WWJMER 2023;1(02): 00-00
www.wwjmer.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal

Tone Toka
Animal Health Department, Livestock and Fisheries Development Office, Zala Woreda, Gofa Zone, Ethiopia.

Tariku Geinoro
Faculty of Veterinary Medicine, Hawassa University, Hawassa, Ethiopia.

Correspondence:
Tone Toka
Animal Health Department, Livestock and Fisheries Development Office, Zala Woreda, Gofa Zone, Ethiopia.

Vaccine Failure and Its Control Methods in Poultry Production: A Review

Tone Toka, Tariku Geinoro

Abstract
A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A successful vaccination program is dependent on many factors including vaccine handling, quality and nature of the vaccine, use of local antigens and immunogenic response inside the body of the bird and following the manufacturer's instructions. The potential threat of disease outbreaks even in vaccinated flocks cannot be avoided completely due to vaccine failures. Vaccine failure could be because of host factors such as stress, interference with maternally derived antibodies, lack of genetic factors and vaccination for immunosuppressed flocks. Moreover, it could also be due to managemental, technical and practical errors such as:- use of inappropriate dosage, improper formulation of vaccine and diluent used, improper route of administration and untimely vaccination schedule, improper storage and use of expired vaccine. Better understanding of the causes of vaccine failure will result in identifying prophylactic measures regarding disease outbreaks in poultry flocks. However, these factors can be avoided by proper vaccine storage, use of an adjuvant, none use of expired vaccines, use of stabilizers, practicing proper vaccination schedule, preparing flocks for vaccination, supplementation of vitamins and minerals and following vaccine manufacturer's guideline. Therefore, chicken farmers should follow strict biosecurity to prevent the outbreaks and vaccine manufacturers' guidelines for storage, timing, and due dates, consult veterinarians before any vaccine administration and monitor the health status of chickens before vaccine administration.

Keywords: Antibody; Antigen; Poultry; Vaccination; Vaccine Failure.

Introduction
Ethiopia in general is endowed with a huge livestock population in Sub-Saharan Africa. It has been estimated that livestock supports the livelihoods of about 80% of the 60 million rural population [1]. In terms of poultry, 94% of the country's poultry population comprises indigenous birds [2], which are favored by household producers due to their perceived traits such as their adaptability to local agro-ecological conditions, taste, low price and input requirements as compared to exotic or improved breeds [3].
Poultry production is the fastest growing component of global meat production in developing and transitional countries [4]. The demand for chicken meat has increased over time because of the increasing demand for quality food in the form of meat and eggs. They are considered to be cheap sources of quality animal protein. As a result Ministry of Agriculture has identified poultry production as key sector to deal with food security issues [5].
Poultry birds are prone to different types of fowl diseases and result in high economic losses to the poultry industry especially in developing countries. Even though chickens are susceptible to bacterial, viral, parasitic and fungal infections, the outbreaks due to viral infection such as Newcastle disease (ND), Avian Influenza (AI), Infectious Bursal Disease (IBD), Infectious Bronchitis (IB), cause a great production loss in terms of reduction in meat and egg production [6].
The high prevalence of poultry disease creates major constraints in the development of the poultry sector and this requires immunization intervention of chickens before disease entry. Different strategies can be implemented to effectively prevent and control the entry and spread of poultry diseases control plans often include the use of vaccination [7].
Vaccination is one of the most important tools for preventing diseases and in reducing the

economic losses of the poultry producers. Vaccination is the cheapest, reliable, effective, economical, affordable and suitable alternate for prevention of diseases in poultry flocks [8].

Vaccine failure is the consequence of the inability of the chicken to develop adequate immunity after immunization or susceptibility of bird to field outbreak after administration of vaccine. High rates of 53.5% of vaccination failures have been recorded in vaccinated poultry flocks. Rates of 25.6, 25.6 and 2.3% of vaccine failure in Newcastle disease, infectious Bursal disease (Gumboro) and fowl pox, respectively have been recorded [6].

In general vaccination failure in poultry production is the major problem in many part of the world. The actual protection obtained will be determined by the sum of all the factors which can affect vaccine efficacy [9].

Therefore, information on the use of vaccine is extremely important; because vaccines are the likely mainstay of poultry disease control in the near future. Increasing number of reports on vaccine failure on poultry production further emphasize the importance of such knowledge in order to extend the effective life span of the existing vaccines on the market and to avoid the use of inefficient vaccination. Therefore, the objectives of this paper are to review the possible causes of vaccine failure in poultry production; to review the intervention strategies used to control for vaccine failure; to review the optimal time of vaccination in poultry

General Information on Vaccine and Poultry Vaccination

Vaccine

The word “vaccine” originates from the Latin Variolae vaccinae (cowpox), which Edward Jenner demonstrated in 1798 could prevent smallpox in humans. He used the phrase in 1798 for the long title of his inquiry into the Variolae vaccinae Known as the Cow Pox, in which he described the protective effect of cowpox against smallpox [10]. In 1881, to honor Jenner, Louis Pasteur proposed that the terms should be extended to cover the new protective inoculations then being developed. Today the term ‘vaccine’ applies to all biological preparations, produced from living organisms that enhance immunity against disease and either prevent (prophylactic vaccines) [11]. A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease [12].

Nature of vaccine

A vaccine is “an inactivated or attenuated pathogen or a component of a pathogen (nucleic acid, protein) that when administered to the host, stimulates a protective response of the cells in the immune system,” or it is “an immune-biological substance designed to produce specific protection against a given disease [13]. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic (to fight a disease that has already occurred, such as cancer) [14]. Some vaccines offer full sterilizing immunity in which infection is prevented completely [15].

Mechanisms of action of vaccine

Vaccines work by stimulating a response from the immune system to a virus or bacterium. This creates a 'memory' in the immune system. This immune memory allows the body to 'remember' a specific virus or bacterium, so that it can protect itself against this virus or bacterium and prevent disease that it causes. During vaccination, a modified form of a disease-causing microorganism or toxin, which does not have the capacity to grow or cause symptom is introduced into the body. The vaccine does, however, display the antigens that characterize a particular virus or bacterium. The immune system therefore responds in the same way that it would to the natural form of the disease-causing microorganism or toxin. It mounts a response and learns to recognize the antigens from the microorganisms within the vaccine, so that if the body is later infected with the active disease-causing microorganism it will identify it as being harmful and will act rapidly to destroy it [16].

Types of poultry vaccines

Different strains of vaccines can be selected to be used in different production system and different epidemiological areas. To select an appropriate vaccine strain for a given production system or epidemiological area, it is advisable to know the characteristic futures of different vaccines produced in many part of the world. Therefore, on selection process of vaccines especially for village system is mainly based on the transportability and cost. The most common poultry vaccines are for viral diseases, however, bacterial and fungal diseases vaccines are also available. Other parasitic diseases such as coccidiosis vaccines are at the testing level in different parts of the world [17].

There are several options for application of the immunization in poultry and these should fit to the conditions of the disease in the locality, the standard of farm biosecurity and the level of challenge for each type of poultry operation. An inactivated or killed vaccine confers a long-term immunity for the flocks [18]. So, successful vaccination with inactivated vaccines requires multiple inoculations and the presence of adjuvants to enhance immunogenicity [19]. Unlike live attenuated vaccine strains, the non-attenuated vaccines have a great potential to cause disease in the vaccinated host especially in chickens with decreased immunity and are not preferred as a first choice [20]. This is due to reversion to virulence during virus replication in the host and inadequate attenuation results in clinical disease and adverse vaccine reactions and this cause’s great difficulty in controlling the disease [17]. Vaccines most commonly used in poultry production in are classically described as live or inactivated.

Live vaccines

Vaccination can be performed using live non-attenuated or attenuated vaccines. Live attenuated vaccine is a type of vaccine that is contains attenuated viral strains whose virulence is reduced via series of cell culture or embryo passages that induces both cell- and antibody mediated immune responses by stimulating the body’s immune response [21].

The use of a live attenuated vaccine strain has a great advantage since it can be administered through the natural route of infection and enables to induce mucosal and systemic immunity [22]. Moreover, it helps with a large number of flocks since it is easy and suitable for administration [20].

Live vaccines are vaccines that contain the organism that infect the bird and subsequently proliferate in the chicken’s

body there by activating immune response of the chicken against organism. Only small amount of the organism is administered in the chicken body to proliferate. By proliferation in the chicken, increased number of the organisms is identified by the chicken's immune system, then results in an improved immune system [23]. Commonly used live vaccines against diseases of poultry are Newcastle disease, infectious bronchitis, infectious Bursal disease [24]. Live vaccines are the most commonly preferred vaccines used in poultry production. These vaccines are selected to be used due to their broad advantages. The most common advantages of live vaccines are; it is easy to apply, relatively inexpensive, and give moderately good immunity to individual bird and to the flocks in general.

But the disadvantage is that, the birds can react to the vaccination in manifesting some of the
signs of the disease. The severity of this reaction depends on strain of the vaccine or
presence of concurrent infection with other pathogens [25].

Inactivated vaccines

Most poultry vaccines were either inactivated organisms that were formulated with an oil-based adjuvant or live attenuated vaccines and were not very effective in many cases. Thus, the discovery of antigen/gene delivery systems has facilitated the development of novel prophylactic and therapeutic veterinary vaccines. Recently, reverse vaccinology is the best approach and uses several bioinformatics algorithms to predict antigen localization and it has been successfully applied to immunize against many veterinary diseases [26].

Inactivated vaccines are vaccines that comprise micro-organisms whose pathogenicity has been inactivated through the use of physical and chemical means, but the protein coat structure has been maintained, which acts immunogenic and it requires injection individual chicken. Inactivated vaccines give very good immunity without vaccine reactions and have been widely used, but are relatively expensive and require considerable attention to training when used by non-veterinary personnel. This type of vaccines is mixed with an adjuvant before administration. The adjuvants usually used include aluminum hydroxide or oil. Adjuvant help in enhancing the immune response through increasing vaccine stability in the chicken body [23].

Inactivated or killed virus vaccine is considered safer than the conventional live attenuated vaccines since are they are less immunogenic and do not promote the endogenous production of antigenic proteins stimulating the cell mediated immune response [6]. Such vaccines are made inactive by using physical (use of ultraviolet radiations and heat) and chemical (use of formalin) means to inactivate their pathogenicity, but the protein coat structure has been maintained, which acts as immunogenic.

Scope of vaccination in poultry production

The goal of this artificial induction of immune responses is to protect the animals against infectious
diseases [27]. The idea of vaccinations is used to keep away or reduce havoc that can happen when the diseases causing organisms appear on farm. Vaccinations involve cost of preventing the occurrence of the diseases. The costs involve that of the vaccine price, labor, time, tissue damage while administering the vaccine and losses due to vaccine reactions [23]

Table 1. General characteristics of live and inactivated vaccines for poultry.

Live vaccines	Inactivated vaccine
Smaller quantity of antigen. Vaccination response relies on multiplication within the bird	Large amount of antigen. No multiplication after administration
Easily killed by chemicals and heat	Easier to store
Relatively inexpensive, easy to administer, and can be mass administered**:** drinking water, spray	Expensive to produce and to apply, since almost always individually administered
Adjuvanting live vaccines is not common	Adjuvanting killed vaccines is frequently necessary
Susceptible to existing antibody present in birds (e.g. maternal immunity)	More capable of eliciting an immune response in the face of existing antibody
In immune birds, booster vaccination is ineffective	In immune birds, additional immune response is frequently seen
Local immunity stimulated (i.e. trachea or gut)	Local immunity may be restimulated if used as a booster but secondary response is poor or absent
Danger of vaccine contamination (e.g. EDS)	No danger of vaccine contamination
Tissue reactions (commonly referred to as a 'vaccine reaction') are possible and frequently visible in a variety of tissues	No microbe replication; therefore, no tissue reaction outside that which is adjuvant dependent
Relatively limited combinations, due to interference of multiple microbes given at the same time (e.g. IB, ND and LT)	combinations, are less likely to occur
Rapid onset of immunity	Generally slower onset of immunity

Source: [28]

The poultry vaccination is to immunize the birds through inoculation of non-pathogenic components of the pathogen in question, or closely related organisms that is nearly similar to naturally acquired immunity. This provides assurance to reduce the clinical and production impacts of the infections rather than the prevention of various infections outbreaks in poultry flocks [29]. Proper vaccination also used to develop a very high antibody levels in hens to increase the maternally derived antibodies (passive immunity) in the hatched offspring to protect the chickens against different infectious diseases during the early phase of life [17].

Evidences on Poultry Vaccine Failure

Vaccination failure occur when, following vaccine administration, the chicken do not develop the adequate antibody titer levels and or are susceptible to a field disease outbreaks. The effective application of vaccine and

vaccination program requires good quality vaccines and proper application. There are several factors that cause immunization failure in vaccinated poultry and all these various factors should be considered with equal importance [30]. Therefore, the most common factors responsible for vaccine failure are described under below.

Evidences associated with the vaccine itself

Vaccination itself is a stress. Stress may reduce the chicken's ability to mount an immune
response. Stress could include environmental extremes (temperature, relative humidity),
inadequate nutrition, parasitism and other diseases. Vaccination of sick birds not only
interferes with the response to vaccination but also interferes with the bird's ability to
overcome the disease challenge present. Delay vaccination until the birds are healthy.
Chickens may already be incubating the disease at the time of vaccine administration. Despite
proper administration, the birds become diseased because time is needed for antibody
production to begin and reach protective levels. Worthy to mention that after first exposure to
a live virus – type vaccine, antibodies IG, M, G and A, are first detected approximately 4 to 5 days
following exposure. Additional days are required for titers to reach protective levels [31]. The vaccines are manufactured in a processing plant where the titer of antigen of specific virus or bacteria may not be maintained properly as a result, the inoculums may not initiate protective immune response in birds. The titer of antigen in the vial of vaccine may be low which results in low immunity level in birds. Virus concentration has a significant effect on immunogenicity of vaccines [32].

Failure of the vaccine due to expiration

The use of vaccines after the date of expiry may not result in optimal immune response and can also results in vaccine failure. The effectiveness of vaccine depends on the viability of the agents (virus and bacterial) in the vaccine and the replication in the birds. The potency of vaccines is maintained to a certain period; however, its viability may be lost due to past their expiration date even it is stored under the appropriate temperature. Moreover, the vaccine can be inactivated if it is mixed with different types of residual disinfectant on the syringes and needles [19].

Antigenic differences between existing vaccine and field strains

Lack of vaccine efficacy due to antigenic variation amongst the vaccine and field strains (such as antigenic drift, antigenic shift) are usually a problem with killed vaccines than modified live vaccines. Accordingly, effective antibody-mediated immunity is developed if the antibodies exactly bind to the specific antigenic strain on the bacterial or viral surface. In contrast to antibody mediated immunity, cell-mediated immunity lacks strain specific immunization. Thus, it is necessary to isolate the circulating field strain and compare it with the existing vaccine strain [33].

Inadequate level of protection

The vaccine strain should elicit effective and sufficient immune response and this depends of the antigenicity of viral strain. Eggs are the source of maternal antibodies or passive immunity in poultry and remain effective for the first two weeks. After proper vaccination, most poultry vaccines reach their peak response typically between 2-6 weeks and the protection or immunity level then starts to gradually decline. If birds are typically vaccinated with virulent infectious agents during these periods of time where protection by maternal antibodies reaches high, the vaccine may fail to stimulate immune response due to neutralization. Even though birds are frequently vaccinated, the bird may become susceptible to different poultry diseases before they develop their own active immune responses. It is advised to give booster dose on the recommended schedule to develop the better protection level [7].

Evidences associated with the poultry

Previous exposure status of the bird to the virus and passive protection may affect the response to vaccination. Passive immunity comes about in two ways: the first is through hyper immune sera and the second one is transmitted from the breeder bird to her chick via the yolk and protects the chicks until the age between 14 - 30 days. The passive immunity passes from maternal immunity to baby chicks can influence the response to vaccination [34].

Stress factors

Stress is a non-specific response to change in the environment that poses an excessive demand on the physiological and behavioral adaption abilities of the birds. The body composition of birds normally has inadequate resources to defend itself from diseases and environmental changes. Different predisposing factors cause stress in poultry birds. This includes stress due to poor ventilation, cold, heat, excess humidity, transportation, high stocking density (overcrowding), low spacing, improper sanitation, excess load of litter, under and malnourishment(nutritional deficiency), parasitism, fever, and so on [17]. Since poultry birds are very much sensitive to extreme weather conditions, health-related and other management problems and this, in turn leads to reduced immune response. Accordingly, chickens become generally unresponsive to vaccinations and are susceptible to infection during disease outbreaks. Furthermore, live vaccines can cause huge outbreaks if it is administered to immune compromised chickens. Hence, stress predisposes chicken to reduced immunity, vaccine failure and economic losses due to low production [35].

Interference with maternal antibodies

Poultry are regularly vaccinated against different infectious diseases on the basis of their disease prevalence and the newly hatched chicks are passively immunized due to maternal antibodies in their blood. According to some research findings, maternal immunity can protect the chickens from various infectious diseases such as Newcastle disease virus and Gumboro (IBD) disease during the first week of birth. However, these maternal antibodies have potential to interact with the vaccine antigens and result in neutralizing antigen. Thus, vaccines such as live vaccines affect the development of immunity production by reducing the level of antibodies in the newly hatched chicken if they are vaccinated for first weeks [19].

Immunosuppressive and co-existing diseases

Immunosuppression is caused due to compromised immune

response and resulted in increased risk of infectious diseases in flocks of birds such as mycotoxicosis, infectious Bursal diseases (Gumboro), infectious anemia, Marek's disease, and others. All this stress conditions resulted in impaired immune response that may also lead to vaccine failure and affect effective immunization [19]. Additionally, the effectiveness of vaccine will be reduced if the infected or stressed birds are vaccinated for the same disease since the vaccine antigens are neutralized due to reaction with naturally produced antibodies against infectious pathogens. This causes vaccine reaction in birds and the disease condition may worsen and leads increased morbidity and fatality rate. Accordingly, it is highly recommended and important to secure the health status of birds before vaccination [6].

Genetic factor

Response to vaccine varies depends on the type of species of birds. The structures of major histocompatibility complex (MHC) are responsible for the individual variation of birds and this helps to determine the response of birds towards the bacterial and viral antigens. Birds might be more susceptible to pathogen due to the lack of some structure in MHC helps to recognize one of the antigens [36].

Evidences associated with managemental, technical and practical errors

Lack of proper storage and vaccine instability in cold chain

Vaccines should be properly stored, transported and applied as per the manufacturer's recommendations. In developing countries, the common encountered problems during vaccine storage that led to inactivation of vaccine are shortage of storage equipment, inappropriate storage temperature and lack of functional and effective refrigerators, mixing vaccines with other food items, interaction of vaccine with the disinfecting agents. According to Nelson et al. (2004) [37] trying to store or transport the vaccine without proper preservation, handling and following cold chain results in denatured antigen thereby ends with vaccine failure. Antigens are killed when the vaccine is exposed to direct sunlight which leads to reduced antigen concentration in the vaccine and vaccine effectiveness. Therefore, the vaccine should be well placed and protected from direct sunlight for better efficiency [7].

Inappropriate route of administration

Poultry vaccines can be administered through oral, subcutaneous, intramuscular, wing web, drinking water, eye dropping and spray. If a vaccine is not delivered using appropriate vaccination site or recommended route of administration, it may result in poor protection by the vaccine in poultry flocks. Besides, mass vaccination through drinking water and spray (aerosol) lacks uniformity in dosage between individual birds during administration that results in lack of effective immunity [7].

Insufficient dosage

The use of incorrect dosage such as under and over dosage of vaccines results in vaccine failure and vaccine reaction. There are various factors that contribute for improper formulation of vaccine dosage, among these, the high level of chlorine in water during vaccine preparations, use of water having antimicrobial contents and miscalculation of vaccine dosage. Additionally, the use of vaccine for large flocks of bird's application beyond the recommended dosage of the manufacturer, it will be resulted in inadequate dosage that causes low level of vaccine titers and inactivation of vaccine [24].

Improper formulation of vaccine and diluent used

Poultry vaccines should be prepared and properly formulated using specific diluent (saline water) as per the manufacturer's guidelines. Some diluents are specific for a single vaccine (diluents for lyophilized vaccines) and contain some preservatives that can demolish the activity of the other vaccine. Improper dilution and lack of standard procedure of vaccines formulation using the diluent in a single syringe may also decrease the potency of vaccines. Thus, during formulating different type of vaccines in a single syringe, the possible outcome after interaction should be adequately examined [7].

Use of single adjuvants

The use of single adjuvant has several drawbacks since it does not fulfill the requirement of all the vaccine requirements. Induction of weak, inadequate and short-lived immune responses is among the limitations of using single adjuvant [38].

Hygienic practices

The vaccine can increase the animal's resistance to disease, but this resistance can be overwhelmed if good management practices are not followed. Poor sanitation together with other factors such as stress, overcrowding and concurrent infection reduced the effectiveness of poultry vaccines. Without clean-out and disinfection over successive flocks, the challenge dose might be too high, or infection might occur too soon [39].

Failure due to concurrent administration of multiple vaccines

Poultry vaccines are commonly administered concurrently to birds for various types of infections. However, there are limited literatures that describes about the safety and efficacy of when administering multiple vaccines. According to different studies, in some vaccines, there is a possibility of reduced the antibody response to the vaccine when administered in combination and increase the risk of morbidity and mortality [39].

Faulty timing and schedule of vaccination

Mostly the recommended time vaccination in poultry is during cold hours of the day especially early in the morning and late hours of the day or evening. This is the most suitable and comfortable time of vaccination to get a better response from the vaccination. However, the outcome of the vaccine may be less in vaccinated flocks if the birds are vaccinated during the hot hours of the day (heat stress) [17]. During the time of vaccination, it is important to consider the age of the bird. Some antigenic receptors are age specific since they develop starting from day old (as early as they hatch of a chick) to old age. In early age, birds start to develop the receptors of Newcastle disease, infectious bronchitis, and infectious Bursal disease (IBD) whereas the receptors for infectious bursa disease and fowl pox develop with advancing age. Accordingly, it is advisable to vaccinate birds after development of these receptors in the bodies since

lack of receptors for the antigen in the host result in vaccine failure [17].

Lack of repeat or booster dosage

A booster dose is a dose of antigen designed to develop effective immunization after an initial immunization dose. Thus, administration of repeated dose in fixed period of time depending on the type of vaccine is essential. Besides, earlier immunization is necessary for introduction of the antigen of the vaccine into the birds' body whereas booster dosage is mandatory to maintain maximum level of protection against an antigen. However, low level of antibody titers is caused due to the absence of booster dose that in turn results in failure of vaccine [17].

Lack of strict biosecurity

Biosecurity is a compulsory comprehensive practice in poultry farms to protect the farms both from intentional and unintentional biological threats. Biosecurity measures can be designed for and implemented on small-scale production systems in rural areas. Ideally, bio-security requires periodic risk assessment and the measures used in an area may need to be modified as local

circumstances change. Many risk factors for infection are related to the farm, movement of animals on and off the farm and general management practices. Thus, the lack of inclusive biosecurity strategies makes susceptible to different poultry disease outbreaks. This makes the chicken immunocompromised and contributes to vaccine failure as a result of the change of the vaccine strain to pathogenic one [40]. Accordingly, numerous practical aspects affect vaccination and contribute to vaccine failure.

Table 2: Summary of the factors that deteriorates vaccine efficacy.

Factor	Description
Maternal immunity	Earlier interfere with antigens of the vaccine
Concurrent disease with immunosuppressive agents	Birds immune system fail to produce sufficient immune response against the infectious agents
Mismatch between field virus and the vaccine (Pathotype of field strain)	Lack of antibodies similarity between the circulating viral strain (field virus) and the vaccine strain to produce full protection
The quantity of Antigen and immunogenicity of the vaccine	An adequate immune response is not induced if a load of antigen is not enough to elicit immune response
Health status of the chickens	When the bird's immune system does not produce a sufficient response
Vaccine coverage (the total number of birds vaccinated)	Large number of birds must be protected to restrict the transmission
Species or breed of bird	During preparation, the target species should be considered for optimal Response
Duration of immunity or	Immunocompromised birds are exposed to infection and disease since the immunity declines
Quantity of doses	Booster doses should be given to improve immunity over time
Quality of administration	An optimal and full dose should be administered properly with proper equipment.
The Time or Speed to develop optimum level of protection after vaccination	Any exposure before sufficient development of sufficient immunity may lead to infection

Source: [40].

The Major Control Strategies For Vaccine Failure

Poultry vaccines are commonly used in several types of production systems. A cost-benefit assessment should be conducted to identify the suitable approach available before implementing the control options, while considering various situations. Thus, cost-benefit analysis should consider the following conditions such as: the species of birds, the production system, fowl densities, the antigenicity/virulence of the viral strain involved, provision of veterinary facilities and the impact on trade [20, 39]. The following strategies are considered as a best option to control the vaccine failure in poultry.

Proper formulation of the vaccines

It is always recommended to follow the instruction provided by the vaccine producer since there are some variation in preparation and formulation of the vaccines. For instance, the viable components of vaccines can be destroyed during preparation if the chemicals (sanitizers) used to clean the drinkers are mixed with the vaccine. In addition, during preparation of vaccines, the timing, the duration of efficacy and the type of diluent should be considered [41].

Attention to maternal immunity

In most poultry farms, fowls especially parent stocks are regularly vaccinated depending on the various outbreaks and prevalent infectious disease of birds. Thus, newly hatched day-old chicken by default has developed passive immunity in their blood from their parent stock through antibodies transferred in eggs. However, when vaccines especially live one administered during the first two weeks where these maternal antibodies are reaches their peak, the vaccine will be neutralized. According to different research findings and poultry manuals, vaccine should be given for newly hatched chicken based on the antibody titration level against the proposed vaccines to get the maximum immunization from the vaccine. For instance, the recommended time of vaccination for Gumboro disease (IBD) should have a gap of minimum of 11 days post hatching whereas for Newcastle disease, the chicken should be 7 days old at the time of vaccination [42].

Proper storage and maintain cold chain temperature

Poultry vaccines should be properly stored and transported at the optimum temperature as per the manufacturer's standard since temperature variation has a direct effect on the efficacy of the vaccine. Besides, during storage the vaccine must be stored separately from other items such as food item, chemical, pathological samples. For this reason, certain live vaccines like Marek's disease vaccines are easily inactivated due to improper handled and storage [19]. The proper cold chain temperature should be maintained to keep the viability of the vaccine. However, there are several factors that affect the cold chain temperature like shortage of

electric source and lack of cooling systems (refrigerator), over chilling and lack of vaccine transporting equipment (ice box). Likewise, the extra chilling of oil-based vaccines results in reduced potency of vaccines due to crystal formation of adjuvants (aluminum salts) in the vaccines. Thermostable vaccines are produced in such a way to cope up with the fluctuation of temperature such as cold and hot environments, while freeze-dried vaccines should be stored in the refrigerator at 4°C and transported using ice blocks/cooling system to keep at the recommended temperatures [19].

Avoiding use of expired vaccines

Most poultry vaccines that are produced worldwide have different table shelf life and are clearly described on the leaflets prepared by manufacturer. For instance, some vaccines like live lyophilized vaccines have wide range (1-2 years) of shelf life whereas other like oil-based vaccines have limited range (3-6 months) of shelf-life. The vaccine vial should be carefully checked and assessed for the date of expiration prior to application. The use of expired vaccines must be avoided and advisable to discard them properly or replaced with the new one from the manufacturers [36].

Use of adjuvant and stabilizers

An adjuvant is a supplementary substance that is added to the vaccine to increase the bioavailability of vaccines and to enhance immune response to the target antigen. This in turn, helps to increase the immunogenicity of vaccines to confer long-term protection and to reduce the required antigenic dose to produce effective immunity. Adjuvants have a potential effect on inducing a mucosal immune response that helps to improve the safety of the vaccine. For instance, vaccine given orally faces a great difficulty due to the microbial barriers in gastrointestinal tract and the antigen must be protected using adjuvants to overcome, these problems that help to activate the immune response. A combination adjuvant platform is promising and beneficial for suboptimal vaccines and particularly advantageous for vaccines against specific and more susceptible flocks of poultry populations. In contrast single adjuvants, combined adjuvants act synergistically by stimulating and activating various types of immune cells such as dendritic cells, macrophages, lymphocytes [38].

A stabilizer is a substance that is added to a vaccine in order to stabilize and increase the shelf life of the vaccine during formulation and administration of different vaccine. There are different types of stabilizers available in the market for the various kind of vaccine preparation. For example, for live oral vaccines such as infectious bronchitis, Newcastle disease, Gumboro disease, Vac-Safe (Intervet) and Vital Blue are the best stabilizers [36].

Controlling stress and use of antimicrobials

Stress can be managed by identifying the potential sources and causes that can be categorized into predictable stress that are related with management and handling problems and unpredictable stress related with variation in temperature and different incidence of disease outbreaks. A method of assessing and identifying stress should be developed to control the vaccine failure due to unforeseen stress. For this reason, firstly, the feeding, housing, microbial flora, and breeding system should be adjusted in the proper standard to increase the quality of life and increase the immune response sources. Secondly, administration of different kinds of therapies to minimize the level of immune-suppression in birds due to non-specific or unidentified factors to increase the quality of life and increase the immune response sources. However, such therapies should not be necessarily considered as the only means of prevent stress and its consequences. Besides, corrective measures should be taken after identifying the source of the stress such as reducing the bird density, increasing the number of feeders and drinkers, improving the ventilation and others [27]. In poultry production, Antimicrobial can be used pre and post vaccination and are given to minimize and prevent the development of a high risk of secondary bacterial infections due to opportunistic microorganisms during the periods of stress. When selecting the antimicrobials compatible with the immune defense system, spectrum of activity and its potential against the pathogenic opportunistic microbes. For instance, antimicrobial like Erythromycin have a special immune modulating capacity through stimulating the secretion of interleukins by leukocytes that help to maintain strong immunity for the birds [43].

Administration of vitamin and mineral

Vitamins and minerals should be provided to immune-compromised birds that supports the immune response by acting on the immune cell and rapidly enhances the production of antibodies; as a result, the birds get a better immunity in a shorter time. Administration of vitamins (vitamins A, E, C and B) in poultry feed helps to improve some of the adverse effects due to stress that help to support the immune defense system. Besides, the use of vitamins prior to a predictable stressing condition is very important and should remain till the whole stressing scenario ends. This should be done administered 24 hours prior to vaccination and vitamins are involved in all kinds of stress reaction and are used up directly during synthesis of glucocorticosteroids (Vitamin C) or indirectly by increasing the number in most intermediate metabolic reaction (Vitamin B)[19].

Correct vaccination schedule and strict biosecurity

A proper vaccination program should be there for poultry flocks depending on the prevalence of the disease in the area in order to minimize disease outbreaks and financial loss associated with the disease. It is better to vaccinate the birds prior to the incidence of the disease so that the birds develop the required amount of antibody titration. For instance, vaccination against infectious bronchitis and avian influenza should be given before winter period since the outbreak of diseases is commonly occurs in birds during winter. Besides, biosecurity is the most important and crucial component of any poultry outbreak prevention and control strategy and should be maintained at a high level to complement vaccine use. In addition, it is advised to follow strict stamping-out (all in all-out) principles to avoid cross-contamination between flocks [40].

Flocks preparation for vaccination

During administration of vaccines, the flocks of birds should be properly prepared for vaccination depends on the route of administration, age of the birds, technique of vaccination and type of vaccine. Besides, precautionary measures such withholding feed and water for 2-3 hours prior to vaccination, should be followed strictly to increase the

efficacy of the vaccine. For instance, spray vaccination is administered to day old chicks post-hatch in cabinets for mass-vaccination through aerosol method. While eye drop day, old chicks are applied to individual chickens through eye. Oral vaccinations are the most common means of vaccine administration. The vaccination should be given after fasting the flock for few days that later helps to finish the vaccine within short period (up to 2 hour) of time and the vaccines should be prepared and administered in clean equipment (drinkers). For this purpose, sufficient number of drinkers must be available and proper follow up as well as regular moving of birds ensure all birds drink sufficient amount of the vaccine [36].

Strictly follow the manufacturer's guidelines

When applying vaccines, the type (inactivated, live attenuated, DNA and recombinant vaccines) and use of vaccine should be considered as per the guidelines put by the manufacturer like preparation, usage, storage, and route of administration. Hence, it is always advisable for vaccination to be given by trained or qualified veterinarian in order to minimized the adverse reactions related with the vaccine such as local tissue reaction (in activated or killed vaccines) and vaccine reaction (live attenuated vaccines). Moreover, most manufacturers advised to avoid any stressing environment (transportation, overcrowding and hot weather) by testing for proper titration level of antibodies before application of poultry vaccines. For instance, early or late hours of the day are considered as the most suitable periods of vaccination especially during summer [41].

Conclusion and Recommendations

Poultry production is the fastest growing component of global meat production in developing and transitional countries. Infectious Poultry diseases are threat to the poultry producers and industry that results in great financial losses. Vaccinations is one of the most important tools and cost-effective method to protect fowls from disease and reduces a great loss as well as reduce the need for antibiotics in poultry products. However, there are challenges concerning poultry vaccines that contribute to vaccine failure including the instability of the vaccine, incorrect handling, preservation, and transportation as well as the administration that require new solutions in vaccine development. Hence, to address these problems, it is advisable to follow the vaccine manufacturer's guidelines that have a paramount importance controlling failure. Besides, when administering vaccine, the health of flocks and the level of maternally derived titers should be a consideration. Therefore, based on the above conclusion; the following recommendations were forwarded: Veterinarians working at different field clinics should follow vaccine manufacturers' guidelines for storage, timing, expiration dates and administration. Monitoring the health status of chicken before vaccination is very crucial. Using proper vaccination strategies and the right dose in the right way at the right time is important. Awareness creation of poultry owners should be conducted for the appropriate use of vaccination in preventing poultry infections. Further evaluation of optimal time of vaccine delivery in vaccinated parent flock is needed. Large scale evaluation of different commercially available vaccines should be carried out. Chicken farmers should consult veterinarians before any vaccine administration. More ever, studies are needed based on a comparative efficacy on vaccines from reliable source

References

1. FAO, (2004): Livestock sector brief: Ethiopia.
2. CSA, (2013): Agricultural Sample Survey. Report On Livestock And Livestock Characteristics (Private Peasant Holdings) Volume II.
3. Alemu, D. T., Degefe, S., Ferede, S., Nzietcheung, D. R. (2008): Overview and Background Paper on Ethiopia's Poultry Sector: Relevance for avian flu Research in Ethiopia. DFID Pro-poor avian flu risk reduction Strategies Project Africa/Indonesia Region Report No. 1.
4. Assa, M. (2012): Poultry production and rural poverty among small scale farmers in Mzimba District of Malawi. Livestock Res for Rural Dev.24, 177-82.
5. LMP (Livestock Master Plan), (2015): Road maps for Growth and Transformation. Poultry Development Roadmap 2015/16-2019/20, 48 – 62.
6. Bosha, J. and, Nongo, N. (2012): Investigating vaccine handling and administration in Makurdi metropolis, Benue state, Nigeria. Paper presented at Proceedings of 37th conference of Nigerian society of animal production (NSAP), University of Agriculture Makurdi, Bennue state, Nigeria.
7. Bosha, J. (2012). Common breaches in poultry vaccine handling and administration in Makurdi Metropolis: A recurrent phenomenon in the tropics. Vom Journal of Veterinary Science 9(1): 11-16.
8. Ramirez, L. A., Arango, T. and Boyer, J, (2013): Therapeutic and prophylactic DNA vaccines for HIV-1. Expert Opinion on Biological Therapy.13:563-573.
9. Paul McMullin, (1985): Factors which interfere with vaccine efficacy. Proceedings of the 1st Sta. Catarina Poultry Symposium pp10-20.
10. Bax, D. (1999): "Edward Jenner's Inquiry; a bicentenary analysis" Vaccine. 17 (4): 301–307.
11. Plotkin, S. L. and Plotkin, S. A. (2008): A short history of vaccination. In Vaccines 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China.
12. Fiore, A. E., Bridges, C. B. and Cox, N. J. (2009): "Seasonal influenza vaccines". Vaccines for Pandemic Influenza. Curr. Top. Microbial. Immunol. Current Topics in Microbiology and Immunology. Vol. 333.
13. Melief, C. J., van Hall, T., Arens, R., Ossendorp, F. and van der Burg, S. H, (September 2015). "Therapeutic cancer vaccines". The Journal of Clinical Investigation. 125 (9): 3401–3412.
14. Ledford, Heidi, (2020): "What the immune response to the coronavirus says about the prospects for a vaccine". Nature. 585 (7823): 20–21. Bibcode: 2020 Natur.585.20 L.
15. World Health Organization, (2013): Global vaccine action plan, 2011–2020. WHO https://www.who.int/immunization/globalvaccine_action_plan/GVAP_doc_2011_2020/en/.
16. Sharif, A. and Ahmad, T. (2018): Preventing Vaccine Failure in Poultry Flocks. Immunization-Vaccine Adjuvant Delivery System and Strategies: Intech Open.
17. Furuya, Y., Regner, M., Lobigs, M., Koskinen, A. and Müllbacher, A. (2010): Effect of inactivation method on the cross-protective immunity induced by whole 'killed' influenza A viruses and commercial vaccine preparations. Journal of General Virology 91(6): 1450-1460.
18. Hassan, A. M., Garba, and M. S. and Durodola, O. S, (2017): Causes of Vaccination Failures among Poultry

Farms in Kano Metropolis, Kano State, Nigeria. Fudma-Journal of Agric & Agric Tech 3(1): 104-110.
19. Alexander, D. J. and, Shenne, D. (2003): Newcastle disease. Diseases of poultry 11(1): 64-87.
20. Ganguly, S., Paul, I. And Mukhopadhayay, S. (2010): Different types of vaccines and vaccination. The most accepted trend to control and eradicate infections. Indian Pet Journal 5: 34-37.
21. Sanda, M, (2015): Effects of Vitamin-Mineral Supplement on the Immune Response of Broilers to Newcastle Disease Vaccination. International Journal of Agricultural and Veterinary Sciences (IJAVS) 1(1): 10-13.
22. Butcher and Miles, (2017): Vaccine Failure in Poultry: Factors to Consider. University of Florida Institute of Food and Agricultural Sciences, http://edis.ifas.ufl.edu/vm174, Accessed on September 17th, 2019.
23. Wambura, P. N. and Kataga, S, (2011): Putative protective antibody response following oral vaccination of multi age free ranging helmeted guinea fowls (Numidia meleagris) with Newcastle disease virus strain I-2 coated on oiled rice. Tropical animal health and production 43(1): 99-102.
24. Bell, J. G. (2000): A comparison of the different vaccines available for the control
of Newcastle Disease in village chickens. In: SADC planning workshop on Newcastle disease.
25. Jorge, S., Dellagostin, O. A, (2017): The development of veterinary vaccines: a review of traditional methods and modern biotechnology approaches. Biotechnology Research and Innovation 1(1): 6-13.
26. Abdul Careem, M. F. (2015): Main challenges in poultry farming: Vaccination failure. Zaragoza, Spain: Grupo Asis.
27. Bermudez, A. J. and Stewart-Brown, B. (2003): Disease prevention and diagnosis. In disease of poultry (Y.M. Saif, ed.), 11th Ed. Iowa State University Press, Ames, 17-54.
28. Dana, S., Rathore, B. and, Kaul, P. (2000): Morbidity and mortality pattern in desi chicken reared by the santal tribe of West Bengal. Indian Journal of Animal Research, 34(1): 49-51.
29. Saif, Y. M. and Barnes, H. J, (2003): Diseases of poultry. 11th Edition. Ames, Iowa: Iowa State Press.
30. Mojtaba, Y., Gary, D., Butcher, Amir, Nilipour, Richard, D., Miles, and Ali, R. (2012). The
culprits of vaccination failures. World Poultry - Elsevier Volume 18, No 8. '02.
31. Brugh, M. and, Siegel, H. S. (1978): Inactivated Newcastle disease vaccines: Influence of virus concentration on the primary immune response. Poultry Science, (57): 892-896.
32. Terfa, Z., Garikipati, S., Dessie, T. P., Wigley, J. M. and Bettridge, (2015): Farmers' willingness to pay for a village poultry vaccine service in Ethiopia: Prospect for enhancing rural livelihoods. Food Security 7(4): 905-917.
33. Nasser, M., Lohr, J. E., Mebratu, G. Y., Zessin, K. H., Baumann, M. P. O. and Ademe, Z. (2010): Oral Newcastle disease vaccination trials in Ethiopia. Avian Pathology, 29: 27– 34.
34. Abdullah, U., Adamu, S., Ahmed, A. (2009): Investigating on some causes of poultry vaccination failure in Bauchi Metropolis and environs, Nigeria. Nigerian Journal of Experimental and Applied Biology 14(1): 47-50.
35. Marangon, S. and Busani, L. (2007): The use of vaccination in poultry production. Revue Scientifique ET Technique-Office International des Epizooties 26(1): 265-274.
36. Nelson, C. M., Wibisono, H., Purwanto, H., Mansyur, I. and Moniaga, V. (2004): Hepatitis B vaccine freezing in the Indonesian cold chain: evidence and solutions. Bulletin of the World Health Organization 82(2): 99-105.
37. Garg, R. Babiuk, L. and Gerdts, V. (2017): A novel combination adjuvant platform for human and animal vaccines. Vaccine, 35(35): 4486-4489.
38. Shane, S. M, (2005): Handbook on Poultry Diseases. (2nd Edn.): American Soybean Association, Singapore.
39. Spackman, E., Pantin, J. and wood, M. J, (2014): Practical aspects of vaccination of poultry against avian influenza virus. The Veterinary Journal 202(3): 408-415.
40. Butcher, G. D. and Yegani, M. (2009): Investigating Vaccination Failure in Poultry Flocks.
41. Nwanta, J., Umoh, J., Abdu, P., Ajogi, I. and Egege, S, (2005): Comparison of the Cost of unvaccinated and oral vaccinated local chickens with a Malaysian Thermostable Newcastle Disease Vaccine (NDV4HR) In Kaduna State, Nigeria. Bulletin of Animal Health and Production in Africa 53(3): 203- 210.
42. CEVA, (2005): Factors affecting vaccination. Vaccines and Vaccination in Poultry Production: Santé Animal Pp. 81-98.