a skin lesion obtained from a farmer suffering from cowpox was capable to protect humans from smallpox infection⁹. It was the first step and milestone start in vaccine production. Furthermore, vaccination by rabies virus was the actual initial

virus intentionally attenuated in the lab to generate an attenuated virus vaccine for humans¹⁰. In the following decades, succeeding in the adaptation of different viruses in the embryonated chicken eggs and tissue culture cells resulted in a revolution of viral vaccine production and facilitated the in vitro mass production of vaccines¹¹.

Inactivation or attenuation of viruses was the standard procedures in the 20th century to produce a vaccine¹². During the period between 1950 and 1980 many attenuated vaccines were developed using tissue culture propagation¹³. Since the 1970s, the introduction of DNA manipulation techniques empowered an additional technological jump in vaccine development¹⁴. Usage of genomic information delivered not only new methods for viral attenuation but also supported novel vaccine invention. Antigens expression from its cDNA was innovate, subsequently, the production of huge quantities of pure immunogens was enabled. Furthermore, the development of tissue culture cell lines allowed the production of a large volume of vaccine batches¹⁵.

ASPECTS TO DEVELOP AND IMPROVE VIRAL VACCINES

Animal aspects: The animal species has to be considered in vaccine improvement as it is frequently the main element of the economic importance. Naturally, vaccination is not only directed to target the susceptible animal hosts but also for the reservoir animals that keep the risk for other animal species. On the same hand, vaccination of animals against some zoonotic diseases protects human from infection. For Example, vaccination of the domestic and wild canines against the rabies virus¹⁶.

Different animal hosts might be infected with the same virus. Accordingly, the immunological effect of a vaccine may differ among the variable animal hosts as in foot and mouth disease virus in foot cloven animals, also Lumpy skin disease with goat pox virus¹⁷.

The IgG subclasses play an important role in humoral and mucosal immunity in equines. In 2004, the equines immunoglobulin heavy chain constant region genes were discovered¹⁸. Equines are dissimilar in their ability to express seven IgG subclasses. Best immune response to infection is produced by the Fc receptor. So, an effective vaccine has to provoke IgG antibodies of particular subclasses, while other IgGs could contribute weakly in the active immunity¹⁹.

Sometimes many animals do not adequately respond to the delivered vaccine and are unable to develop immunity, so they are considered as non-immunized. Several factors affect the progress of the immune response in the host and could lead to apparent vaccination failure. Some causes of this

failure were determined and being avoided in the recently developed vaccines¹⁵. The causes related to the animal are the age, individual variation, nutrition, physiological status, immunodeficiency, immunity interference and stress²⁰.

Concerns about the best suitable method of vaccine delivery and local immune reaction are determined by try and error method. The sites of infection for many viruses are the mucosa, so stimulation of immunity at a mucosal level is important to avoid viral pathogens infection. Hence, many trials were prepared to apply the vaccine through the oral, ocular and nasal mucosa^{21,22}. Usually, stimulation of any mucosal surface results in secretion of IgA at different mucosal spots²¹. Based on the vaccine type, different routes of administration could be used with the oral one which is highly preferred in the large herds particularly in the wild animals. Nevertheless, vaccination delivery to the later necessities application of specific tools like baits as in rabies vaccine²³.

DNA vaccines need special injection tools for effective antigens delivery, like intradermal inoculation, biolistic particle injection, gold nanoparticle and electroporation, but these devices are not yet in routine use with farm animals²⁴.

Vaccine types

Inactivated virus vaccine: Inactivation of viruses was carried out through different methods either chemically like using formalin or binary ethyleneimine treatment or physically as using heat or irradiation²⁵. For several years, immunization with the inactivated vaccines was carried out to provide protection against different diseases such as bovine respiratory syncytial virus²⁶, equine influenza virus²⁷ and bovine viral diarrhea virus (BVDV)^{28,29}.

A vaccine based on the inactivated virus is usually constant and preserve a whole sum of the viral antigenic make-up²⁹. Nonetheless, the inactivated virus is not capable to infect or multiply inside animal tissue. The inactivated virus vaccines exert their effect through humoral immunity stimulation not the cellular one which provides more broad cross reactivity but, this drawback may be overcome by development of polyvalent inactivated sero or genotypes strains in the same vaccine formula. Consequently, the inactivated vaccines often need to be boosted in addition to using of potent adjuvants combination to confirm proper immunization³⁰.

Moreover, reduction in the cost and duration of inactivation of a virus is an important part in vaccine improvement; for example rabies virus was inactivated quicker by H₂O₂ 3% than that done by Beta-propiolactone and mice

immunized with the H₂O₂ inactivated viruses induced adequate level of antibodies and had been protected when challenged with wild rabies virus³¹.

Live-attenuated virus vaccine: The live-attenuated vaccine is a reduced virulent virus of the wild parent type that could multiply within the animal host. So, prompting cellular and/or humoral immunity which confer protection against the pathogenic wild virus. It seldom requires an adjuvant addition. Viral attenuation process could be done through virus inoculation into tissue culture or in non-specific hosts resulting in virulence reduction³². It is worth to note that, eradication of rinderpest virus in Egypt, was the result of the effective application of successful live-attenuated vaccination³³.

As the attenuated virus vaccines induce stronger T cellular immunity and high amount of specific humoral immunity, it is considered to be more effective than the inactivated ones. On the other side, one of the drawbacks of this type is the possibility of the vaccine virus strain to return to a wild type or remerge with wild viruses resulting in inducing an infection as in BVDV and porcine reproductive and respiratory syndrome virus (PRRSV). Furthermore, using of the live-attenuated vaccines during pregnancy is so risky for the reason that may be transmitted to the embryos that can cause persistent infection of the offspring³⁴.

Subunit vaccine: Safety is the most prominent advantage of this vaccine type. Meanwhile, the main 2 obstacles are the determination of the protective antigen(s) responsible for inducing the protective immunity and keeping the confirmation and folding structure of the expressed antigen otherwise it will be considered to be a different antigen not resembling the protective one. Such type of vaccine is less available in the vaccine market due to many limitations including; its fair protective effect, the need for boosting, using of adjuvants and the cost of production. Nevertheless, some subunit vaccines are available in the market e.g., the porcine PCV vaccine[®] which is an expressed protein of open reading frame (ORF)2 of the porcine circovirus (PCV)2³⁵.

The virus protein 1 (VP1) is a structural protein produce neutralizing antibodies of foot and mouth diseases virus (FMDV) and the 3D protein is a functional polymerase that is extremely conserved for all serotypes and intensely protective. Subunit vaccine of VP1 and 3D induce humoral immunity, indicating that they can be a subunit vaccine candidates against the infection with FMD³⁶.

Recombinant vector vaccine: It is a nonpathogenic vector organism is carrying the gene(s) of a targeted virus which can be presented and expressed, e.g., the equine influenza vaccine recombinant on canary pox virus³⁷ (Protaq-Flu/Recombitek, Boehringer)[®] and the recombinant parainfluenza virus 5 expressing rabies antigens vaccine³⁸. Usually, the pox viruses are the commonly used vaccines vector as their properties are ecologically strong, genetically steady, safe, produce durable protection and able to carry a long fragment of ligated DNA. Another vector is the vaccinia virus used for rabies vaccines which is the most effective vaccine vector against rabies in wild carnivores³⁹. A novel approach is to produce an attenuated vector virus carries the genes of the target virus to generate a polyvalent vaccine producing protection against both of them⁴⁰. It is important to mention that continuous determining of the circulating field pathogens through surveillances is crucial for developing suitable vaccine for each country⁴¹⁻⁴³, adding to establishment of new laboratory animal models to evaluate such developed vaccine and any biological products^{44,45}.

DNA vaccine: The inoculated naked recombinant-plasmid can express viral proteins in animal tissue cells, precisely cells of muscles and epidermis epithelia. The DNA vaccines are comparatively of low cost in production and adequately steady to avoid the need for transportation and storage in special temperature. Nevertheless, it needs a large dose to be injected to elicit protective immunity. Recently, the using of DNA vaccines declared promising results for controlling of the highly contagious viral infections⁴⁶. A DNA vaccine containing FMDV VP1 epitopes has the ability to elicit both cellular and humoral immunity in swine⁴⁷. Improvement of DNA vaccine efficacy resulted from using a new technique by delivering the specific immunogens to the specific antigens presenting cell (APC)⁴⁸.

Virus like particle (VLP) vaccine: During the intracellular virus multiplication process, non-replicating, nonpathogenic VLP(s) are produced and they are similar to the parent virus particles in the antigenic structure. It is different than the live-attenuated virus because of the inability to produce a viral infection. The VLP vaccine is a fairly novel trend in vaccine research although there are no disadvantages comparing to other vaccines types because of the absence of the nucleic acid of the virus adding to neither reassortment nor revertant to the virulent wild virus^{49,50}.

Animals innate immunity are extremely adjusted to identify and phagocyte the VLPs after administration. A significant small dose of VLP immunogens is adequate to

induce homologues defensive immune response adding to initiating CD⁴⁺ T cell invasion and cytotoxic T cells reaction⁵¹. It can produce strong solid, long immunity to a variety of viruses. The antigenic structure differs between the variant families, so not all types could be suitable for forming the VLP vaccine⁵¹. However, a better understanding of the virus multiplication is required to produce VLP vaccines⁵⁰.

For instance, the recombinant (pentamer) structure of FMDV was carried out by expressing the P1 and 3C antigens⁵². They were physically analogous to the authentic pentamer subunit from FMDV. A swine vesicular disease virus (SVDV) like particle was produced by synchronized expression of P1 and 3CD antigens to protect against the SVDV⁵³. As a try to generate new vaccines against porcine encephalomyocarditis virus (EMCV), a plasmid containing P12A and 3C genes of EMCV was produced and expressed in insect expression cells⁵⁴. For porcine reproductive and respiratory syndrome virus (PRRSV), VLPs which express M and N antigens were produced in insect cells and injected into mice to assess their ability to induce PRRSV specified immunity. PRRSV-VLP provoked strong immunity in addition to an appropriate antibodies production⁵⁵.

Plant based/edible vaccine: Expressing of the recombinant virus immunogen(s) that could be nourished to target animals with the intention of producing and maintaining a protective immunity is a smart choice that has been sight seen for the last twenty years, for example blue tongue virus and PRRSV⁵⁶. Multiple studies showed that the developed examples of plant-based veterinary vaccines declared strong indication in terms of efficacy in animal disease prevention plants⁵⁷. A recombinant cucumber mosaic virus based expression system has been developed for the production of an immunogenic PCV epitope. The results indicated an eliciting of specific immune response in mice and pigs, when administered parenterally⁵⁸.

In spite of the production of external proteins in plants is generally considered safe if compared to mammalian cell systems, as they are less likely to harbor microbes or prions that are pathogenic to humans or animals⁵⁹, there are worries about the public approval of the genetically modified food stuffs for farm animals and the bio-risk may be carried to contaminate the human plant for feeding or the plant ecology⁶⁰.

Antigen selection: The answers to the question whether adequate protecting immunity can be obtained using an antigen or several antigens are necessary to be taken into consideration during developing of vaccines. Even when the

protective antigen is identified, there are significant respects and restrictions that frequently command the nature of the vaccine that will be developed. The single stranded RNA viruses including lentiviruses as feline immunodeficiency virus (FIV) are characterized by continuous occurrence of antigenic drift and shift which means that a vaccine settled to only a single variant offers partial cross-protection to other variants, giving a main difficulty for vaccines improvement⁶¹.

Type of adjuvant: The main roles of adjuvant are to improve or to extend the period of immunity, rapid initiation of cellular and humoral immune responses, lengthen the immunological memory, decreasing the amount of antigen required to create immunity and or a mixture of these actions^{62,63}. Accordingly, the selection of adjuvants is significantly important. Although usage of adjuvant in animals is not devoid of prominent drawbacks; the incidence of vaccines related malignant sarcoma of felines is endorsed to the usage of alum-adsorbed vaccines^{64,65}. The bleeding disorder (bovine calf pancytopenia) that occurred in many countries was described to be related to the usage of BVDV vaccines (PragSure), which, it was discovered that might be due to the existence of sufficient quantities of bioprocess contaminations inside the vaccines combined with the potent adjuvant³⁷.

On the same side of vaccine improvement, Montanide (IMS 3015) was assessed the assessment was done in how to improve the quality of rift valley fever virus (RVF) vaccine related to the classical adjuvant which is alum gel⁶⁶. Evaluation of the vaccinated sheep was carried out through measuring renal function tests, hepatic activity tests and other immunological tests. Furthermore, the vaccine prompted quick start of immunological reaction with longer duration different than inactivated RVF vaccine with alum gel⁶⁶. While, a study of polyvalent inactivated vaccine against bovine respiratory disease viruses combined with *Nigella sativa* oil as adjuvant induced protective antibody levels in Buffalo-calves up to the 7th month after birth, so the vaccine provided a long term period of protection and safe in buffalo and their calves⁶⁷. Recent studies about the use of Montanide AS 206 instead of alum gel in the inactivated respiratory virus vaccine Pneumo-4 resulted in longer immune response and higher antibodies titer in the vaccinated calves with Montanide adjuvant vaccine⁶⁶. A study for the control FMDV for stopping viral invasion was applied using two FMDV vaccine preparations; Montanide ISA 206 oil-based FMD inactivated vaccine and Montanide IMS 1313 VG NPR-based concentrated semi-purified FMD mucosal vaccine. Intranasal vaccination by

the FMD mucosal vaccine produced IgA level in both nasal and salivary secretions and also a high reaction of lymphocytes proliferation to protective level reached 20 and 40%, respectively⁶⁸.

Special aspects

Vaccine interference: Vaccine interference is a complicated phenomenon and usually is difficult to be understood but simply it could be defined as a state which vaccination against a specific virus may hinder other vaccine or the protecting immune response prompted by a vaccine to another as in case of an existence of maternal antibody that interferes with vaccine in newly born offsprings. Interference of maternal antibodies is an important concern of a variety of animal viral vaccines. That is considered a source of complications for the young swines vaccine of Influenza⁶⁹. Also, the presence of maternal antibodies inhibits the induction of humoral response after immunization with killed or live-attenuated BVDV vaccines. Foot and mouth disease is one of the most viral epidemics affecting cloven hoofed animals with world wide distribution⁷⁰. Many countries specially the poor ones depend on establishment of vaccine programs to control the FMDV. Accordingly, the offspring calves having maternal antibodies within the colostrum from the immunized dams offer not only immunity against infection with the virus but also interfere with the progress of active immune response after vaccination, allowing young animals vulnerable to FMDV infection when colostrum antibody diminishes at the weaning time. It is worth noting that, the recent existing vaccines do not stop these criteria⁷¹.

Incomplete protection and vaccine escape variants:

Incomplete protection does not necessary to ascend from the emergence of a novel mutant but can arise from the usage of a vaccine that does not offer adequate cross-protection of one virus to other causing domination of single type by the time in the circle of infection. This describes the failure to control canine distemper virus (CDV) disease, as more than two diverse CDV mutants are in circulation which varied from the strains in the vaccines. Accordingly, the preparation of multiple geno/serotypes in the same vaccine formula could be a solution to overcome this drawback. Otherwise, autogenous vaccines can be applied^{72,73}.

These cases of incomplete protection are clear in viral pathogens of a high mutation rate resulting in the emerging of different variants, e.g., TJ strain of pseudorabies virus (PRV), which is a mutant of PRV that seems to be emerging along

with other pig herds as a result of immunization by the live-attenuated vaccine strain Bartha-K61, which up to the present played a serious problem in the eradication of pseudorabies virus⁷⁴.

Marker vaccines: Different countries are using marker vaccine in immunization programs to protect the animals against diseases with the ability of differentiation between the vaccinated animals and those that have been naturally infected and or are potential carriers of the latent virus⁷⁵.

The research in this area was greatly developed in the recent years, especially with virus families related to the latent or the persistent infection like herpes viruses. As an early trial to control bovine herpes virus-1 (BHV-1) in cattle was done by DNA vaccination to glycoprotein D. Although DNA immunization elicited weak immune response due to a weak adjuvant combination, results were promising for the application of this technology⁷⁶. Focusing on the marker vaccine against BHV-1 was continued until the construction of a glycoprotein E negative mutant of BoHV-1 Egyptian strain "Abu-Hammad" and evaluated in calves. The constructed BHV-1.1 gE(-) mutant was shown as safe and immunogenic and can be launched in the market⁷⁷. Specially, after the construction of the accompanied diagnostic kit⁷⁸. It is recommended that, cattle with positive BHV-1 infection are required to be vaccinated with a glycoprotein E (gE)-negative BHV-1 vaccine. The vaccine may be either an inactivated or live vaccine both based on a spontaneous BHV-1 mutant without the complete gE gene⁷⁵.

The equine herpes virus (EHV) infection has great influence on the equine industry in different countries specially the abortion and neurological forms. The disease is endemic in many countries all over the world including Egypt^{79,80}. Promising studies on EHV-1 showed that mutant construction in the ORF68 could be a potential entrance for the improvement of a vaccine marker⁸¹. Furthermore, studying of the EHV-1 ORF 51 revealed its role in the life cycle of the virus, the mater that could provide new insights for identifying novel antiviral targets and/or different vaccine design strategies that can be used to improve the current approaches for the control of EHV-1 infection⁸².

CONCLUSION

Vaccination is the most used approach to control the animal viral diseases in many countries. Live attenuated and the inactivated vaccine formulas are still the most commonly used types. Several newly developed vaccines are now

accessible on the market including protein subunit, DNA vaccine, vectored vaccine, virus like particles and edible vaccines but not widely used. Using the marker vaccines in eradication programs is important to differentiate between the vaccinated and the infected animals. Selection of the pathogen strain, choosing of the proper antigen(s) and adjuvants are the most important factors to provoke efficient immune response.

SIGNIFICANCE STATEMENT

This study cleared that, most of the available vaccines are produced by the classical technology which in some conditions may not be ideally used in the disease free areas. Characterization of the circulating strains with updating its genomic map is crucial to develop an efficient vaccine especially for the mutant RNA viruses. The presented information will help researcher to focus on finding new solutions for some phenomena like incomplete protection, vaccine escape variants and vaccine interference. It is important to apply more bio-risk assessment studies about the plant edible vaccines in relation to the human and animal health and the plant ecology.

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