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Review on Recent Advance in Veterinary Vaccine

Tesfa Mossie

Ethiopian Institute of Agriculture Research, Jimma, Ethiopia

Email address:
mtesfa6@gmail.com

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Abstract: The licensed veterinary vaccine is the most cost-effective strategy for the prevention, control, and eradication of a wide variety of new and re-emerging infectious diseases in both humans and animals. This in turn leads to improvements in animal welfare, decreased antibiotic residues in food chains, being able to reduce the human susceptibility to zoonotic diseases and decreasing the production cost of food animals. There has also been a great improvement in the country's economy. Killed or live modified viral and bacterial vaccines are conventional vaccines that have been used for many centuries in the routine vaccination of production animals, companion animals, and human beings. The limitations of conventional vaccines are alleviated by novel concepts of vaccine development. Numerous novel, safer, and more effective vaccinations have been created as a result of current advancements in molecular biology, immunology, microbiology, and genetics. The development of vaccinations that provide immunity to many diseases simultaneously is one of the innovative vaccine technological improvements enabled by genetic editing. Vaccines that are designed based on genetic engineering are DNA/RNA vaccine, live attenuated vaccine, live recombinant vaccine, polynucleotide vaccine, and marker vaccine. Since they provide several advantages over conventional vaccines, these vaccines are actively being investigated against a variety of livestock and human diseases. Easy production, amount of vaccine produced, safety, immunogenicity, multivalency in a single host, ease of administration, and improved stability made the advanced vaccine more appropriate than a conventional vaccine.

Keywords: Vaccine, Advance Vaccine, Live Attenuated Vaccine, Killed Vaccine

1. Introduction

Edward Jenner used the term "vaccine," which is derived from the Latin word for "inoculation," to refer to the process of vaccinating people with the cowpox virus in order to protect them from the human smallpox virus. The protection of the cowpox virus against the smallpox virus exemplifies the tight connection between infectious diseases in humans and animals. He made a smallpox vaccination discovery that forever altered medicine. In 1881, the term "vacca," meaning cow, was used by Louis Pasteur. Pasteur investigated the possibility of attenuating or inactivated virulent microbes before vaccination. Through the attenuation process, Luis Pasteur created three vaccines: one each for rabies, poultry cholera, and anthrax [14]. The virulence of the pathogen partially or completely reduced or eliminated through serial passage in animals and cultural passage of the microbes. These developments eventually led to successful immunization programs against the viral and bacterial diseases of humans and animals [11]. The ultimate objective of vaccination for industrial animals is distinct from that of human vaccines, despite certain similarities between animal and human infectious diseases in the pathophysiology and effects resulting from immunization. The primary goal of human and companion animal vaccination is to maintain health and welfare by preventing specific infectious diseases. On the other hand, the main concern of livestock vaccination is to improve the productivity and profitability of animals for livestock producers. and production of the animals [12] Vaccinating wildlife is typically only done to protect against diseases that can spread to people and other animals (zoonotic diseases), though animal welfare issues are becoming more and more important.

The pathogens used to create vaccines have been eliminated or have undergone attenuation. It should induce both non-specific and specific immunity to the target pathogen after injection without running the danger of generating the diseases and their related side effects [9]. When infection subsequently arises, the body's immune system will be able to identify and

eliminate the pathogen. Developed immunity following vaccination might not only give protection from clinical disease (morbidity and mortality). But, it also blocks the infection and spread of the infectious agents [16]. Compared to chemotherapy and prevention against many infectious diseases, vaccination is the most economical means of preventing or reducing clinical signs and eradicating infectious diseases.

The development of a vaccine in both humans and animals has grown over time as a result of new technological advancement, ongoing drug resistance development by pathogens, and the emergence of new and re-emerging diseases around the world [14]. In addition to enhancing animal health and production, the veterinary vaccination plays a key role in public health by lowering the use of antibiotics and hormones and the residues left behind in the human food chain [9].

Veterinary vaccines address a wide range of intentions. It provides cost-effective infectious disease control and prevention, improves animal welfare, and lowers food animal production costs. The eradication of smallpox, rinderpest, and other eonomically and zoonically significant infectious diseases demonstrates that vaccination is the most feasible and cost-effective strategy for preventing, controlling, and eradicating infectious diseases [3].

The majority of currently approved veterinary vaccines have historically been killed or live modified viral and bacterial vaccines that have been used for many years in the routine vaccination of livestock, pets, and people. It has been possible to control many infectious diseases using both dead and modified live vaccines, but there is always room for improvement in terms of their potency, cost, and safety [11]. Although the widespread use of these vaccinations has significantly improved both public and animal health around the world, they contain significant flaws and are far from perfect. Conventional vaccines typically cost more to make and require repeated doses and adjuvants to produce the best immune response. Additionally, it may disrupt maternal antibodies, which may result in little to no protection for newborns. The limitation of conventional vaccines has been overcome by the evolution of new technology in the field of molecular biology and immunology. Modern molecular approaches can be used to create novel and improved vaccinations [5].

2. Type of Vaccine

Current licensed veterinary vaccinations are made using traditional techniques and are based on ideas that were first proposed by Jenner and Pasteur, respectively, 200 and 100 years ago. Modified live vaccines and killed vaccines are types of classical vaccines [1].

2.1. Modified Live Vaccine

A live microorganism that has been significantly reduced in virulence, if not completely eliminated, is used in live-attenuated vaccines. Live modified vaccines are attenuated and have the power to trigger immunological reactions on the humoral and cell-mediated levels. The traditional methods of attenuation of virulent part of the pathogens are using experimental animals and in vitro techniques [3]. The virulent component of the pathogen is typically reduced through repeated passages in heterologous or artificial hosts or cell lines, and occasionally by distant relatives of pathogenic bacteria that are not pathogenic to the target host. After numerous serial passages in heterologous systems, the agent develops random changes in their genome that cause loss of pathogenicity without impairing immunogenicity [14]. The limitation of live attenuated vaccines is the potential pathogencity in immunocompromised animals and the possibility of conversion to the wild type, which results in the disease to the target host [16].

2.2. Killed Vaccine

Killed vaccines are vaccines in which the whole organism is inactivated by formaldehyde without affecting the immunogenic property of the pathogenic organisms. The most common adjuvants used in the formulation of killed vaccines are oil or aluminum hydroxide. Live vaccinations are more expensive to produce than inactivated vaccines, which are also more stable in outside circumstances. Despite having better safety profiles, inactivated vaccinations are ineffective for long-term protection because they prevent pathogen proliferation [8]. Live attenuated vaccine has drawbacks that are overcome by killed vaccine.

3. Genetically Engineered Vaccine

The direct modification of an organism's genome via biotechnology is known as "genetic engineering." Recent developments in molecular biology, immunology, microbiology, genetics, and understanding microbial pathogenesis have resulted in the development of a wide range of new approaches for developing safer and more effective vaccines, some of which are marker vaccines with potential for use in diagnostics for DIVA [9]. It is possible to introduce new DNA into the host genome by first extracting and duplicating the genetic material of interest using molecular cloning techniques to produce a DNA sequence [16]. Based on sequencing methods, the focus of genomics in vaccine development has changed. To find genes encoding proteins with characteristics of immunogenic vaccine targets, scientists use high-throughput in silico screening of a pathogen's whole genome [8]. The genes are expressed utilizing foreign protein expression vectors like E. coli, yeast, insect or mammalian cells. *Escherichia coli* are the most commonly used vector for protein expression as heterologous host besides limitation in the form of yield, posttranslational modification, and folding of expressed recombinant proteins. The host is then given purified proteins to induce immunity. The specific adjuvant can solve the frequent occurrence of low immunogenicity of a subunit vaccine.

Genetically engineered vaccines can alleviate the limitations of clasical vaccines. The vaccines don't replicate, simple to make, inexpensive, and safe to deliver. They also

don't have any negative effects from unintended antigenic components [14]. For attenuated vaccines, mutations can be selectively introduced into the genome of the agent to attenuate it so that it is nonpathogenic but still immunogenic [3]. New and better vaccines can be created using contemporary molecular techniques (Figure 1).

After being injected with a live vector or a modified plasmid, the gene encoding the antigenic is extracted, produced, and purified from a protein-production system, or it is expressed directly by the vaccine recipient. In order to increase the scope of the immune response, prime-boost tactics combine various antigen delivery methods.

Genetically engineered Veterinary vaccines can be divided into four categories according to USDA (Table 1).

Table 1. *Classification of genetically engineered vaccine.*

Category	Genetically Engineered Veterinary Biologics
	Description
I	A vaccination made from purified antigens generated from inactivated recombinant organisms or recombinant organisms
II	The vaccine containing live organisms that contain gene deletion or heterogenous marker
III	The vaccine that uses diverse genes expressed by living expression vectors to immunize against foreign substances or other stimuli
IV	Polynucleotide vaccines, among other genetically modified vaccinations

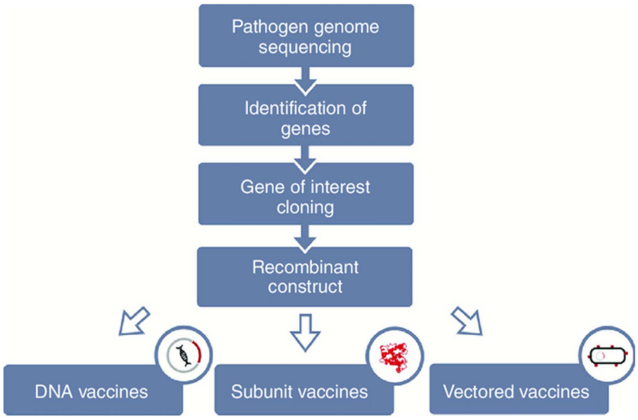

Figure 1. *General molecular techniques approaches for vaccine development.*

3.1. Category I: DNA Vaccine Using Gene Cloning Technique

DNA vaccination has become the fastest-growing field in vaccine technology. DNA vaccines induce antigen production in the host itself. A DNA vaccine is a plasmid carrying a gene for a mammalian protein or a virus, bacterium, or parasite that can be produced in mammalian cells (noninfectious diseases) [8].

First, a pathogen's DNA encoding for an interesting antigen is extracted using culture methods. Gene cloning is employed to cultivate a sizable quantity of pure antigen of interest. A eukaryotic promoter for transcriptional control, a polyadenylation signal sequence for reliable and efficient translation, and a plasmid origin of replication are all introduced with the gene of interest into bacterial or yeast plasmids. After being transfected into host cells, the recombinant plasmid undergoes transcription into mRNA and translation into protein. The expressed proteins are recognized as foreign by the host immune system, which might result in the emergence of a cellular and humoral immunological response (Figure 2). The first successful gene-cloning vaccine was for foot and mouth disease [15].

DNA vaccine stimulates both innate and adaptive immunity. While the adaptive immune response entails the processing of antigen and its presentation in class I and class II MHC molecules to CD8+ and CD4+ T cells, respectively, the innate immune system can be activated by recognizing the dsDNA of the plasmid backbone. DNA vaccination is a novel and appealing medical technique that can effectively guard against a variety of infectious agents with viral, bacterial, or parasitic origins in both humans and veterinary medicine [15].

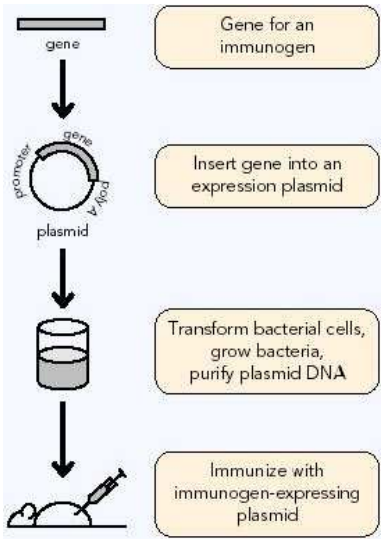

Figure 2. *DNA vaccine development procedures based on cloning.*

3.2. Category II: Genetically Attenuated Live Vaccine

An early kind of genetic engineering could be thought of as attenuation by extended tissue culture. Molecular genetics technique used to identify specific virulence genes and modified the genes of an organism so that it becomes irreversibly attenuated (Figure 3). Depending on the pathogen, it can be accomplished by introducing several mutations or even by deleting the entire gene. Then, rather than using conventional methods, it is conceivable to develop a vaccination that is both safe and less expensive. The proper gene or gene set(s) should be deleted or altered to adjust the degree of attenuation. It is significantly less likely to get virulent again [1]. Marker vaccines are created using

genetically modified vaccines. Marker vaccinations are becoming more and more common in nations where a certain disease is either alien or targeted for elimination.

A cell line that expresses the gene function can be used to cultivate the organism that lost pathogenic genes in vitro (transfected cell line). This makes it possible to produce lots of different species in a production facility. The genetically modified vaccination is incredibly safe for the environment and is never shed into it. The ability to administer genetically attenuated live vaccinations through methods that mimic an actual infection is their main benefit. As a result, they ought to trigger an immune reaction similar to the one brought on by virulent field strains of the virus [1].

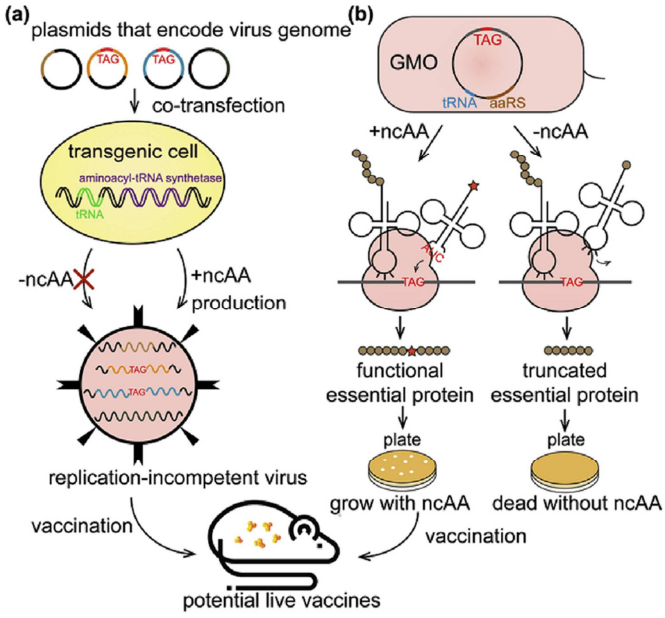

Figure 3. *(a) Principles of live-attenuated vaccines (LAVs) using genetic code expansion, (b) Genetically modified organism (GMO) principles, NCAA stands for noncanonical amino acid.*

3.3. Category III: Live Recombinant Vaccine

A promising method for finding recombinant vaccines for viral and parasitic illnesses is reverse vaccinology. There is a clear need to create stronger, safer, and better defined vaccines that can combine many antigens to produce vaccinations that can protect against various pathogen strains [8].

Protein antigen-coding genes can be easily cloned into a number of species. A live viral or bacterial vector that has been genetically modified to express a range of exogenous antigens in the cytoplasm of target cells is the basis for live recombinant vaccines (Figure 4). The recombinant organism itself can be as a vaccine [9]. The adenoviruses, herpesviruses, and poxviruses the most common virus used as a vector for the development of live recombinant virus vaccine. Poxviruses such as vaccinia, fowlpox, and canarypox have been most widely employed for live recombinant vaccine designing since they have large stable genomes that make it relatively easy to insert a new gene [4]. Bacterial vectors like Mycobacterium Bovis bacillus Calmette–Guérin (BCG) or salmonella have to express a lot quantity of antigens and create a strong immune response [14].

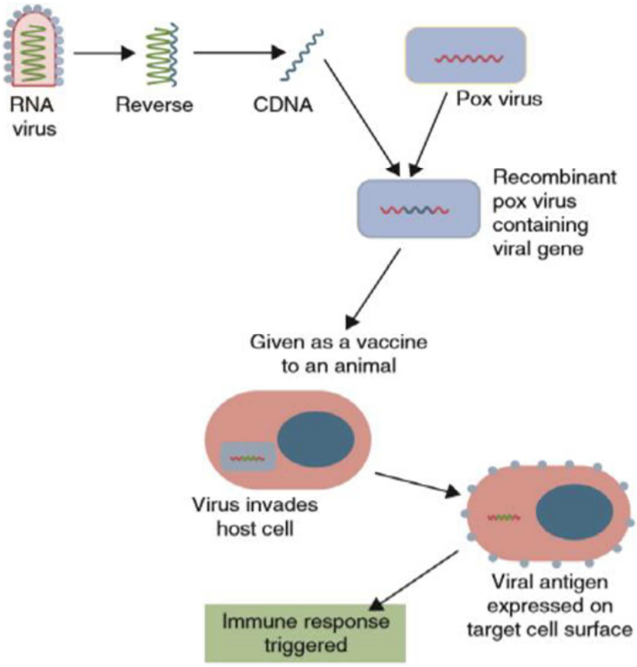

Figure 4. *The creation of recombinant vaccines with vaccinia vectors. The vaccinia virus was selected because it has room to spare in its genome and is easy to administer to an animal.*

For example, the Vaccinia-vectored rabies vaccine can be developed as follow. The gene for the rabies envelope glycoprotein, or G-protein, is inserted into vaccinia. The glycoprotein is the only rabies antigen capable of inducing virus-neutralizing antibodies and conferring protection against the rabies virus. Production of antibodies to the G-protein antigen and development of immunity has occurred after the administration of rabies vaccinia-recombinant vaccine. Rinderpest vaccine consists of a vaccinia or capripox vector containing the hemagglutinin (H) or fusion (F) genes of the rinderpest virus.

Strong humoral and cell-mediated immune responses brought on by live recombinant vaccines can produce immunological memory. Additionally, it can encode for a number of antigens from various diseases. There is a chance that multiple diseases will soon have a single vaccine. The vaccine is relatively inexpensive and easily transportable. The drawbacks of the vaccine are the possibility of reversion to virulence since it is live attenuated organisms (either virus or bacteria).

3.4. Category IV: Polynucleotide Vaccines

Polynucleotide vaccine is the third revolution in vaccinology. Since the introduction of polynucleotide vaccination against numerous viral, bacterial, and parasitic pathogens, there have been hundreds of reports of plasmid immunization in practically all species [1].

The following is the underlying principl behind the

development of polynucleotide vaccination (Figure 5): A bacterial plasmid, a fragment of circular DNA that serves as a vector, can be modified to accept DNA coding for a vaccination antigen. Strong mammalian promoter sequences are responsible for putting the vaccination antigen gene under their control. The genetically modified plasmid will be absorbed by host cells after being injected intramuscularly into an animal. After that, the messenger RNA from the DNA is translated into endogenous vaccine protein. The animal's immune system reacts to the translated protein because it is regarded as foreign. In contrast to viral vectors, the plasmid cannot reproduce in mammalian cells.

The formation of long-lasting immunity, a broad spectrum of immunological responses (both cell-mediated immunity and humoral responses), and the simultaneous induction of protection to a number of diseases through the use of multivalent vaccinations are all potential advantages of this type of vaccine [2]. The polynucleotide vaccine does not require adjuvants and does not have any issues related to adjuvants.

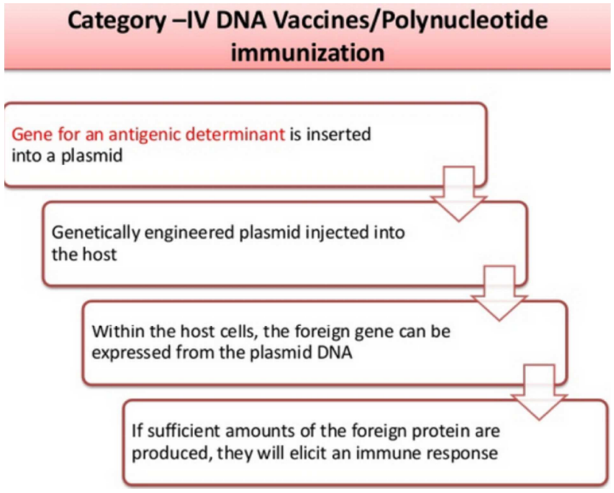

Figure 5. *Sequential steps of developing polynucleotide vaccine.*

4. Marker Vaccine / Diva Vaccine

The creation of marker vaccines and the related diagnostic tests has been made easier because to the development of a number of new technologies. When a companion diagnostic technique is used, marker vaccinations have been developed and have made it possible to tell infected animals from animals that have received the vaccination. It has at least one fewer antigenic protein than the associated wild-type virus [6] The wild-type virus incites antibodies against the protein of the deleted genes, whereas the DIVA vaccines are unable to do so, allowing the antibodies to be distinguished using the appropriate diagnostic methods. Vaccinated animals cannot be distinguished from infected animals bearing wild-type viruses [9] Today, it is possible to create marker vaccines for foreign animal diseases, enabling vaccination campaigns to be carried out in regions at risk of disease outbreak without affecting the capacity to transport animals domestically or abroad or changing the status of trade [7].

The creation of marker vaccines can be accomplished using genetically modified components (Figure 6). The creation of "marker vaccines" that work in conjunction with appropriate diagnostic assays has been made possible by the capacity to recognize and selectively remove genes from a pathogen [12]. DNA vaccines can be created through deletion mutagenesis, which causes attenuation, insertion of foreign immunogenic genes into a vector organism, and expression of an immunogenic gene using plasmids [7].

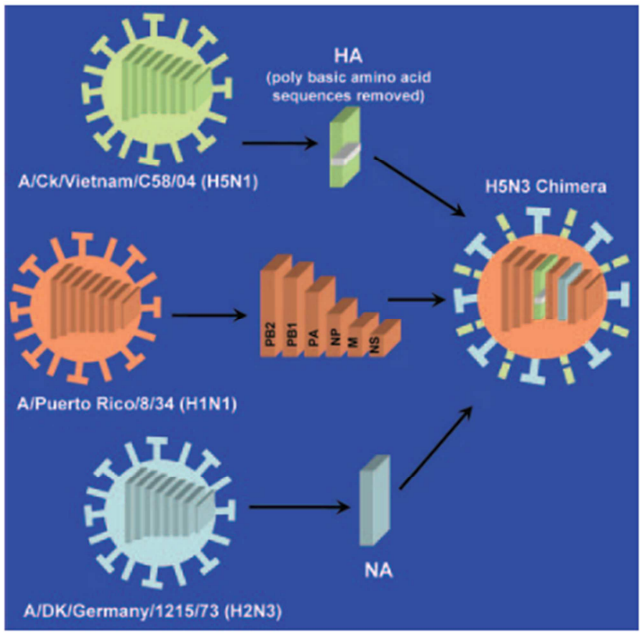

Figure 6. *The reverse genetic approach was used to create the chimera vaccine Poulvac FluFend I AI H5N3 RG to protect poultry against the pathogenic H5N1 virus. The HA gene was extracted from an H5N1 virus, inactivated by removing the polybasic amino acid sequences, and combined with the NA gene from an H2N3 virus on an H1N1 'backbone"virus. DIVA could be detected using an immunoassay that detects antibodies against N3 and N1 proteins (N3+ N1- indicates vaccinated, and N3-N1+ indicates infected).*

5. RNA Vaccine

Because of their high potency, ability to produce quickly, potential for low-cost manufacturing, and potential for safe administration, mRNA vaccines represent a promising alternative to traditional vaccine techniques [13]. mRNA-based vaccines are superior to pDNA and viral vector-based vaccinations in a number of ways. The host cells' genome is not altered by mRNA vaccines, which neither produce nor incorporate infectious particles. Without having to break through the nuclear membrane barrier to express proteins, they can be used to transfer antigens for in-situ expression and can express complex antigens without being constrained by packing requirements. After obtaining sequence information, it can be built quickly, possibly in a day [10].

The idea behind creating an mRNA vaccination is rather simple (Figure 7). The target pathogen's antigen of interest is first separated from it. The gene is then produced, sequenced, and cloned into the plasmid's DNA template. The vaccine is

administered to the target host after being translated into mRNA in vitro. The mRNA vaccine mimics a viral infection by using the host cell's machinery to translate mRNA into the appropriate antigen in vivo, inducing strong humoral and cellular immune responses. The signal peptide and transmembrane domain dictate the antigen's final cellular location [17]. A successful RNA vaccination requires mRNA that is stable and capable of being translated. To measure mRNA stability and protein production during translation, purity is essential.

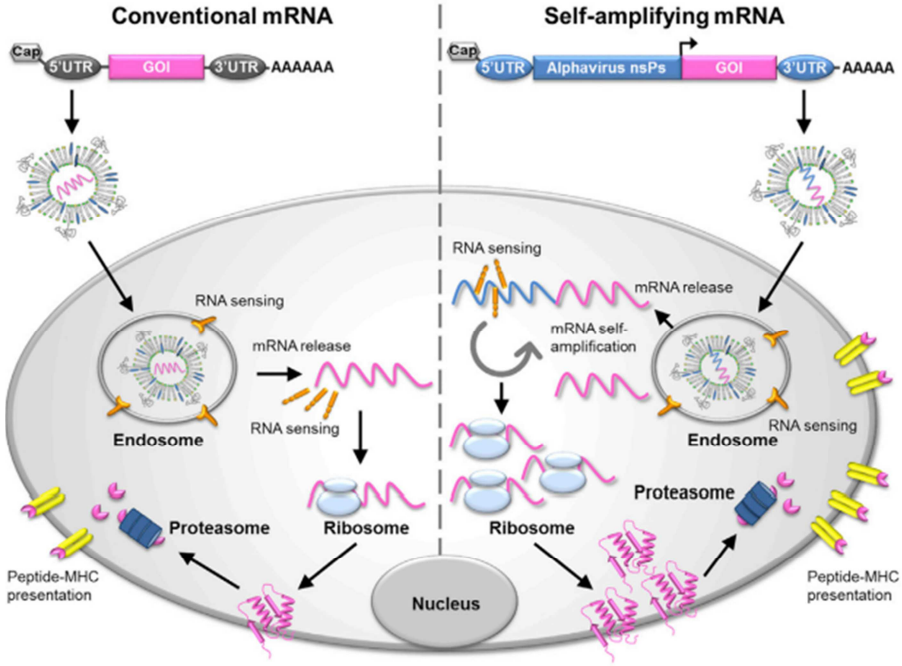

Figure 7. *mRNA vaccines development and Mechanism of Antigen Expression.*

6. Conclusion

Veterinary vaccines are the most cost-effective strategy for the prevention and control of new and re-emerging infectious diseases. This in turn leads to improvements in animal welfare, decreased antibiotic residues in food chains, being able to reduce the human susceptibility to zoonotic diseases and decreasing the production cost of food animals. Novel and more effective vaccines have been developed as a result of the current advancements in molecular biology and genetics through genetic engineering.

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