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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 importance[1]. 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 purposes[2].

Controlling of viral diseases through using effective vaccines is the best economically effective approaches not only to control outbreaks[3], 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 virus[4]. 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 animals[5].

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 herds[6]. 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 viruses[7]. 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 infection[9]. 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 humans[10]. 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 vaccines[11].

Inactivation or attenuation of viruses was the standard procedures in the 20th century to produce a vaccine[12]. During the period between 1950 and 1980 many attenuated vaccines were developed using tissue culture propagation[13]. Since the 1970s, the introduction of DNA manipulation techniques empowered an additional technological jump in vaccine development[14]. 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 batches[15].

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 virus[16].

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 virus[17].

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 discovered[18]. 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 immunity[19].

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 vaccines[15]. The causes related to the animal are the age, individual variation, nutrition, physiological status, immunodeficiency, immunity interference and stress[20].

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 spots[21]. 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 vaccine[23].

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 animals[24].

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 irradiation[25]. For several years, immunization with the inactivated vaccines was carried out to provide protection against different diseases such as bovine respiratory syncytial virus[26], equine influenza virus[27] 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-up[29]. 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 immunization[30].

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 H_2O_2 3% than that done by Beta-propiolactone and mice immunized with the H_2O_2 inactivated viruses induced adequate level of antibodies and had been protected when challenged with wild rabies virus[31].

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 reduction[32]. It is worth to note that, eradication of rinderpest virus in Egypt, was the result of the effective application of successful live-attenuated vaccination[33].

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 offspring[34].

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 porcilis PCV vaccine® which is an expressed protein of open reading frame (ORF)2 of the porcine circovirus (PCV)2[35].

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 FMD[36].

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 virus[37] (Protaq-Flu/Recombitek, Boehringer)® and the recombinant parainfluenza virus 5 expressing rabies antigens vaccine[38]. 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 carnivores[39]. 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 them[40]. It is important to mention that continuous determining of the circulating field pathogens through surveillances is crucial for developing suitable vaccine for each country[41-43], 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 infections[46]. A DNA vaccine containing FMDV VP1 epitopes has the ability to elicit both cellular and humoral immunity in swine[47]. 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 CD^{4+} T cell invasion and cytotoxic T cells reaction[51]. 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 vaccine[51]. However, a better understanding of the virus multiplication is required to produce VLP vaccines[50].

For instance, the recombinant (pentamer) structure of FMDV was carried out by expressing the P1 and 3C antigens[52]. 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 SVDV[53]. 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 cells[54]. 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 production[55].

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 PRRSV[56]. Multiple studies showed that the developed examples of plant-based veterinary vaccines declared strong indication in terms of efficacy in animal disease prevention plants[57]. 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 parenterally[58].

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 animals[59], 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 ecology[60].

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 improvement[61].

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-adjuvanted 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 adjuvant[37].

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 gel[66]. 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 gel[66]. 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 calves[67]. 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 vaccine[66]. 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 N PR-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%, respectively[68].

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 Influenza[69]. 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 distribution[70]. 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 criteria[71].

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 virus[74].

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 virus[75].

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 technology[76]. 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 market[77]. Specially, after the construction of the accompanied diagnostic kit[78]. 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 gene[75].

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 marker[81]. 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 infection[82].

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.

REFERENCES

1. Jiménez-Clavero, M.Á., 2012. Animal viral diseases and Global change: Bluetongue and West Nile fever as paradigms. Front. Genet., Vol. 3. 10.3389/fgene.2012.00105.
2. Meeusen, E.N.T., J. Walker, A. Peters, P.P. Pastoret and G. Jungersen, 2007. Current status of veterinary vaccines. Clin. Microbiol. Rev., 20: 489-510.
3. Bayer, W., R. Lietz, T. Ontikatze, L. Johrden and M. Tenbusch *et al.*, 2011. Improved vaccine protection against retrovirus infection after co-administration of adenoviral vectors encoding viral antigens and type I interferon subtypes. Retrovirology, Vol. 8. 10.1186/1742-4690-8-75.
4. Njeumi, F., W.D. Taylor, A. Diallo, K. Miyagishima, P.P. Pastoret, B. Vallat and M. Traore, 2012. The long journey: A brief review of the eradication of rinderpest. Rev. Sci. Tech. Off. Int. Epiz., 31: 729-746.
5. Rupprecht, C.E., C.A. Hanlon and D. Slate, 2004. Oral vaccination of wildlife against rabies: Opportunities and challenges in prevention and control. Dev. Biol., 119: 173-184.
6. Lee, N.H., J.A. Lee, S.Y. Park, C.S. Song, I.S. Choi and J.B. Lee, 2012. A review of vaccine development and research for industry animals in Korea. Clin. Exp. Vaccine Res., 1: 18-34.
7. Lutticken, D., R.P. Segers and N. Visser, 2007. Veterinary vaccines for public health and prevention of viral and bacterial zoonotic diseases. Rev. Sci. Tech., 26: 165-177.

8. Thole, J.E., P.J. van Dalen, C.E. Havenith, P.H. Pouwels and J.F. Seegers *et al*., 2000. Live bacterial delivery systems for development of mucosal vaccines. Curr. Opin. Mol. Ther., 2: 94-99.
9. Riedel, S., 2005. Edward jenner and the history of smallpox and vaccination. Baylor Univ. Med. Cent. Proc., 18: 21-25.
10. Clark, H.F. and D. Kritchevsky, 1972. Growth and attenuation of rabies virus in cell cultures of reptilian origin. Proc. Soc. Exp. Biol. Med., 139: 1317-1325.
11. Weller, T.H., J.F. Enders, F.C. Robbins and M.B. Stoddard, 1952. Studies on the cultivation of poliomyelitis viruses in tissue culture I. The propagation of poliomyelitis viruses in suspended cell cultures of various human tissues. J. Immunol., 69: 645-671.
12. Hussein, I.H., N. Chams, S. Chams, S. El Sayegh and R. Badran *et al*., 2015. Vaccines through centuries: Major cornerstones of global health. Front. Public Heal., Vol. 3. 10.3389/fpubh.2015.00269.
13. Plotkin, S.A., 2005. Vaccines: past, present and future. Nat. Med., 11: S5-S11.
14. Khan, S., M.W. Ullah, R. Siddique, G. Nabi and S. Manan *et al*., 2016. Role of recombinant DNA technology to improve life. Int. J. Genomics, 2016: 1-14.
15. Rice, D., E.D. Erickson and D. Grotelueschen, 1986. G86-797 Causes of vaccination-immunization failures in livestock. Historical Materials from University of Nebraska-Lincoln Extension, 229. https://digitalcommons.unl.edu/extensionhist/229
16. Yang, D.K., H.H. Kim, K.W. Lee and J.Y. Song, 2013. The present and future of rabies vaccine in animals. Clin. Exp. Vaccine Res., 2: 19-25.
17. Weir, E., 2001. Foot-and-mouth disease in animals and humans. Can. Med. Assoc. J., 164: 1338-1338.
18. Wagner, B., D.C. Miller, T.L. Lear and D.F. Antczak, 2004. The complete map of the Ig heavy chain constant gene region reveals evidence for seven IgG isotypes and for IgD in the horse. J. Immunol., 173: 3230-3242.
19. Lewis, M.J., B. Wagner and J.M. Woof, 2008. The different effector function capabilities of the seven equine IgG subclasses have implications for vaccine strategies. Mol. Immunol., 45: 818-827.
20. Barratt-Boyes, S., 2017. Antiviral Immunity and Virus Vaccines. In: Fenner's Veterinary Virology, MacLachlan, N.J. and E.J. Dubovi (Eds.)., Chapter 4. Academic Press, USA., ISBN: 978-0-12-800946-8, pp: 79-104.
21. Yang, W.T., Q.Y. Li, E.B. Ata, Y.L. Jiang, H.B. Huang, C.W. Shi and G.L. Yang, 2018. Immune response characterization of mice immunized with *Lactobacillus plantarum* expressing spike antigen of transmissible gastroenteritis virus. Applied Microbiol. Biotechnol., 102: 8307-8318.
22. Zhou, Y., C. Chen, Y. Chen, Z. Liu and J. Zheng *et al*., 2019. Effect of route of inoculation on innate and adaptive immune responses to porcine epidemic diarrhea virus infection in suckling pigs. Vet. Microbiol., 228: 83-92.
23. Beasley, J.C., T.C. Atwood, M.E. Byrne, K.C. Vercauteren, S.R. Johnson and O.E. Rhodes Jr., 2015. A behaviorally-explicit approach for delivering vaccine baits to mesopredators to control epizootics in fragmented landscapes. PLoS One, Vol. 10, No. 1. 10.1371/journal.pone.0113206.
24. Van Drunen Littel-van den Hurk, S., S.L. Babiuk and L.A. Babiuk, 2004. Strategies for improved formulation and delivery of DNA vaccines to veterinary target species. Immunol. Rev., 199: 113-125.
25. Delrue, I., D. Verzele, A. Madder and H.J. Nauwynck, 2012. Inactivated virus vaccines from chemistry to prophylaxis: Merits, risks and challenges. Expert Rev. Vaccines, 11: 695-719.
26. Kalina, W.V., A.R. Woolums, R.D. Berghaus and L.J. Gershwin, 2004. Formalin-inactivated bovine RSV vaccine enhances a Th2 mediated immune response in infected cattle. Vaccine, 22: 1465-1474.
27. Pavulraj, S., N. Virmani, B.C. Bera, A. Joshi and T. Anand *et al*., 2017. Immunogenicity and protective efficacy of inactivated equine influenza (H3N8) virus vaccine in murine model. Vet. Microbiol., 210: 188-196.
28. Chung, Y.C., L.T. Cheng, J.Y. Zhang, Y.J. Wu, S.S. Liu and C.Y. Chu, 2018. Recombinant E2 protein enhances protective efficacy of inactivated bovine viral diarrhea virus 2 vaccine in a goat model. BMC Vet. Res., Vol. 14. 10.1186/s12917-018-1520-2.
29. Wang, W., X. Shi, Y. Wu, X. Li and Y. Ji *et al*., 2014. Immunogenicity of an inactivated Chinese bovine viral diarrhea virus 1a (BVDV 1a) vaccine cross protects from BVDV 1b infection in young calves. Vet. Immunol. Immunopathol., 160: 288-292.
30. Hong, S.H., Y.H. Byun, C.T. Nguyen, S.Y. Kim and B.L. Seong *et al*., 2012. Intranasal administration of a flagellin-adjuvanted inactivated influenza vaccine enhances mucosal immune responses to protect mice against lethal infection. Vaccine, 30: 466-474.
31. Abd-Elghaffar, A.A., A.E. Ali, A.A. Boseila and M.A. Amin, 2016. Inactivation of rabies virus by hydrogen peroxide. Vaccine, 34: 798-802.
32. Roeder, P., J. Mariner and R. Kock, 2013. Rinderpest: The veterinary perspective on eradication. Philos. Trans. R. Soc. B: Biol. Sci., Vol. 368 10.1098/rstb.2012.0139.
33. Reid, H.W., 1981. Rinderpest. In: Diseases of Cattle in the Tropics. Current Topics in Veterinary Medicine and Animal Science, Vol. 6, Ristic, M. and I. McIntyre (Eds.)., Springer, Dordrecht, ISBN: 978-94-015-6895-1, pp: 133-152.

34. Ficken, M.D., M.A. Ellsworth, C.M. Tucker and V.S. Cortese, 2006. Effects of modified-live bovine viral diarrhea virus vaccines containing either type 1 or types 1 and 2 BVDV on heifers and their offspring after challenge with noncytopathic type 2 BVDV during gestation. J. Am. Vet. Med. Assoc., 228: 1559-1564.
35. Kim, Y., J. Kim, K. Kang and Y.S. Lyoo, 2002. Characterization of the recombinant proteins of porcine circovirus type2 field isolate expressed in the baculovirus system. J. Vet. Sci., 3: 19-23.
36. Bae, J.Y., S.H. Moon, J.A. Choi, J.S. Park and B.S. Hahn *et al*., 2009. Recombinant DNA and protein vaccines for foot-and-mouth disease induce humoral and cellular immune responses in mice. Immune Network, 9: 265-273.
37. Mastelic, B., N. Garçon, G. Del Giudice, H. Golding, M. Gruber, P. Neels and B. Fritzell, 2013. Predictive markers of safety and immunogenicity of adjuvanted vaccines. Biologicals, 41: 458-468.
38. Chen, Z., M. Zhou, X. Gao, G. Zhang and G. Ren *et al*., 2013. A novel rabies vaccine based on a recombinant parainfluenza virus 5 expressing rabies virus glycoprotein. J. Virol., 87: 2986-2993.
39. Gerdts, V., G.K. Mutwiri, S.K. Tikoo and L.A. Babiuk, 2006. Mucosal delivery of vaccines in domestic animals. Vet. Res., 37: 487-510.
40. Han, Y.W., A.G. Aleyas, J.A. George, S.J. Kim and H.K. Kim *et al*., 2008. Polarization of protective immunity induced by replication-incompetent adenovirus expressing glycoproteins of pseudorabies virus. Exp. Mol. Med., 40: 583-595.
41. El Shanawany, E.E., S.A. Nassar and E.B. Ata, 2019. Detection of humoral and cellular immune responses in buffaloes naturally infected with sarcocystosis with risk factor assessment. Acta Vet. Brno., 69: 275-289.
42. Kandil, O.M., N.M.F. Hassan, D. Sedky and E.B. Ata, 2019. Studies on the specific immunodiagnosis of cystic echinococcosis in camels using enzyme-linked immunosorbent assay. Bulg. J. Vet. Med., 22: 305-313.
43. Ata, E.B., M.A.E.F. Mahmoud and A.A. Madboli, 2018. Molecular detection and immunopathological examination of *Deltapapillomavirus* 4 in skin and udder of Egyptian cattle. Vet. World, 11: 915-920.
44. Kandil, O.M., N.M. Hassan, D. Sedky, E.B. Ata, S.A. Nassar, H.A. Shalaby and M. Gabrashanska, 2018. Anthelmintic efficacy of *Moringa oleifera* seed methanolic extract against *Fasciola hepatica*. J. Parasitic Dis., 42: 391-401.
45. Kandil, O.M., K.A. Abdelrahman, M.S. Mahmoud, O.A. Mahdy, E.B. Ata, A.S. Aloufi and E. Al-Olayan, 2020. Cystic echinococcosis: Development of an intermediate host rabbit model for using in vaccination studies. Exp. Parasitol., Vol. 208. 10.1016/j.exppara.2019.107800.
46. Redding, L. and D.B. Weiner, 2009. DNA vaccines in veterinary use. Expert. Rev. Vaccines, 8: 1251-1276.
47. Wong, H.T., S.C.S. Cheng, F.W.Y. Sin, E.W.C. Chan, Z.T. Sheng and Y. Xie, 2002. A DNA vaccine against foot-and-mouth disease elicits an immune response in swine which is enhanced by co-administration with interleukin-2. Vaccine, 20: 2641-2647.
48. Serezani, C.H.C., A.R. Franco, M. Wajc, J.K.U. Yokoyama-Yasunaka, G. Wunderlich, M.M. Borges and S.R.B. Uliana, 2002. Evaluation of the murine immune response to *Leishmania* meta 1 antigen delivered as recombinant protein or DNA vaccine. Vaccine, 20: 3755-3763.
49. Liu, F., S. Ge, L. Li, X. Wu, Z. Liu and Z. Wang, 2012. Virus-like particles: Potential veterinary vaccine immunogens. Res. Vet. Sci., 93: 553-559.
50. Crisci, E., J. Bárcena and M. Montoya, 2012. Virus-like particles: The new frontier of vaccines for animal viral infections. Vet. Immunol. Immunopathol., 148: 211-225.
51. Young, K.R., S.P. McBurney, L.U. Karkhanis and T.M. Ross, 2006. Virus-like particles: Designing an effective AIDS vaccine. Methods, 40: 98-117.
52. Oem, J.K., J.H. Park, K.N. Lee, Y.J. Kim, S.J. Kye, J.Y. Park and H.J. Song, 2007. Characterization of recombinant foot-and-mouth disease virus pentamer-like structures expressed by baculovirus and their use as diagnostic antigens in a blocking ELISA. Vaccine, 25: 4112-4121.
53. Ko, Y.J., K.S. Choi, J.J. Nah, D.J. Paton and J.K. Oem *et al*., 2005. Noninfectious virus-like particle antigen for detection of swine vesicular disease virus antibodies in pigs by enzyme-linked immunosorbent assay. Clin. Vaccine Immunol., 12: 922-929.
54. Jeoung, H.Y., W.H. Lee, W. Jeong, Y.J. Ko, C.U. Choi and D.J. An, 2010. Immune responses and expression of the virus-like particle antigen of the porcine encephalomyocarditis virus. Res. Vet. Sci., 89: 295-300.
55. Jeoung, H.Y., B.H. Shin, W. Jeong, M.H. Lee, W.H. Lee and D.J. An, 2012. A novel vaccine combined with an alum adjuvant for porcine encephalomyocarditis virus (EMCV)-induced reproductive failure in pregnant sows. Res. Vet. Sci., 93: 1508-1511.
56. Loza-Rubio, E. and E. Rojas-Anaya, 2010. Vaccine production in plant systems-An aid to the control of viral diseases in domestic animals: A review. Acta Vet. Hung., 58: 511-522.
57. Liew, P.S. and M. Hair-Bejo, 2015. Farming of plant-based veterinary vaccines and their applications for disease prevention in animals. Adv. Virol., Vol. 2015. 10.1155/2015/936940.
58. Tombácz, K., Á. Gellért, K. Salánki, E. Balázs and T. Tuboly, 2013. Oral immunogenicity of a plant virus vector based porcine circovirus antigen. Acta Vet. Hung., 61: 547-552.

59. Mason, H.S., H. Warzecha, T. Mor and C.J. Arntzen, 2002. Edible plant vaccines: Applications for prophylactic and therapeutic molecular medicine. Trends Mol. Med., 8: 324-329.
60. Howard, J.A., 2004. Commercialization of plant-based vaccines from research and development to manufacturing. Anim. Health Res. Rev., 5: 243-245.
61. Cunningham, A.L., N. Garçon, O. Leo, L.R. Friedland and R. Strugnell *et al*., 2016. Vaccine development: From concept to early clinical testing. Vaccine, 34: 6655-6664.
62. Savelkoul, H.F.J., V.A. Ferro, M.M. Strioga and V.E.J.C. Schijns, 2015. Choice and design of adjuvants for parenteral and mucosal vaccines. Vaccines, 3: 148-171.
63. Zimmermann, P. and N. Curtis, 2019. Factors that influence the immune response to vaccination. Clin. Microbiol. Rev., Vol. 32, No. 2. 10.1128/CMR.00084-18.
64. AbdelMageed, M.A., P. Foltopoulou and E.A. McNiel, 2018. Feline vaccine-associated sarcomagenesis: Is there an inflammation-independent role for aluminium? Vet. Compa. Oncol., 16: E130-E143.
65. McEntee, M.C. and R.L. Page, 2001. Feline vaccine-associated sarcomas. J. Vet. Internal Med., 15: 176-182.
66. Hussein, M.A., H.A. Ali, B.A. Abd El-Rhman, T.N. Morcoss and A.E. Fakhr *et al*., 2019. Efficacy of Montanide (IMS 3015) as an adjuvant for an inactivated Rift Valley fever (RVF) vaccine in sheep. Acta Trop., 190: 193-203.
67. Samira, S.T., M.M.A. El-Sabbagh and A.M.M. Allam, 2009. Preparation of multivalent inactivated vaccine against some bovine respiratory viruses adjuvanted by *Nigella sativa* oil and its evaluation in pregnant buffaloes and their calves. Global Vet., 3: 429-433.
68. Khalifa, M.E., A.H. El-Deeb, S.M. Zeidan, H.A. Hussein and H.I. Abu-El-Naga, 2017. Enhanced protection against FMDV in cattle after prime-boost vaccination based on mucosal and inactivated FMD vaccine. Vet. Microbiol., 210: 1-7.
69. Vidor, E., 2007. The nature and consequences of intra-and inter-vaccine interference. J. Comp. Pathol., 137: S62-S66.
70. Abou-Zeina, H.A.A., S.M. Nasr, S.A. Nassar, T.K. Farag and M.K. El-Bayoumy *et al*., 2019. Beneficial effects of antioxidants in improving health conditions of sheep infected with foot-and-mouth disease. Trop. Anim. Health Prod., 51: 2379-2386.
71. Bucafusco, D., S. Di Giacomo, J. Pega, M.S. Juncos, J.M. Schammas, M. Pérez-Filgueira and A.V. Capozzo, 2014. Influence of antibodies transferred by colostrum in the immune responses of calves to current foot-and-mouth disease vaccines. Vaccine, 32: 6576-6582.
72. Anis, E., A.L. Holford, G.D. Galyon and R.P. Wilkes, 2018. Antigenic analysis of genetic variants of Canine distemper virus. Vet. Microbiol., 219: 154-160.
73. Bae, C.W., J.B. Lee, S.Y. Park, C.S. Song and N.H. Lee *et al*., 2013. Deduced sequences of the membrane fusion and attachment proteins of canine distemper viruses isolated from dogs and wild animals in Korea. Virus Genes, 47: 56-65.
74. Wang, L., B. Byrum and Y. Zhang, 2014. Detection and genetic characterization of deltacoronavirus in pigs, Ohio, USA, 2014. Emerg. Infect. Dis., 20: 1227-1230.
75. Francis, M.J., 2018. Recent advances in vaccine technologies. Vet. Clin. North Am.: Small Anim. Pract., 48: 231-241.
76. Abdelrahman, K.A., 2004. New approach to control Infectious Bovine Rhinotracheitis using DNA encoded glycoprotein D. Ph.D. Thesis, Faculty of Veterinary Medecine, Cairo University, Egypt.
77. El-Kholy, A.A., D.I. Rady, E.R. Abdou, M.M. Elseafy, K.A. Abdelrahman and H. Soliman, 2013. Construction, characterization and immunogenicity of a glycoprotein E negative bovine herpesvirus-1.1 Egyptian strain "Abu-Hammad". J. Virol. Methods, 194: 74-81.
78. El-Kholy, A.A., E.R. Abdou, D.I. Rady and M.M. Elseafy, 2013. Baculovirus expression and diagnostic utility of the glycoprotein E of bovine herpesvirus-1.1 Egyptian strain “Abu-Hammad”. J. Virol. Methods, 191: 33-40.
79. Ata, E.B., A. Salama, A. Zaghawa, A.A. Ghazy and A. Elsify *et al*., 2018. Seroprevalence of equine herpes virus-1 in endemic area of Egypt with risk factors. Bulg. J. Vet. Med. 10.15547/bjvm.2168
80. Ata, E.B., A. Zaghawa, A.A. Ghazy, A. Elsify and R.M. Shaapan, 2018. Equine herpes virus type-1 infection: Etiology, epidemiology, pathogenesis, identification and recent diagnosis. Asian J. Epidemiol., 11: 34-45.
81. Ata, E.B., A. Zaghawa, A.A. Ghazy, A. Elseify, K. Abdelrahman, S. Kasem and M. Nayel, 2018. Development and characterization of ORF68 negative equine herpes virus type-1, Ab4p strain. J. Virol. Methods, 261: 121-131.
82. Badr, Y., A. Okada, R. Abo-Sakaya, E. Beshir, K. Ohya and H. Fukushi, 2018. Equine herpesvirus type 1 ORF51 encoding UL11 as an essential gene for replication in cultured cells. Arch. Virol., 163: 599-607.