Academic Journal of Animal Diseases 8(2): 23-33, 2019
ISSN 2079-200X

DOI: 10.5829/idosi.ajad.2019.23.33

Advances in the Development of Vaccine for the Control and Prevention of Animal Diseases

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Abstract: Vaccination has proven to be the most cost-effective strategy for controlling a wide variety of infectious diseases in humans and animals. For the last decade, veterinary vaccines have been substantially developed and demonstrated their effectiveness against many diseases. The sector has showed a progressive advancement due to new technological advances in vaccine development. Recombinant DNA technology has indeed made tremendous breakthrough in the discovery of various vaccines or diagnostic antigens. The advancement is not only in vaccine production, but also in delivery system. Vaccine development has played a hugely important role in combating infectious disease. Despite the remarkable progress in understanding of immune responses to infection, there exists knowledge gap in the understanding of the immune responses required specifically for protection, or appropriate adjutants and delivery systems to induce the required responses. The technical challenges facing development of new vaccines at present are two-fold. The first challenge relates to the characteristics of the pathogens themselves and the second to the characteristics of the target populations. Quality veterinary vaccines should be used strategically to prevent, control and eradicate transboundary animal diseases. Appropriate vaccine strategy and route of administration should be followed because "vaccine failure" is most often associated with a faulty vaccination program rather than a faulty vaccine.

Key words: Vaccination · Adjuvants · Recombinant DNA Technology,

INTRODUCTION

Vaccination has proven to be the most cost-effective strategy for controlling a wide variety of infectious diseases in humans and animals. Veterinary vaccines have been substantially developed over the past years and demonstrated their effectiveness against many diseases. This is partly attributed to the biotechnological advancements as well as the high demand for new vaccines that are intended to effectively control newly emerging and re-emerging pathogens in livestock [1]. Historically, vaccines have been developed using the conventional methods that follow the paradigm of isolating, sometimes inactivating and injecting the disease-causing pathogen or pathogen component. Due to the global desire to avoid exposure to disease-causing organisms by both patients and manufacturers, recombinant expression of proteins and viral vectors is the modern vaccine development method of choice to remove pathogens from the system. The advantages of subunit and recombinant vaccines include: virtual elimination of safety risks, vaccine feasibility even with a difficult-to-cultivate virus, defined process components, more controlled bioprocesses and a shorter production process (e.g., cell culture vs. egg) which is critical for pandemic response [2]. Despite the massive expansion in understanding of immune responses to infection, research is often hindered by a lack of understanding of the

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immune responses required specifically for protection, or by a lack of approved adjutants and delivery systems to induce the required responses [3].

Veterinary vaccines comprise only approximately 23% of the global market for animal health products; the sector has grown consistently due to new technological advances in vaccine development, the continuous development of drug resistance by pathogens and the emergence of new diseases [4]. According to Balamurugan *et al*. [5], the advent of recombinant DNA technology and its application in the industry has brought a rapid growth of biotechnology companies for the production of the recombinant DNA products in human and animal healthcare. Due to problems in obtaining sufficient quantities of natural subunit proteins, it became the goal of many researchers to produce large quantities of those proteins in a sufficiently pure form to generate safe and effective vaccines using recombinant DNA technology. The objective of this article is to review current status and the advancement in veterinary vaccines development.

History of Vaccine Development: The term "vaccine" derived from the Latin word "vacca," meaning cow was first coined by Edward Jenner. The term firstly adopted for the process of inoculating humans with weakened or killed "immunogens" obtained from cowpox to prevent them from getting smallpox. In 1794 Jenner, provided the scientific demonstration that vaccination was an effective way of preventing smallpox [6]. A vaccine is a suspension of weakened, live, or killed microorganisms or selected proteins normally associated with the organisms administered to prevent, improve, treat an infectious disease and they are biological frauds; they mimic infections by pathogens to trigger the immune response in to mounting a reaction [7].

Types of Vaccines: The widely used conventional vaccines are based on the entire disease-causing microbial agent and consist of the killed or live attenuated organism that does not lead to infection but is capable of inducing protective immunity [8]. Vaccines can be categorized based on the properties of the antigens. These are killed, attenuated or modified live and live vaccines [7].

Numerous important legacy vaccines are still in use today despite their traditional manufacturing processes, with further development focusing on improving stability and updating formulation and delivery methods. Modern vaccine development is currently exploiting a wide array of novel technologies to create safer and more efficacious vaccines. Universal demand for vaccines requires that a manufacturer plan to supply tens and sometimes hundreds of millions of doses per year at low cost. To enable broader use, there is intense interest in improving temperature stability to allow for excursions from a rigid cold chain supply, especially at the point of vaccination. Finally, there is progress in novel routes of delivery to move away from the traditional intramuscular injection by syringe approach [2].

Killed Vaccines: Killed or inactivated vaccines**:** are made from microorganisms, microorganism parts, or microorganism by-product that have been chemically treated, heated, or exposed to gamma radiation to kill the microorganism. In this process, the antigenic structure of the microorganism is kept intact so that it can stimulate an immune response [7]. Killed organisms are commonly much less immunogenic than living ones. As the result, vaccines that contain killed organisms or their products usually require the use of adjuvants to increase their effective antigenicity. Thus, it is often advantageous to use subunits or subcomponents of microorganisms as vaccine antigens [9]. Although inactivated virus vaccines have been used for preventing various types of viral diseases over the decades, they need further development for controlling newly emerging diseases. For examples, influenza virus vaccines are continually improved to contain all serotypes because many new serotypes emerge in new outbreaks [1]. Although inactivated vaccine gives good protection, it is relatively expensive to produce. It also carries a slight risk to the user of accidental self-injection [10].

Attenuated (Modified-Live) Vaccines: Attenuated or Modified-Live vaccines (MLVs)**:** contain microorganisms that go through a process of losing their virulence (called attenuation). However, they must be able to replicate within the patient to provide immunity. They produce the same level of immunity, but the duration of immunity is shorter. Attenuated or Modified-Live vaccines are typically free-dried and need to be reconstituted prior to administration [7]. As compromise, the virulence of an organism can be reduced (attenuated) so that it is able to replicate but is no longer pathogenic. Attenuation has traditionally involved adapting organisms to unusual conditions. Bacteria can be attenuated by culture under abnormal conditions and virus can be attenuated by growth in species to which they are not naturally adapted [9].

Live Vaccines: Live vaccines are made from live microorganisms that may be fully virulent (able to cause disease) or avirulent. They may revert to a fully virulent type or spread to unvaccinated animals, causing persistence infection and disease within a group of animals [7]. Live vaccines can be derived also using genetic engineering techniques since cloning procedures enable the generation of live viruses from plasmid DNA copies containing the whole virus genome. Vaccine candidates can thus be designed by site-directed mutagenesis, gene insertions or deletions and by generation of chimeric viruses [8]. The major advantage of live vaccine is a broader scope and duration of protection because the animals are exposed to all stages of the replicating bacteria. However, it is critical to ensure that live bacterial vaccine is neither over- or under-attenuated in target animals. Whereas under-attenuated strains may be pathogenic and consequently causes their natural diseases, over-attenuation would not elicit enough amount of an immune response to be an effective vaccine [1]. It is, however, a disadvantage in that since an infection with a live virus is involved; the animals can react to the vaccination in manifesting some of the signs of the disease. The severity of this reaction depends on the particular vaccinal strain used and the presence or otherwise of concurrent infection with other pathogens [10].

The Role of Adjuvants in Vaccine Development: The pure recombinant and synthetic antigens used in modern day vaccines are generally less immunogenic than older style live/attenuated and killed whole organism vaccines. One can improve the quality of vaccine production by incorporating immunomodulators or adjuvants with modified delivery vehicles. Adjuvants accomplish this task by mimicking specific sets of evolutionary conserved molecules which include lipopolysaccharides (LPS), components of bacterial cell wall, endocytosed nucleic acids such as double stranded RNA, single stranded DNA, etc. [11]. Thus, the use of adjuvants and, especially, the rational development of new adjuvants and immunostimulators for animals demand special attention and it is appropriate to consider some recent examples of adjuvant research with a specific focus on their use in animals of veterinary significance [12].

Adjuvants can be defined as molecules, compounds or macromolecular complexes that boost the potency and longevity of specific immune response to antigens with minimal toxicity [13]. Modern adjuvants should induce strong and balanced immune responses and it is often desirable to induce specific types of immune responses. As an example, efficient Th1-immunity inducing adjuvants are highly in demand. Such adjuvant promotes good cellular mediated immunity against subunit vaccines having low immunogenicity themselves. The development of such adjuvants may take advantage of the increased knowledge of the molecular mechanisms and factors controlling these responses [12]. According to Janet [7] there are four types of adjuvants: depot, particulate, immunostimulatory and mixed. Aluminum was first used in human vaccines in 1932 and was the only adjuvant in use in licensed vaccines for approximately 70 years. Despite its extensive and continuous use, the immune mechanism of action of aluminum remains incompletely understood [14]. Another early adjuvant attempt was a mineral oil-in-water emulsion (Freund's incomplete adjuvant) which was considered too reactogenic for continued use in humans. Adjuvants have been used for more than 90 years and are currently components of more than 30 licensed vaccines from different manufacturers [15]. Modern adjuvants are being designed to overcome the pathogen and population-related challenges facing 21st century vaccines [16].

New Vaccine Technologies: The approaches used in the development of vaccines have expanded rapidly as the result of increased knowledge of the mechanisms by which protective immunity is induced and the explosion of genomic data on both pathogens and their hosts. The associated evolution of new technology in the field of molecular biology and immunology has furthermore had a large impact on the development of new vaccine strategies and the quality of the products that are produced. There are a range of technologies that are used to produce vaccines engineered for a specific purpose. The categorization is aimed to assist the reader to understand the technologies employed, but it should be recognized that the categories are not mutually exclusive. In principle, the technologies can be used to change the target pathogen itself to alter its properties by deletion; insertion, other genetic modifications, or they can be used to modify the isolated genes or coding sequences of pathogens to produce specific immunogens associated with protective immunity [17].

Recombinant DNA Technology: Recombinant DNA is artificially created from two or more DNA incorporated into a single molecule. Genetic engineering, recombinant DNA technology, genetic modification/manipulation and

gene splicing are terms that are applied to the direct manipulation of an organism's gene. The development of these new technologies have resulted into production of large amount of biochemically defined proteins of medical significance and created an enormous potential for pharmaceutical industries [18]. Recombinant technologies will likely become the way of the future for influenza vaccines since the upstream processes are fast compared to in ovo and cell culture production and due to the fact that they avoid the handling of live virus and the associated costly biosafety containment. A recombinant process would also allow for quick cloning of a new strain and the use of non-specialized production facilities for surge capacity during a pandemic [2].

Gene-deleted Vaccine Technology: This technology has been successfully used to create live attenuated vaccine strains of viral pathogens that are genetically stable and can be used as marker vaccines to differentiate between vaccinated and infected animals. A double gene deleted pseudo rabies virus marker vaccine has been licensed for use in pigs [4]. The approach of creating and testing defined gene deletions ultimately aids in reducing the pathogenicity/virulence of the organism without affecting the immunogenicity. Such gene-deleted organisms can be used as vaccines as they retain the immunogenic features of the wild-type organism but cannot cause disease. However, to be effective as viable vaccine(s), these organisms should be genetically stable, easy to grow and easy to administer. So far, genes involved either in determining virulence or regulating key metabolic pathways of the organism(s) have been targeted for such deletions [17]. Genes may be deleted from a pathogenic microorganism modifying its genes so that the pathogen becomes irreversibly attenuated. Gene deletions can also result in the microorganism's inability to replicate so that it cannot cause disease. An example of a vaccine developed from gene deletion is the pseudo rabies virus vaccine for swine [7].

Recombinant Vector Technology: Advances in reverse genetics, genomics and proteomics have facilitated the identification of mechanisms of virulence, host-pathogen interactions and protective antigens from many pathogenic microorganisms and also the development of suitable vehicles/vectors for delivery of these antigens to the host. The availability of bacterial and viral genome sequences has facilitated the rapid construction of defined deletions in the genomes of a wide variety of pathogens, which not only results in attenuation, but also creates space for the insertion of foreign genes coding for antigens from heterologous microbes. In general, live bacterial or viral vectors share several characteristics including ease and economy of production, non-integration into the host genome, stability and a reasonable capacity to insert genes coding for heterologous antigens. In addition, as with any live vaccine, the vector should be avirulent and the impact of immunity to the vector should be evaluated [17]. Recombinant genes (DNA) coding for a surface or other molecule are isolated from the pathogen. This DNA is then inserted into a non-pathogenic cloning vector and the recombinant antigen is expressed. The first successful use of gene cloning to prepare an antigen in this way involved the foot-and-mouth disease virus [7].

Recombinant Vaccine: Recombinant means combining the physiology of one micro-organism and the DNA of the other, immunity can be created against diseases that have complex infection processes [19]. The general principle of this technology is that a gene or part of a microorganism is isolated and removed from one organism (usually the pathogen) and inserted in to another microorganism.

The microorganisms are "recombined" to make something new [7]. The use of recombinant DNA technology has made the development of subunit vaccines more efficient. The basics of this technology is to transfer a gene encoding an antigen, responsible for inducing immune responses sufficient for protection, to a non-pathogenic host, thereby making the production of the antigen safer and generally more efficient. Recombinant subunit vaccines can be delivered as purified recombinant proteins, as proteins delivered using live non-pathogenic vectors (bacterial or viral) or as nucleic acid molecules encoding the antigen. There are several advantages in using recombinant subunit vaccines. No pathogen is present in the production and purification procedure, thus making the production procedure [20]. As stated by Balamurugan *et al*. [5] recombinant DNA technology has indeed made tremendous breakthrough in the discovery of various vaccines or diagnostic antigens. The advent of recombinant DNA technology and its application in the industry has brought about a rapid growth of biotechnology companies for the production of recombinant DNA in human and animal healthcare. The new generation vaccines prepared from the viral or microbial proteins; their fragments or nucleic acid sequences have been attractive because of their stability, non-infectious nature and homogeneity as well as their-effectiveness.

Nucleic Acid Vaccines: By definition, nucleic acid vaccines are based on DNA or RNA encoding the antigen (s) of interest. In their simplest form, they can consist of highly purified nucleic acids formulated in a buffer. Most often, however, specialized delivery systems are utilized to increase vaccine potency. Means to facilitate nucleic acid delivery involve viral particles to take advantage of the efficiency of viral entry mechanisms, non-viral formulations of DNA or RNA involving lipids, polymers, emulsions or other synthetic approaches to avoid the use of viral vectors and physical delivery technologies, such as electroporation in situ. The majority of the preclinical and clinical experiences with nucleic acid vaccines so far have been with DNA vaccines and DNA-based viral vectors [21]. Nucleic acid vaccines represent a rather recent approach to the control of infectious agents. These novel vaccines consist of DNA (as plasmid) or RNA (as mRNA), although the use or RNA has not yet been as such-well-studied [20].

DNA Vaccines: DNA vaccines are the gene based vaccines which involves recombinant DNA technology, in which a gene of interest (transgene), coding for target protein from a pathogen is carried by a plasmid vector under the control of a strong eukaryotic promoter [22]. DNA Vaccine is created from an infectious agent's DNA called DNA vaccination. It works by insertion (and expression, triggering immune system recognition) into human or animal cells, of viral or bacterial DNA [19]. Naked DNA-based immunization has become a relatively novel approach in developing vaccines since the concept was reported in the 1990s. DNA vaccines have since been produced for a variety of diseases and tested in laboratories with considerable successes. They have successfully elicited efficient immunity to the antigen encoded by introduced genetic materials, which offer the potential for further advancement in the production of effective vaccine [1]. DNA, the essential part of the life is making way in to new vaccine technology. Plasmid vectors from the bacteria have revolutionized the world of vaccine design by its new technology - DNA vaccines. Small portion of the nucleotides from the pathogen held under the control of promoter in a plasmid vector can be used as a vaccine. DNA vaccines alleviate the odds of the other vaccines by having good hold on both the faces of the immunity. The key to the success of DNA vaccine lies in the route of administration of the vaccine which can be done in many ways. Prime boost strategy is an approach used to boost the action of DNA vaccine. To date there are only four DNA vaccine available in the market [23].

The major reason for continued interest in DNA-based vaccines is their simplicity in concept, ease of production, potential to develop a broad range of immune responses, as well as their perceived safety and ability to induce immunity in neonates in the absence or presence of maternal antibodies.

With regards to simplicity, a DNA vaccine is comprised of a plasmid containing various regulatory elements to ensure efficient production of the plasmid in bacterial systems, such as an origin of replication and a selectable marker as well as an expression cassette containing the gene of interest under a eukaryotic promoter usually human cytomegalovirus for efficient expression of the gene inserted into mammalian cells. Since the general features of a plasmid are identical for all vaccines, the single platform makes DNA vaccines very attractive from the prospective of manufacturing. Thus, the only difference between different vaccines would be the gene insert. Thus, if a company establishes a process for manufacturing one plasmid-based vaccine, they can use the same process for production and purification of a variety of different vaccines. Recent advances in our understanding of pathogenesis, comparative biology, molecular biology, bioinformatics and immunology make identification of putative protective antigens to most pathogens relatively easy [24]. Although no DNA vaccines are currently commercially available, they are likely to enter the veterinary market in the near future in preventative and therapeutic forms [9].

RNA Vaccines: RNA viruses are capable of rapid spread and severe or potentially lethal disease in both animals and humans. The development of reverse genetics systems for manipulation and study of RNA virus genomes has provided platforms for designing and optimizing viral mutants for vaccine development. Advancements in recombinant DNA technology and virus reverse genetics have provided key critical insights into the replication and pathogenesis of RNA viruses and facilitate vaccine development through targeted modifications and directed attenuation. The advent of reverse genetics and molecular engineering of viruses has transformed the field of virology by permitting study of targeted genetic changes in virus genomes [25]. RNA vaccines, including those based on mRNA and self-amplifying RNA replicons, have the potential to overcome the limitations of plasmid DNA and viral vectors. Possible drawbacks related to the cost and feasibility of manufacturing RNA vaccines are being addressed, increasing the likelihood that RNA-based vaccines will be commercially viable [21]. One major

advantage of RNA vaccines over DNA vaccines would be that no risk of host-genome integration of the delivered gene exists. However, a disadvantage of using RNA-based vaccines is that the preparation and administration of RNA is troublesome because of the low stability of the RNA. This might lead to rapid in vivo degradation and thus a short-lived expression of the encoded gene. Furthermore, certain reagents needed for RNA preparation [20].

Viral Vectors: The concept of the viral vector was introduced in 1972 [26]. Recent discoveries that led to increased understanding of viral molecular biology and genetics has rendered the used of viruses as vaccine platforms and as potential anti-cancer agents. Due to their ability to effectively induce both humoral and cell-mediated immune responses, viral vectors are deemed as an attractive alternative to the traditional platforms to deliver vaccine antigens as well as to specifically target and kill tumor cells [27]. The concept of viral vector vaccines are different from that of subunit vaccines, as the latter help prevent infectious diseases by eliciting a humoral response.

Recombinant viral vectors have potential for therapeutic use because they enable intracellular antigen expression and induce a robust cytotoxic T lymphocyte (CTL) response, leading to the elimination of virus-infected cells [28].

Vectors based on adenoviruses and poxviruses have been studied extensively, although several other viral vectors are being evaluated at earlier stages of development [29]. Most of the currently available viral vector based veterinary vaccines are based on other platforms such as Canary Pox virus, Fowl Pox virus and Baculovirus [30]. Despite the many advantages of this technology there are some potential drawbacks to consider, such as the potential toxicity of adenoviral vaccine vectors. For example, viral based vectors elicit an inflammatory cytokine response (by stimulating both innate and adaptive immune responses), thus promoting harmful side effects in the host [31]. The specific properties of a vector are determined by the virus from which it derives. Each vector has distinct advantages and disadvantages. Generally, viral vectors achieve high immunogenicity without an adjuvant. Viral components stimulate the innate immune response, leading to the production of interferon's and inflammatory cytokines [32].

Bacterial Vectors: A number of species of live bacteria have been used for vaccine carriers that enable the delivery of cloned vaccine antigen enterically or intransally. For enteric bacteria, most of them are species with the ability to colonize intestinal mucosa, in particular, mucosa-associated lymphoid tissue, which is the main point of invasion of enteric bacteria [1]. Among the various live vectors studied, bacteria have the additional advantage over viruses that their genome is able to harbor many, in principle unlimited numbers of foreign genes, in contrast to viruses. Most recombinant bacterial vaccine vectors have been designed to be administered by mucosal routes [33]. In general bacterial vectors are attenuated by deletion of genes required for key metabolic processes or genes associated for virulence. Although they are not used routinely in animals, rapid progress is being made in developing and evaluating different bacteria as vectors [17]. However, the reality of application for this type of vaccine is complicated and less efficient due to low level of expression of the inserted protein and the antigen is less efficiently translocated on the surface of bacteria, where most protective antigens are displayed [34].

Plant Based Vaccines: Plant-based vaccines are recombinant protein subunit vaccines. Ideally, the choice of plant species used to produce the selected antigen should allow for oral delivery in the form of an edible vaccine. These vaccines are well suited to combat diseases where there is a clear antigen candidate and where the costs of production or delivery for any current vaccine are prohibitive. Several academic and industrial research groups are currently investigating the use of plant-based vaccines in both humans and animals [35]. Transgenic plant vaccines are genetically engineered plant vaccines in which a selected gene is encoded for the desired antigen and modified which when taken orally elicits a strong immune response in the body. Plant-cell produced vaccines are inherently safe because they pose no risk of microbiologic contamination associated with animal-derived vaccines and eliminate the risk of pathogenicity, reversion to virulence and shedding. Oral delivery stimulates mucosal immunity (the first line of defense) in the tissues lining the respiratory system and eliminates injection-related hazards. Plants structure may help in maintaining the antigenic property even after degradation in intestine. Plenty of availability of plants makes the vaccine production of low cost apart from low

cost in storage and transportation. They act through different mechanism of action mainly stimulating the lymphoid structure in the intestine [36].

The employment of plants as potential production and delivery platforms for the expression of vaccines to infectious diseases is one promising approach that emerged from this initiative. Plant-derived vaccines and therapeutic proteins retain similar biological activities as their mammalian-derived counterparts, unlike bacterial expression systems. Vaccines produced from plants have the dual advantage of acting as the vaccine delivery vehicle as well as protect the vaccine protein from degradation by the harsh environment of the gastrointestinal tract, so that it can reach the mucosal immune system more effectively [37].

The use of plants as factories for the production of novel vaccines, antibodies and other therapeutic proteins will undoubtedly continue to develop. Molecular farming may become the premier expression system for a wide variety of new biopharmaceuticals and "plant bodies". Important economic advantages will likely be realized as the technology continues to evolve and improve. Efforts will need to focus on increasing yields, on scale-up of production, on distribution and handling of transgenic plant material and on the development and validation of production techniques which effectively isolate pharmaceutical production from human and animal food. The advantages of recombinant plant DNA technology for the production of antibodies, vaccines, other pharmaceuticals and even high-volume plasma proteins are becoming increasingly apparent. As the technology involves, it appears highly likely that plant-derived pharmaceuticals will play a significant role in the future of clinical therapeutics [38].

Plant-produced purified hepatitis B virus antigens were highly immunogenic when injected, but their yields were initially insufficient for practical purposes. However, knowledge and technology have progressed, hence new plant-derived anti-hepatitis B virus vaccines can be proposed today. All hepatitis B virus antigens can be efficiently produced in stable or transient expression systems [39]. The first licensed anti-hepatitis B virus vaccine appeared after almost 20 years [40]. This first-generation vaccine contained sub viral particles of hepatitis B virus purified from the inactivated serum of carriers. The vaccine revealed very high efficacy [41].

Antiparasitic Vaccines: Parasitic infections adversely affect animal's health and threaten profitable animal production, thus affecting the economy of our country. These infections also play a major role in the spread of zoonotic diseases. Parasitic infections cause severe morbidity and mortality in animals especially those affecting the gastrointestinal system and thus affect the economy of livestock owner by decreasing the ability of the farmer to produce economically useful animal products. Due to all these reasons proper control of parasitic infection is critically important for sustained animal production. The most common and regularly used method to control parasitic infection is chemotherapy, which is very effective but has several disadvantages like drug resistance and drug residues. The most sustainable and economical approach to control parasitic infection in our country is to vaccinate animals, although vaccines increase the initial cost, but the immunity offered by the vaccine are long lived. Thus, vaccination of animals for various clinical, chronic, subclinical parasitic infections will be a cheaper and effective alternative to control parasitic infection for long time and improve animal production [42].

Vaccine development against parasites faces several fundamental challenges like the isolation of native antigens from none blood feeders which elicit protective immunity if delivered to the immune system in an appropriate manner. Vaccination could be applied either to protect the most susceptible animals in a flock/ herd or to minimize the buildup of larvae on pasture and so reduce the rate of infection in susceptible animals. However, vaccines have not been widely used at field level to control the widely distributed parasitic infections globally [43]. Recent advances in vaccination with recombinant helminth antigens have been successful against cestode infections of livestock and new vaccines are being tested against nematode parasites of animals. Numerous vaccine antigens are being defined for a wide range of helminth parasite species, but greater understanding is needed to define the mechanisms of vaccine-induced immunity, to lay a rational platform for new vaccines and their optimal design [44]. Vaccines play a major role in the control of parasitic diseases. Delivery systems of vaccines are very much important in order to induce an effective protective immunity by the vaccines specially to ensure the slow release of vaccines [45].

Advancements in Delivery System: Vaccine delivery improvements may include the use of novel routes of delivery including intradermal, intranasal, transcutaneous

and needle free delivery. Intradermal delivery includes delivery of vaccine to the dermis or epidermis for enhancement of immunogenicity. Needle free delivery present lowest risk of needle stick injury and transmission of blood borne pathogen through needle and increase compliance [46]. Till now we are dependent upon intravenous route to administer vaccine which, in general, fails to induce a pathogen-specific mucosal immunity because of mucosal invading nature of most of the pathogens. Second important difficulty in case of injectable vaccine is cold-chain management failing which adequate response of vaccine cannot be expected although lyophilized vaccines are available but they require reconstitution in diluents at the time of use under sterile conditions which may sometime affect it adversely. Along with these challenges universal fear of needle sticks and difficult administration has attracted the attention towards vaccine delivery through other route [47].

Oral Delivery: Oral vaccines used in rabies vaccination of wildlife such as foxes were initially based on attenuated rabies vaccine viruses such as the ERA strain, but concerns that these vaccines could rarely cause rabies [48]. The live oral vaccinia-rabies glycoprotein (V-RG) vaccine is widely used elsewhere and attempts are being made to optimize the vaccine baits for efficacy for other species including dogs [49]. Rabies infection in stray dogs and wildlife represents a serious problem for humans globally and research for safer, more stable and efficacious live oral rabies vaccines continue [50]. Other possibilities for mass vaccination using edible plant-made vaccines have been actively investigated, but in spite of biotechnological advances in plant expression of vaccine antigens, no commercial products for oral use have been identified to date [51].

Intranasal Delivery: Intranasal vaccine is a licensed product for nasal route at the same time dry powder inhaler brought lots of innovative way for vaccine delivery. Dry powder formulations can afford better stability characteristics for a vaccine and potentially reduce the requirements for cold-chain management or the addition of preservatives [52]. On contact with the nasal mucosa, dry powder inhaler generates a muco-adhesive gel with entrapped antigen and provides a mechanism for the prolonged exposure of the antigen to the nasal mucosal tissue. This method of vaccine delivery is potentially adaptable for inactivated antigens, live attenuated viruses and DNA vaccines [47]. Dry Powder Inhaler and Optimist an exhalation-actuated device for bidirectional intranasal drug and vaccine delivery [53].

Intradermal Delivery: Intra dermal delivery (IDD) is being used as the route of choice for Tuberculosis (TB) and Post-exposure rabies vaccination. It has also been investigated in recent decades as an alternative delivery route for hepatitis B (HBV), measles and influenza [54].

Mucosal Delivery: Mucosal vaccination is proving to be one of the greatest challenges in modern vaccine development. Although highly beneficial for achieving protective immunity, the induction of mucosal immunity, especially in the gastro-intestinal tract, still remains a difficult task. As a result, only very few mucosal vaccines are commercially available for domestic animals [56]. The primary reason for using a mucosal route of immunization is that most infections affect or initiate the infectious process at the mucosal surfaces and that in these infections, mucosal application of a vaccine is often required to induce a protective immune response [57].

Current Challenges for Vaccine Development: Vaccine development has played a hugely important role in combating infectious disease. Despite this success, there is still a great need for new vaccines and these are emerging far more slowly than we would wish. Despite the massive expansion in understanding of immune responses to infection, research is often hindered by a lack of understanding of the immune responses required specifically for protection, or by a lack of approved adjuvants and delivery systems to induce the required responses. In addition, the financial commitment required to license new vaccines is significant and the more lucrative markets are often not those with the greatest need [3]. In relation to medical and scientific challenges, many developing countries face lack of awareness regarding existence of problem, limited data on disease burden and a weak scientific basis. Under societal and cultural issues, the major obstacles are poverty, religious taboos, superstition, influence of traditional healers/shamans and an overemphasis on curative, rather than preventive medicine. Along with these problems, economic issues like limited resources, high cost of vaccines, competing priorities, national pride and fear of dependence on industrialized countries also hinder the mass commercialization of vaccines in developing world [47]. Thus, in the 21st century the technical challenges facing development of new vaccines are two-fold: the first

challenge relates to the characteristics of the pathogens themselves and the second to the characteristics of the target populations [58].

CONCLUSION

Vaccination has been proven to be a cost-effective means to prevent infectious diseases and eradicate such infectious agents. Developing procedures for most animal vaccines relies on a classical strategy with live pathogens that possess a strong immunogenicity either with high virulence or without virulence. However, there has been great acceleration in the advancement of modern molecular techniques and the compilation of genomic data of many pathogens. Such advances provide a great opportunity to create desirable vaccine strains which are less dangerous but more effectively immunogenic than those of vaccines achieved by usual methods. Another notable advancement in immunology is vaccine adjuvant functions, which is often ignored despite their significant influence on vaccine developments. Recently discovered new adjuvants are used for inducing or enhancing vaccine reactions. Currently many types of adjuvants are in use for animal vaccines. With consideration of the commercial market, overall demand of animal vaccines is steadily growing due to the fast increasing livestock population. As vaccine research and development continues to become more sophisticated with its use of state-of-the-art molecular techniques, so do the costs. Overall, along with less stringent regulatory requirements, research and development of animal vaccines would be the forefront of experimental trials of innovative techniques and commercial opportunity. Therefore, the following recommendations are forwarded. Quality veterinary vaccines used strategically to prevent, control and eradicate trans-boundary animal diseases. Educate livestock owners to vaccinate their animals, particularly with new vaccines. Follow appropriate vaccine strategy and route of administration because “vaccine failure” is most often associated with a faulty vaccination program rather than a faulty vaccine. Proper handling and storage of vaccines is very important because vaccines are sensitive to extreme heat or freezing. Vaccine handling, including shipment and storage, is critical to maintaining potency to the expiration date.

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