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Veterinary Vaccines: Unlocking the Power of Immunization for Livestock Health — A Review

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Abstract

Vaccines are all biological substances produced from living things and administered to trigger the host's body defense system to develop immunity against a specific pathogen from which they were produced. They work by stimulating either humoral or cell-mediated immunity, or both, to differentiate. There are several types of vaccines, like live attenuated, killed, or inactivated vaccines, cell membrane compounds, or toxoids. Vaccines are important for disease prevention, enhancing the efficiency of food production, and reducing or preventing transmission of zoonotic and foodborne infections to people. Even though vaccination is the most powerful and cost-effective weapon of disease prevention, there are several factors such as alterations in the vaccines, maternal antibodies, immunosuppression, wrong timing of vaccination, missing booster vaccination, inadequate dosage, and adjuvants used in the vaccine that can cause vaccine failure. Therefore, Care should be taken in vaccine handling, storing, transporting, and administering; care should be taken in the timing of vaccination; serotypes of agents should be identified before preparing vaccines; and there should be a training program for people who are involved in vaccination, vaccine storage, and handling activities to ensure vaccine potency and maximize effectiveness.

Keywords: veterinary vaccines, live vaccine, live attenuated vaccine, T cell, B cell

1. Introduction

The growing demand for livestock products (fueled by population growth, increased urbanization, and the greater purchasing power of individuals in developing or middle-income countries) coupled with the necessity of complying with the standards of trade agreements mean that governments must improve animal health in their countries, particularly as it relates to infectious disease control (Delgado *et al*., 2001; FAO, 2002), limits on residues in commodities, and animal welfare. Recent assessments show that infectious diseases will continue to be a major constraint on sustained international exports of livestock commodities from developing countries unless targeted sanitary measures are instituted in those countries to reduce the burden of these diseases (Morgan & Prakash, 2006).

Vaccinology led to effective vaccines, lowering disease impact in animals. These vaccines contain whole or partial microbes. They're from weakened organisms, genetic modification, or inactivated components. Most veterinary vaccines today are live attenuated, killed, or inactivated microorganisms, toxins, or cell membrane compounds (Clem, 2011). Today, the vast majority of licensed veterinary vaccines are in the form of live attenuated, killed, or inactivated microorganisms, cell membrane compounds, or toxoids (McVey & Shi, 2010; Unnikrishnanet *et al*., 2012).

Live attenuated vaccines contain whole viruses or bacteria that have been weakened, or 'attenuated'. They offer better stimulation of the immune response and require lower doses of the bacteria or viruses. Ideally, they should not cause any clinical signs of disease. Live attenuated vaccines can be very effective because they induce both

cellular and humoral immune responses (Rizzi *et al*., 2012). However, a major concern that is associated with vaccines of this nature is the potential risk of reversion of the microorganism to a virulent phenotype (Shimoji *et al*., 2002; Unnikrishnan *et al*., 2012).

Inactivated (killed) vaccines contain whole viruses or bacteria that have been inactivated by heat or chemical treatment. They are usually coupled with an 'adjuvant' that acts as a stimulant to enhance the animal's immune response. Inactivated or killed vaccines are typically safer; however, they may be less effective than attenuated vaccines. Subunit vaccines contain only viral or bacterial antigens that can trigger an immune response (Redding & Weiner, 2009).

Toxoids are used as vaccines because they induce an immune response to the original toxin or increase the response to another antigen since the toxoid markers and toxin markers are preserved (Matsuda, 2002). Toxoid vaccines are used to treat illnesses caused by bacterial toxins. Toxins can be inactivated using formalin, formaldehyde, and sterilized water. Once inactivated, the toxin becomes a toxoid, safe for use in vaccines. The immune system produces antibodies to block the toxin, preventing reversion to virulence (WHO, 2016).

Recombinant vaccines provide an alluring method of overcoming the drawbacks of traditional vaccinations, and several subunit vaccines with well-considered designs have already entered the veterinary market. Around the world, work is being done to create vaccinations that are more effective against a wide range of illnesses utilizing recombinant DNA technology. Recombinant vaccines are created using structure-based design, epitope-focused screening, or genomic-based screening techniques using recombinant, highly pure antigens that have been rationally created (Correia *et al*., 2014; Dellagostin *et al*., 2011).

Vaccines prevent animal diseases by exposing animals to harmless pathogens, triggering antibody and cellular defenses. Livestock vaccination enhances production, while zoonotic and foodborne infection vaccines reduce consumer risk and improve animal productivity. Wildlife vaccination targets zoonotic illnesses, focusing on animal welfare (Meeusenet *et al*., 2007).

According to Knight-Jones et al. (2014), there are reportedly immunizations for 400 illnesses that affect mammals, birds, fish, agricultural animals, companion animals, and wildlife. The main deciding variables for vaccination service delivery were a shortage of transport, a refrigerator at the veterinary clinic, and a lack of understanding of the value of vaccinations among the farmers. (Samrawit *et al*., 2020). Thus, the objective of this seminar paper is:

- To review the diversity and mechanisms of Veterinary Vaccines and to highlight the significance of Vaccination in livestock health.

2. Importance of Veterinary Vaccines

Veterinary vaccines are important for animal health, animal welfare, food production, and public health. They are a cost-effective method to prevent animal disease, enhance the efficiency of food production, and reduce or prevent the transmission of zoonotic and foodborne infections to people. Safe and effective animal vaccines are essential to modern society. Without companion animal vaccines (especially the rabies vaccine), many people would not keep a pet in the household and would not experience the satisfaction of the human-animal bond (James, 2011).

2.1 Efficient Food Production

Veterinary vaccines are used in livestock to maintain animal health and improve overall production. More efficient animal production and better access to high-quality protein are essential to feeding the growing population. According to the United Nations Department of Economic and Social Affairs Population Division, the world population was approximately 7 billion in 2014 and is estimated to increase to just over 8 billion in 2025 and reach 9.1 billion people in 2050. The United Nations Food and Agriculture Organization estimates that 805 million people were undernourished in 2014 (FAO, 2014; IFAD, 2014; WFP, 2014).

There were dramatic increases in world meat and egg production between 1962 and 2006. The FAO projected that feeding a world population of 9.1 billion people will require overall food production to increase by 60% between 2007 and 2050 (FAO, 2009; Alexandratos & Bruinsma, 2012). The global demand for beef, pork, poultry, and other animal protein sources will increase sharply by the year 2050. Vaccines that preserve animal health and improve production will be important components in meeting this need (James, 2011).

2.2 Control of Zoonotic Diseases

Vaccines used to control zoonotic diseases in food animals, companion animals, and even wildlife have had a major impact on reducing the incidence of zoonotic diseases in people. Veterinary vaccines for zoonotic diseases that have been or could be used to control infections in animals, thereby reducing transmission of the infectious agent to people, including rabies, brucellosis, leptospirosis, influenza, Rift Valley fever, Nipah, Hendra, Japanese encephalitis, Q fever. Without rabies vaccines, it is unlikely that families would be willing to keep cats and dogs

as pets. Recombinant vaccinia-vectored rabies vaccines have also been used successfully in baits for oral vaccination campaigns to reduce the incidence of rabies in wild animals (Pastoret & Brochier, 1996). Vaccines for Brucellosis were instrumental in the Brucellosis eradication program in the United States (FAO, 2010).

Similarly, vaccinating livestock against various Leptospira serovars can reduce the incidence of human leptospirosis, which in severe cases can cause miscarriage or death. The tapeworm parasite Taeniasolium, which is transmitted between pigs and humans, is a major cause of adult-onset epilepsy in developing countries (Spickler, 2005). In recent field trials, an experimental T. *solium* vaccine administered to scavenging pigs protected them against transmission of the parasite. These promising results suggest that pig vaccination could become an effective way to break the cycle of *T. solium* transmission to people in the developing world (Jayashi *et al*., 2012).

2.3 Control of Emerging and Exotic Diseases of Animals and People

Food security is being threatened by new and exotic animal illnesses, which pose an increasing hazard to both human and animal health. Pathogens can spread more easily within and across species as a result of rising human and animal populations, environmental degradation brought on by climate change, the development of arthropod vectors, and international trade and travel. The ensuing illnesses provide significant now-day and future issues. Most of the world's rising need for animal protein has led to increased "backyard production" or enhanced industrial food animal production. The onset and management of diseases provide distinct issues in both forms of manufacturing. A significant risk to the public's health is posed by newly emerging zoonotic diseases in both food and companion animals. Emerging disease epidemics will unavoidably continue to occur around the planet in the ensuing decades. Animal vaccinations developed quickly can be crucial in preventing and controlling the spread of new illnesses (James, 2011).

Several vaccines have been successfully developed against emerging animal diseases. Several countries have used vaccines, together with other eradication measures, to control the high-pathogenicity avian influenza virus (H5N1) in poultry. From 2002 to 2010, it is reported that many billions of doses were administered to poultry, mostly in China (Swayne, 2012). This practice is considered to have reduced disease and mortality in chicken flocks while also reducing the number of human infections, which have very high fatality rates. Rift Valley fever virus, a devastating pathogen of ruminants and a virulent zoonotic agent is seen as a prime target for animal vaccine development (Momin, 2021).

Emerging diseases of equine viruses include Venezuelan equine encephalitis, West Nile, and Hendra (Young *et al*., 2020). Vaccination against these agents lowers the risk of zoonotic infections. Continued development of more cost-efficient, safe, and effective vaccines against zoonotic agents will foster improvements in human health, animal health, and food security (FAO, 2021).

2.4 Reduction of the Need for Antibiotics

Antibiotics are widely used to control bacterial pathogens in livestock and to promote efficient food production. However, there are increasing concerns related to antibiotic resistance associated with the extensive use of antibiotics in veterinary and human medicine (Dibner & Richards, 2005). Veterinary vaccines reduce the need for antibiotics to treat infections in food-producing and companion animals. Producers may choose either vaccines or antibiotics to control some diseases based on cost if both options are available. If regulatory requirements for a biologics company to obtain and maintain a license to produce the vaccine were to increase, then the cost of the vaccine would increase, and producers would opt to use less vaccine and more antibiotics. Affordable and available vaccines reduce reliance on antibiotics for animal health (James, 2011; FAO, 2021).

2.5 Food Safety Vaccines

Recently, vaccines have been developed to reduce the shedding of organisms that cause foodborne diseases in people. Vaccines for E. coli O157:H7 in cattle and Salmonella enteritidis in chickens are available. These vaccines typically do not improve the health of the vaccinated animal, but they reduce the shedding of pathogens that may contaminate animal products for human consumption (Design *et al*., 2013). The severity of the *S. enteritidis* outbreak in people in the United States in 2010 due to the consumption of contaminated eggs could have been reduced or prevented if the chickens had received the S. enteritidis vaccine (FAO, 2021).

3. Types of Veterinary Vaccines

3.1 Modified Live Virus Vaccines

Modified live virus vaccines (MLV) contain whole viruses that have been altered such that their ability to cause disease has been taken away. Vaccine manufacturers typically achieve this by making the microbe grow under prolonged or slightly abnormal conditions (Gunn *et al*., 2013). MLV vaccines are typically packaged in two vials, one containing a freeze-dried cake that contains the modified microbes and the other containing the diluents, which re-suspend the microbes (Daly & Price, 2010). They need less bacteria or viruses and provide

higher immune response activation. They should ideally not result in any clinical illness symptoms. In healthy animals, a single dosage of the MLV vaccination can give protection due to its quick induction of immunity. It is more effective at getting over maternal antibody interference (Abbas, 2001).

3.2 Killed Vaccines (Inactivated Vaccines)

Killed vaccines comprise whole viruses or bacteria that have been inactivated by heat or chemical treatment. They are typically coupled with an adjuvant that acts as a stimulant to increase the animal's immune response. Adjuvants are compounds that do not specifically stimulate the immune system to respond to and slow down the body's removal of the injected inactivated microbes (Daly & Price, 2010).

Heat or chemicals may be used in the manufacture of killed vaccinations. Beta-propiolactone and formaldehyde are some of the compounds utilized. Formalin has been used traditionally to inactivate viruses. While minimal therapy can leave an infectious virus that can spread illness, excessive treatment can remove immunogenicity. An epidemic of paralytic poliomyelitis occurred in the USA shortly after the introduction of the inactivated polio vaccine, which is a prime example of an improperly inactivated vaccine (Miller & Zawistowski, 2012). After that incident, the formalin inactivation process and other inactivating chemicals for vaccines that are currently available were examined, and it was discovered that they took significantly longer to offer protection (Daly & Price, 2010).

3.3 Toxoid Vaccines

Toxoids are used as vaccines because they induce an immune response to the original toxin or increase the response to another antigen since the toxoid markers and toxin markers are preserved (Matsuda, 2002). For bacteria that secrete toxins or other harmful chemicals, a toxoid vaccine might be found so that they can inactivate the toxins by being treated. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have formalin, a solution of formaldehyde and sterilized water. Such detoxified toxins, called toxoids, are safe for use in vaccines (NIAID, 2013).

The immune system produces antibodies that lock onto and block the toxin. Once the toxin is inactivated, it's called a toxoid, and it can no longer cause harm. A vaccine against tetanus is an example of a toxoid vaccine. Not all toxoids are for microorganisms; for example, the Crotalus Atrox toxoid is used to vaccinate dogs against rattlesnake bites (CCRC, 2013).

3.4 Polynucleotide Vaccines

Additionally, DNA-encoding viral antigens may be injected into animals to immunize them. This DNA may be placed into a plasmid, a circular piece of DNA that serves as a vector and is found in bacteria. The genetically modified plasmid can be taken up by host cells after injection. Following transcription of the DNA, mRNAs are translated to create vaccine proteins. Thus, the vaccine protein is expressed by transfected host cells together with components from the class I MHC. This may result in the production of cytotoxic T cells in addition to neutralizing antibodies. This method has been used experimentally to create vaccines against the viruses that cause Newcastle disease, foot-and-mouth disease, bovine herpesvirus-1-related disease, canine and feline rabies, canine parvo, canine and feline leukemia, feline immunodeficiency virus-related disorders, feline leukemia, and pseudorabies. These polynucleotide vaccines are perfect for use against pathogens that are challenging or harmful to culture in the laboratory because they may elicit a response comparable to that elicited by attenuated live vaccines. (Meeusenet *et al*., 2007).

3.5 Subunit Vaccines

Subunit vaccines, like inactivated whole-cell vaccines, do not contain live components of the pathogen. They contain only viral or bacterial antigens that can trigger an immune response (WHO, 2016). A recent example is a new synthetic vaccine against foot-and-mouth disease. Subunit vaccines contain only parts of the bacteria or virus of interest. Like inactivated vaccines, they do not contain live components and are considered very safe (Postnote, 2013).

3.6 Virus-Vectored Vaccines

The genes that code for protective antigens can also be inserted into an avirulent vector bacterium to create a very effective live vaccination. Genes from the vector are deleted and replaced with genes encoding pathogen antigens to produce these vaccines. The inserted genes then express the antigens when body cells are infected by the vector virus after the recombinant vector has been given as the vaccination. The vector may be host-restricted or attenuated so that it won't multiply in the tissues of the vaccinated people and won't be shed from them (Tizard, 2017). For use against organisms that are challenging or harmful to cultivate in the laboratory, virus-vectored vaccines are ideally suited (Meeusenet *et al*., 2007).

3.7 Gene-Deleted Vaccines

An early type of genetic engineering is the extended tissue culture attenuation of viruses. Ideally, this led to the emergence of a viral strain that was incapable of spreading illness. The risk of reverting to virulence made this often difficult to do. It is now feasible to alter an organism's genes using molecular genetics techniques so that the changes are permanent. It is becoming more and more appealing to purposefully delete the genes that produce virulence-related proteins. For instance, gene-deleted vaccinations were initially employed in pigs to protect against the pseudorabies herpes virus. The thymidine kinase gene was inactivated in this instance. While viruses with this gene deleted can still infect neurons, they cannot reproduce and spread illness (Gunn *et al*., 2013).

3.8 Recombinant Viral Proteins

Recombinant-vector vaccines are experimental vaccines like DNA vaccines, except they deliver microbial DNA to body cells via an attenuated virus or bacterium (NIAID, 2013). The creation of hybrid virus vaccines is another application of recombinant DNA technology. The most well-known instance of this is vaccinia, in which the DNA sequence encoding the foreign gene is put into the plasmid vector together with the promoter and thymidine kinase sequences of the vaccinia virus. The resulting recombination vector is then used to create a virus that expresses the foreign gene by introducing it into cells that have been infected with the vaccinia virus. The recombinant viral vaccine can then grow and generate a variety of virus antigens in infected cells. The ability to incorporate several viral genes makes it possible to create polyvalent live vaccinations. (Nascimento, 2012).

Purified or recombinant products are typically more expensive than conventional MLV or killed vaccines. They also frequently need the same booster schedule and onset time as a killed vaccination. It has been demonstrated that the canine distemper recombinant vaccination offers quick protection equivalent to the MLV vaccines and is effective in young puppies (Miller and Zawistowski, 2012).

3.9 Valence Vaccines

Monovalent or multivalent (polyvalent) vaccines are also available. One antigen or one bacterium is what a monovalent vaccination is intended to protect against. To protect against two or more strains of the same bacterium or against two or more germs, a multivalent or polyvalent vaccination is created. In some circumstances, a monovalent vaccination may be preferred for triggering a powerful immune response quickly (CCRC, 2013).

4. Mechanism of Action of Veterinary Vaccines

Veterinary vaccinations, which rely on complex immunological mechanisms, are essential instruments in reducing the spread of infectious diseases among animals. With an emphasis on the immunization process and the subsequent activation of the immune response, this part offers a thorough investigation of the processes behind the action of veterinary vaccines.

4.1 Immunization Process in Veterinary Vaccines

Veterinary vaccines are based on the immunization process, which involves the introduction of pathogen-derived antigens. These antigens, found on the surface of pathogens, are the focal points of immune recognition. Various forms of antigens, including inactivated, live attenuated, subunit fragments, and synthetic mimics, are used (Orenstein *et al*., 2017).

The core of veterinary vaccines is the immunization procedure, which involves the intentional administration of pathogen-derived antigens. The primary sites of immunological recognition are antigens, which are molecular structures present on the surface of diseases. Various types of antigens, such as inactivated pathogens, live attenuated pathogens, subunit fragments, or synthetic mimics of pathogenic characteristics, are used in veterinary vaccines to trigger immune responses (Orenstein *et al*., 2017).

4.2 Activation of the Immune Response in Veterinary Vaccines

Immune cells participate in complex interactions throughout immune response activation, which results in the development of immunity against certain infections. The primary immune response and the secondary immune reaction are the two key stages of this process.

4.2.1 Primary Immune Response in Veterinary Vaccines

Helper T cells (Th cells) respond to the given antigens by going into action. By releasing cytokines molecular messengers that encourage B cells to develop into plasma cells, which are responsible for producing antibodies these Th cells play a crucial role in directing the immune response (Kuby *et al*., 2013). By binding to antigens, these antibodies in turn neutralize infections while recognizing them for elimination by other immune cells.

Memory B cells, which can "remember" met antigens for an extended period of time, are produced by the main immune response in addition to antibodies. By establishing memories, the immune system is prepared to respond

to the same infection with greater efficiency and speed in future instances (Janeway *et al*., 2001).

4.2.2 Secondary Immune Response in Veterinary Vaccines

The core of vaccine-induced immunity is the secondary immune response. Memory B cells and memory T cells from the initial reaction are active when an animal that got a vaccination comes into contact with the real illness. When compared to the first encounter, these memory cells coordinate a faster and enhanced immune response.

Memory B cells quickly transform into plasma cells, which speeds up the production of antibodies against the pathogen (Doherty & Christensen, 2000). Memory T cells simultaneously aid in immune control and the removal of infected cells, which results in a quick and effective immune response that prevents the development of pathogens.

4.3 Role of Antibodies and Memory Cells

The efficacy of veterinary vaccinations depends significantly on the function of antibodies and memory cells. Immunoglobulins, commonly referred to as antibodies, are vital components of the adaptive immune response, which is important in neutralizing diseases. Animals that get vaccinations develop antibodies against specific antigens that make up the vaccine, defending them from subsequent illnesses. These antibodies have the ability to attach to the surface proteins of infections, blocking their entrance into host cells and aiding immune cells in eliminating them. Memory cells, such as memory B and T cells, are also produced during the immune response to vaccination. Long-lasting immunity is provided by these cells, as they maintain the memory of the encountered antigen and may thus mount an immediate and efficient response when the pathogen is exposed again (Smith *et al*., 1999).

Animal disease management and prevention have benefited significantly from vaccination in veterinary medicine. Vaccines induce an immune system response, resulting in the development of certain antibodies that are directed against pathogens. After receiving a vaccine, memory cells are created, ensuring quick and effective immune responses when the pathogens are later exposed. In veterinary vaccinations, antibodies and memory cells play a crucial role in developing immunity and preserving animal health.

All animals need to detect and eliminate microbial invaders as fast and effectively as possible. This immediate defensive response is the task of the innate immune system. Innate immune responses are activated when cells use their pattern recognition receptors to detect either microbial invasion or tissue damage. The innate immune system lacks specific memory, and, as a result, each episode of infection tends to be treated identically. More importantly, however, the innate immune responses serve as one of the triggers that stimulate antigen-presenting cells to initiate adaptive immune responses and eventually result in strong long-term protection (Andrew & Else, 2021).

Adaptive immunity develops when foreign antigens bind to B- or T-cell antigen receptors. and trigger strong defensive responses. Adaptive immune responses are the basis of successful vaccination. Type 1, or cell-mediated immunity, is mediated by type 1 helper (Th1) cells. Type 1 responses are responsible for immunity to bacteria, viruses, protozoa, and fungi. They generate some antibodies and strong cytotoxic T-cell responses and also activate macrophages. Type 2 immunity, in contrast, is mediated by type 2 helper (Th2) cells. These cells promote antibody formation. Adaptive immune responses can be considered to proceed in four major steps. These are: antigen capture and processing, helper T cell activation, B cell, and/or cytotoxic T cell-mediated responses that eliminate the invaders and ensure the survival of large populations of memory cells. It is these memory cells that provide a vaccinated animal with the ability to respond rapidly and effectively to subsequent infections (Andrew & Else, 2021).

The induction of adaptive immune responses requires the activation of antigen-presenting cells, primarily dendritic cells. This activation is mediated by cytokines generated during the initial innate response. These activated dendritic cells capture, process, and present exogenous antigens. Dendritic cells are found throughout the body and form networks in virtually every tissue. They are especially prominent in lymph nodes, skin, and mucosal surfaces—sites where invading microbes are most likely to be encountered. The number of dendritic cells varies considerably among tissues. Thus, DCs are present in high numbers within the dermis. As a result, intradermally administered vaccines are readily recognized. Likewise, circulating DCs are common in well-vascularized muscles, the preferred site of injection for many vaccines. There are fewer DCs in the subcutaneous and adipose tissues, thus explaining why these are usually less effective routes for vaccine administration (Andrew & Else, 2021).

When DCs encounter foreign antigens, they are matured and activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant. This maturation and activation cause DCs to migrate toward the source of the antigen, either at the injection site or in the draining lymph node. The activated, mature DCs capture antigens by phagocytosis and ingest microbial antigens. These antigens are bound to specialized receptors called major histocompatibility complex (MHC) class II molecules and are expressed on the DC surface (Andrew &

Else, 2021).

Through the T cell receptor (TCR), MHC molecules on dendritic cells deliver peptides from the vaccination protein antigen, activating T cells. The T cells coordinate B cell growth in the lymph node using soluble antigen-mediated B cell receptor (BCR) signaling. Here, the maturation of the antibody response leads to an increase in antibody affinity and the induction of various antibody isotypes as a result of T cell-dependent B cell growth. Over the following two weeks, serum antibody levels rapidly increase because of the development of short-lived plasma cells, which actively generate antibodies specific to the vaccine protein. Additionally, memory B cells, which regulate immunological memory, are created. Long-lived plasma cells go to stay in bone marrow niches where they can continue to make antibodies for decades. When they come into contact with a pathogen, CD8+ memory T cells may multiply quickly, and CD8+ effector T cells are crucial for the eradication of infected cells (Andrew & Else, 2021). The antibody offers protection from infection in several ways. These include neutralizing toxins, inhibiting organism adherence to cells and entrance, stopping viral replication, neutralizing poisons, and complement-mediated death (Andrew & Else, 2021).

Table 1. Summary Mechanism of Action of Veterinary Vaccines

Aspect	Details
Immunization Process	- Introduces pathogen-derived antigens. - Antigens: inactivated, live attenuated, subunit fragments, or synthetic mimics. - Antigens recognized by immune system.
Activation of Immune Response	**Primary Immune Response:** - Helper T cells stimulate B cells. - Antibodies neutralize infections. - Memory B cells for future responses. **Secondary Immune Response:** - Triggered by memory B and T cells. - Faster, enhanced response. - Memory B cells become plasma cells for rapid antibody production. - Memory T cells aid in immune control.
Role of Antibodies and Memory Cells	- Antibodies: vital, attach to pathogens, aid immune cells. - Memory B and T cells maintain antigen memory. - Provide long-lasting immunity, rapid response upon re-exposure.

5. Causes of Vaccine Failure

Vaccines are normally quite effective, although full and lasting immunity to illness is uncommon. One of the reasons vaccines fail to prevent disease is issues with client education or compliance with basic animal care practices. Several factors can impact how effective a vaccine is. Maternal antibodies, immunosuppression, improper vaccination timing, missed booster doses, antigenic differences between vaccine and field strains, use of polyvalent vaccines, adjuvant in vaccines, the age of the animals to be immunized, and insufficient dosage are some of these factors (Altman *et al*., 2017).

5.1 Alterations in the Vaccines

Incorrect handling or storage of the vaccine, resulting in an ineffective vaccine being administered that will not provide protection (e.g., the toxicity of dimethyl sulfoxide (DMSO) for Babesia parasites at temperatures above freezing, is a serious constraint on the infectivity of the vaccine). After thawing the vaccine at between 37 and 40°C, it must be injected immediately. It has been shown that if the vaccine is thawed slowly in melting ice and kept in melting ice, it is still infective for up to 8 hours without showing significant changes in the pre-exponential period (De Waal, 1996).

Vaccines must be maintained at the correct temperature during transport and storage, as well as after reconstitution and during use. Even when stored under appropriate conditions, the vaccine loses viability over

time. Therefore, vaccines that have passed their expiration date should not be used. The use of chemical disinfectants on syringes and needles can inactivate live, modified vaccines if there is any residual disinfectant (Rashid *et al*., 2009).

5.2 Maternal Antibodies

Vaccine failure in young animals may be due to the presence of maternal antibodies, which prevent an adequate response to vaccination. Maternal antibodies derived from colostrum are a well-known cause of vaccine failure (Greene, 1990). These antibodies in the young animal's circulation may neutralize or remove the antigen before it can induce an immune response. Typically, virulent infectious agents are capable of breaking through maternal immunity earlier than life, modified-live, or killed vaccines. This means that even if young animals are immunized frequently, there may be a period when they are vulnerable to infection. The vulnerability occurs between the times that young animals lose their maternal antibodies and before they develop their active immune responses. This period can be shortened by the use of less attenuated and/or higher-titered modified live vaccines or the use of killed vaccines with high antigenic mass and strong adjuvants (Larson & Schultz, 1996).

5.3 Immunosuppression

Immunosuppression due to a variety of factors, including stress, malnutrition, concurrent infection, or immaturity or senescence of the immune system, may also lead to vaccination failure. Poor nutrition can suppress immune responses by decreasing nutrient availability for cell division and protein (e.g., antibody and cytokine) synthesis (James, 2007).

If immune suppression occurs at the time of vaccination, the vaccine may fail to induce an adequate immune response. If the immunosuppression occurs sometime after vaccination, then disease may occur due to reduced immunity despite an adequate response to the original vaccine. Therapy with immunosuppressive drugs (e.g., glucocorticoids) may also cause this to occur (Rashid *et al*., 2009).

5.4 Insufficient Vaccination and Exposure

Vaccination does not confer instantaneous immunity. The body of an animal takes days to weeks if not longer, to respond to a vaccine. It can take up to two weeks following the second immunization in a series for some vaccinations to provide effective immunity. If an animal is exposed to a disease before a vaccine has had time to stimulate the body's immune system, the animal is susceptible to the disease (Rashid *et al*., 2009).

5.5 Wrong Timing of Vaccination and Missing Annual Revaccination

Vaccination of animals during the hot hours of the day, when animals are stressed, affects the function of the immune system of the animals, so the vaccine does not respond efficiently. Instead, the vaccine may result in disease and subsequent vaccine failure. Therefore, the regimen must be in the morning and later in the cold hours when animals feel comfortable (Sharif & Ahmad, 2018).

Booster doses of vaccine are frequently recommended by vaccine producers after an initial course. Most of the time, this advice is based on their immunity tests, which show that animals given a primary round of immunization are immune when challenged for 12 or sometimes 24 months, primarily with inactivated vaccines (Voysey *et al*., 2017). The excessive time between the first and second booster doses reduces the secondary antibody response as well as the length and quality of the resulting immunity (Rashid *et al*., 2009). The first dose primes the host's immunity, which is then completely enhanced by the booster dose. As a result, vaccination failure occurs when a booster dose is missing (Sharif & Ahmad, 2018).

5.6 Antigenic Difference Between Vaccine and Field Strains

For certain types of infectious agents, particularly bacteria that are vulnerable to control by the development of antibodies against surface components and viruses that use RNA as their genetic material and consequently have high mutation rates, there are often several antigenic variants of each agent. For antibody-mediated protection to be effective, the antibodies formed must bind the important strain-specific antigens on the surface of the bacteria or virus. Cell-mediated immunity is usually not as strain-specific as antibody-mediated immunity. To determine if a vaccine's failure to protect is due to antigenic differences between the vaccine and field strains, it is necessary to isolate the field strain and compare it to the vaccine strain. Antigenic differences between strains leading to a lack of vaccine efficacy are usually more of a problem with killed vaccines than modified live vaccines (James, 1999).

5.7 Using Polyvalent Vaccines

Polyvalent vaccines are those that protect against several infectious diseases, and as such, they are all-in-one vaccines. These vaccines culminate in vaccine failure by causing immunosuppression, which may occur as a result of antigen overload or of one antigen component of the vaccine preventing the immune system from responding to another component, which is termed vaccine interference (Rock, 2007).

When utilizing multi-pathogen or multivalent vaccinations, the various components interact with one another, resulting in an inappropriate immune response. This can include antagonistic or synergistic effects, antigenic competition, and/or epitope suppression. Overburdening the immune system is another term for this (Lauer *et al*., 2017).

5.8 Adjuvant Used in Vaccine

A protein subunit vaccine's effectiveness depends on how those proteins are prepared and administered so that they induce immune responses that are simultaneously safe and effective. Although their particular mechanism of action is unknown, it appears to differ between animals and humans. Mineral salt-based adjuvants are extensively used in human and veterinary vaccinations with outstanding safety profiles and largely appear to enhance humoral immunity (Del Giudice *et al*., 2018).

A thorough comprehension of these compositions' immunological mechanisms supports their introduction. Having the ability to induce cellular immune system reactions in several species in a way that mineral salt-based adjuvants cannot is particularly intriguing. For instance, immunostimulating complex (ISCOM)-based vaccines have been demonstrated to elicit cellular recall responses and Th-1-type immunity typified by IFN-c production in horses, cytotoxic CD8+ T cell responses in pigs, and Th-1-type immunity typified by IFN-c production in sheep, which were not possible using traditional mineral-salt-based adjuvants.

5.9 Age of the Animals to Be Vaccinated

With aging, both the immunological and endocrine systems undergo significant changes, including a decrease in the ability to mount suitable antibodies, reducing vaccine efficacy. Innate immune cells' functional capability deteriorates. Dendritic cell phagocytic capability is reduced, which affects antigen presentation and adaptive immune system activation. Aging is linked to deterioration in immunological capabilities, leading to immune senescence as a result of changes such as a drop in the B and T cell repertoires, as well as a drop in the naive cell pool, while memory and terminally differentiated T effector cells of limited diversity rise. As a result, the vaccine's antigenicity is low, and its efficiency is reduced (Castle, 2000).

5.10 Inadequate Dosage

If an optimal dose is not injected into animals, the vaccine does not produce a fruitful result; overdosing leads to a detrimental reaction (mainly live vaccines, which require fewer doses), and underdosing (mainly killed vaccines, which require a higher dose) contains low levels of antigen and thus does not stimulate the immune system, both of which culminate in vaccine ineffectiveness. The use of chlorine-containing water for vaccination, the presence of antimicrobials in the water used, and the use of vaccines beyond the number of animals allowed by the manufacturer are among the factors resulting in suboptimal dosage (Sharif & Ahmad, 2018).

It is common in poultry vaccination to use mass vaccination through drinking water. In drinking water vaccination all birds do not take the optimal amount of the vaccine, or use a spray, in which the temperature and humidity of the room, the type of water used, and the size of the particles used affect the amount of vaccine absorbed (Talebiet *et al*., 2005). One which can be delivered using a high-pressure needle-free device pressed against the skin, offering practical advantages for mass vaccination (Momin *et al*, 2021).

6. Strategies to Improve Veterinary Vaccine Efficacy

Animals' immunity against a variety of infectious illnesses is made possible through vaccines, which play a significant part in preserving their health. It is crucial to increase the effectiveness of veterinary vaccines to protect animals, prevent disease outbreaks, and encourage the continued existence of livestock fields. To improve the immune response, vaccines contain adjuvants. The adjuvant used in veterinary vaccinations can have significant effects on how effective the vaccine is. Researchers are constantly developing novel adjuvants, which trigger potent and long-lasting immune responses without producing negative side effects. Toll-like receptor agonists, mineral salts, and oil-in-water emulsions are a few examples of substances being studied for their potential to enhance vaccination efficacy (Smith *et al*., 1999).

The development of vaccines depends significantly on the selection and development of antigens. Broader protection is accomplished when you include antigens that are highly conserved across many pathogen strains. The establishment of vaccines that protect against a variety of variations made possible by advances in genomics that have made it easier to identify conserved antigens. In veterinary vaccinations against viruses like influenza and coronaviruses, this method has demonstrated prospective (Gerdts *et al*., 2017).

Multiple doses of a vaccine are given via various platforms or vectors during a prime-boost vaccination. This tactic tries to activate several immune system components, leading to a stronger and longer-lasting immunological response. For instance, veterinary vaccinations against diseases like the horse herpes virus exhibit greater efficacy when DNA priming and protein boosting are combined.

Immune modulators are used to manipulate the immune response to improve vaccination effectiveness. Immune

system signaling molecules called cytokines are employed as adjuvants to strengthen particular immune responses. Regulatory T-cell agonists can also used to regulate immune responses and stop overactive inflammation, which will improve vaccine-induced immunity. Optimizing the vector is essential for vaccinations that deliver antigens using viral vectors. The vector's genome is modified to improve immune cell targeting and antigen expression. Adenoviruses and lentiviruses are examples of recombinant viral vectors that are designed for increased stability, safety, and antigen presentation, leading to improved vaccination efficacy.

Maternal antibodies inherited from the mother can prevent newborns from developing vaccine-induced immunity. It is difficult to create vaccinations that successfully combat maternal antibody interference. To guarantee that newborns receive appropriate protection, novel strategies, such as employing greater antigen dosages or modified immunization regimens (Smith *et al.*, 1999). Immunogenetic advancements have brought attention to the variation in animal vaccination responses. Based on an animal's genetic makeup and immunological profile, customized vaccination strategies offer the potential to improve vaccine effectiveness. Individualizing vaccinations to an animal's immunological features may lead to more focused and effective immune responses.

7. Conclusion and Recommendations

Animal vaccinations play a vital role in the global effort to prevent and control livestock diseases. The efficacy of these vaccinations hinges on their quality and the meticulous adherence to proper administration guidelines. Several factors, such as the animals' age, the use of polyvalent vaccines, the choice of adjuvants, maternal antibodies, immunosuppression, the timing of vaccination, and antigenic compatibility with field strains, can collectively contribute to instances of vaccine failure. The development of veterinary vaccine technology stands as a critical factor in averting disease outbreaks and upholding animal well-being. Innovative strategies, including adjuvant refinement, precise antigenic design, prime-boost techniques, immune modulation, vector optimization, and personalized vaccination, are fostering progress in this domain. Collaborative endeavors hold the potential to fortify animal protection and welfare across diverse contexts. Therefore, based on the above findings, the following suggestions aim to improve animal vaccination effectiveness:

- Safeguard vaccine safety and potency by meticulous storage, transport, and administration.
- Administer correct vaccine doses to provoke a strong immune response, avoiding both under-dosing and over-dosing.
- Adhere to established protocols for revaccination, particularly when initial immune responses might be insufficient.
- Align vaccine timing with animals' developmental stages and potential pathogen exposure for optimal immune reaction.
- Thoroughly identify and comprehend circulating pathogen serotypes before vaccine creation to ensure relevance and efficacy.
- Implement comprehensive training for vaccination, storage, and handling, as skilled staff greatly aid vaccination success.
- Invest in veterinary vaccine tech advancements, exploring innovative approaches like adjuvant enhancement, antigen design, and immune modulation.

Foster cooperation among veterinarians, researchers, and stakeholders to exchange insights, best practices, and knowledge for enhanced animal health.

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