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Review Article

A Short Review of Progress in Development of Newcastle Disease Vaccines

Mohammadreza Shafaati[1,2], Mostafa Ebadi[3], and Masoud Ghorbani[4]*

[1]*Department of Cellular & Molecular Biology, Islamic Azad University, Iran*
[2]*Tebeshafa Biotech Co., Department of Research and Development, Science and Technology Park, Islamic Azad University, Iran*
[3]*Department of Biology, Faculty of Sciences, Islamic Azad University, Iran*
[4]*Pasteur Institute of Iran, Research and Production Complex, Department of Research and Development, Iran*

***Corresponding author**

Masoud Ghorbani, Pasteur Institute of Iran, Research and Production Complex, Department of Research and Development, Kilometre 25 Autobahn Karaj, 31599, Iran, Tel: 989362420374; Email: mghorbani2000@yahoo.com

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Abstract

Newcastle disease (ND) is a devastating disease affecting the chicken industry worldwide. Because of its tremendous financial impact and the potential for fast transmission to naive birds in the region, ND is listed on the avian illnesses that must be reported to the OIE as soon as it is discovered. ND is due to ND's tremendous socioeconomic value and its propensity to spread to naive birds in the surrounding area quickly. When it comes to methods of disease prevention and control, traditional ND vaccinations have survived the test of time by establishing a proven track record of protective effect for the last 60 years. However, these vaccinations are unable to prevent the majority of the phylogenetically distinct and virulent NDV isolates that are now circulating from replicating and shedding the virus. Therefore, vaccinations rationally developed to target the predominant genotypes, also known as "genotype-matched vaccines," are of the utmost importance to conquer these difficulties associated with immunization. Vaccines based on reverse genetics looked to be the most promising candidates among the newly developing technologies for producing genotype-matched vaccinations. This was an unambiguous observation. In this study, the target virus proteins and new vaccines' safety are examined to analyze their advantages and disadvantages. Different global vaccine strategies provide a theoretical basis for developing safe, effective NDV vaccines with controllable quality. These trends include both established and new practices. The benefits and drawbacks of each method are also brought to the forefront of this discussion.

INTRODUCTION

Newcastle disease (ND) is one of the primary poultry diseases that significantly affect the poultry industry in the world [1]. Newcastle disease, from the first outbreak in 1927 until now, has caused significant damage to the poultry industry due to numerous epidemics; that is why the World Organization for Animal Health (OIE) has included it in the list of diseases that require immediate notification [2]. The etiology of this disease is Newcastle disease virus (NDV), a single-stranded non-segmented RNA genome of negative sense (ssRNA) virus that encodes six structural proteins, namely NP, P, M, F, HN, and L. as two non-structural proteins V and W [3]. Among these proteins, two proteins, F and HN, are the major virulence factors of the virus [4]. Two glycoproteins, F and HN, play essential roles in the assembly and development of envelop viruses and determining tropism in the host and tissues [4]. The F protein induces fusion, while HN is responsible for binding [5]. HN glycoprotein has activities such as hemagglutination (HA) and neuraminidase (NA) and stimulates F protein activity [6]. The HN binding to the sialic acid receptor on the cell's surface initiates membrane fusion by the F protein [7]. The HN of NDV is an integral membrane protein type II, which contains three main areas: a cytoplasmic tail in the N-terminals, a stalk membrane-proximal domain, and a globular head domain at the C-terminal [8,9]. The globular head in the C-terminal domain is where the receptor binding and enzymatic activity happen [9], while it is also the site for neuraminidase activity. By removing sialic acid from the cell's surface, the HN of NDV prevents the self-aggregation of the virus progenies during budding and helps with the release of the virus from the cell [4]. epidemiological studies show that the Newcastle virus is continuously evolving, and more than eighteen distinct genotypes have been recorded [10]. Therefore, the creation of immunity by any Newcastle strain should be able to cross-protect against other strains because of similar antigenic properties. The vaccine against Newcastle disease, which has been used for more than 60 years, is a killed or live attenuated vaccine commonly used against this disease worldwide [11]. These vaccines are known for their high efficiency due to their ability to multiply effectively and create a robust immune response after a single administration. They are usually administered via spray or drinking water [12]. However, the major drawback of these vaccines is that they do not prevent the proliferation of virulent heterologous NDV, and vaccinated birds may act as a reservoir for potential virus outbreaks. This deficiency has led to improved vaccination strategies worldwide against the Newcastle virus [13]. Vaccination is still the most effective way to control Newcastle disease. ND vaccination strategies are generally divided into two categories: conventional methods developed in the 1940s and, more recently, emerging methods based on recombinant DNA technology [14]. The global poultry industry has recently seen research focus on new vaccines

to control virulent NDV infection. In this review, the target virus proteins and the safety of new vaccines are examined to analyze their advantages and disadvantages. Different global vaccine strategies provide a theoretical basis for the development of safe, effective and NDV vaccines with controllable quality.

CONVENTIONAL VACCINES

Live Attenuated Vaccines; these vaccines have prevented severe losses in the poultry industry in the last few decades [15]. These vaccines are prepared based on some lentogenic NDV strains, including B1, F, LaSota, V4, and I2 [2]. The LaSota strain is the most widely used among these strains due to its superior immunogenicity, and then The B1 strain was used after the Lasota strain due to its Live. V4 and I2 vaccines are also critical because of their high thermal stability as vaccines in the absence of a cold chain in remote areas [16]. Other NDV strains used as live vaccines include Komorov and Mukteswar. Both of these strains are mesogenic and therefore suitable for use as a booster dose of vaccine [17]. All live attenuated ND vaccines function similarly to natural infection due to their ability to stimulate mucosal and systemic immune responses [18]. All live attenuated ND vaccines function similarly to natural infection due to their ability to stimulate mucosal and systemic immune responses and can provide 100% protection against the disease with a single administration of 10^5 EID50 [18]. Since it is not economical due to the high cost of vaccination per bird, the vaccination approach should be improved to make it economical. One of the critical factors determining vaccination's effectiveness is the vaccine's tissue tropism.For example, the LaSota vaccine elicits a strong immune response mainly by inhalation, so immunity occurs in the respiratory tract where initial exposure to the virus might occur [19]. Other vaccines, such as VGGA strains, are enterotropic and stimulate intestinal mucosal immunity in vaccinated birds [20]. Perhaps the most significant advantage of live NDV vaccines is their use through drinking water or spray, which lowers part of the costs from the point of production to the time of consumption [21]. In addition, it can cause horizontal transmission of the virus between vaccinated and non-vaccinated birds [21]. However, despite all the benefits of these vaccines, they have their shortcomings, which include reverting to virulence and causing clinical disease; also, these vaccines may cause respiratory reactions after vaccination in young birds, which, if severe, can severe predispose birds to secondary bacterial infections [22]. In addition, vaccines are mainly prepared based on genotype I or II strains, which are phylogenetically divergent from the common genotypes circulating in different countries [23]. Therefore, the inability of these vaccines to prevent the elimination of the virus after the challenge of the continuous presence of the malignant virus in the environment is an obvious issue. This issue is more dangerous with genotype VII viruses because shedding is significantly more than in other genotypes [23,24]. Therefore, considering the above limitations, the live attenuated vaccines must be used with utmost care and that the state-of-the-art vaccines are urgently needed to address these weaknesses of the conventional live attenuated vaccines.

Another strategy to prevent Newcastle disease is using inactivated vaccines that are inactivated by physical or chemical methods [25]. Virus inactivation methods should be such that the immunogenic epitopes of surface glycoproteins of the virus (F and HN), which are responsible for the production of neutralizing antibodies, are spared [25]. The chemicals binary ethyleneimine (BEI) and formaldehyde are the most common agents for inactivating viruses while preserving their antigenic properties [26]. Inactivated vaccines are typically administered intramuscularly or subcutaneously in mineral oil emulsions. In general, the water-to-oil phase ratio must balance the vaccine's stability and viscosity to remain stable while not being difficult to administer due to the emulsion's high viscosity [27]. These vaccines are not suitable for widespread use because they cannot replicate and spread horizontally among vaccinated birds. Rather, they are administered individually, preferably via the parenteral route, making the process time-consuming and costly. The same nonreplicating property, however, renders them safe, with no risk of reversion to virulence [28]. The disadvantage of using adjuvants is the presence of some unfavorable reactions in birds that have received vaccinations. Another drawback of inactivated vaccines is the requirement for a withdrawal period before birds immunized with those vaccines can be processed. Thus, to ensure adequate protection of chickens to protect against ND, the poultry industry needs vaccines with improved margins of safety and efficacy [28].

RECOMBINANT VACCINE TECHNOLOGIES

Development of vaccines targeting Newcastle virus surface proteins

Recent developments in the field of recombinant DNA technology have made it possible to create DNA vaccines by cloning a gene encoding an immunogen or group of neutralizing epitopes into an expression plasmid. These DNA vaccines can then be used to protect against infectious diseases.When the cell containing the recombinant plasmid is expressed and then the expressed protein is purified. This protein can be administered to the animal along with a suitable adjuvant and cause a protective immune response [4]. In a study conducted by Shafaati et al., the full length of the virus surface proteins (F and HN) genome was expressed separately in eukaryotic and prokaryotic hosts and used as a vaccine in chicken; which was the result of using pure proteins in both expression systems of high antibody titers [29]. Haemagglutinin neuraminidase (HN) and fusion (F) proteins play an essential role in immunogenicity against the virus and are the virus' key virulence factors [30-33]. Two glycoproteins F and HN, play essential roles in the assembly and development of envelop viruses and determining tropism in the host and tissues [33,34]. The F protein induces fusion, while HN is responsible for binding [5,35,36]. HN glycoprotein has activities such as hemagglutination (HA), neuraminidase (NA) and stimulation of F protein activity [6]. The HN binding to the sialic acid receptor on the cell's surface initiates membrane fusion by the F protein [7]. HN and F glycoproteins play an essential role in virus-cell interaction and virulence. Therefore, they are suitable candidates for developing recombinant vaccines and can stimulate immune responses. These vaccines do not have the problems of traditional vaccines and can improve immunity. Also, the administration of these vaccines leads to the production of cytokines and, of course, creates an extensive immune response [37]. IFN-gamma is a Th1-related cytokine and is considered a useful indicator of

cellular immunity. IFN-gamma activates chicken macrophages and thereby enhances major histocompatibility complex I and II antigen expression on a variety of cell types and neutralizes viral replication [37]. According to several studies, the use of subunit vaccines in chickens has increased the adjuvant effect of IFN-gamma. There are reports about IFN-gamma's enhancing effect on humoral response in chickens despite the lack of IgG2a subtype, whose synthesis is enhanced by IFN-gamma in mammals, despite it being claimed that IFN-gamma gives the immune system a Th1 bias [29,37]. Therefore, experimental data show that the use of recombinant surface proteins of the virus increases immunity and can stimulate the cellular and humoral immune response through the secretion of cytokine factors such as interferon-gamma and interleukin 4 to protect against the Newcastle virus [29].

Development of DNA Vaccines

By cloning a gene encoding an immunogen or group of neutralizing epitopes into an expression plasmid, recombinant DNA technology has made the production of DNA vaccines possible [38,39]. By cloning a gene encoding an immunogen or group of neutralizing epitopes into an expression plasmid, recombinant DNA technology has made the production of DNA vaccines possible. Following the administration of the recombinant plasmid into the animal host, the cloned gene has the potential to be transcribed and then later translated into protein. This protein, once processed by the cells of the animal, has the potential to function as potent epitopes that are capable of eliciting a protective immune response. This potential is only activated after the animal's cells have processed the protein [38,39]. In the study of Firouzmendi et al., the full length of the NDV F gene was cloned in the pIRES expression plasmid and used as a DNA vaccine in chicken, which resulted in the observation of a high antibody titer. Furthermore, when a plasmid encoding both the F and HN proteins was used as a primer to vaccinate chickens and then boosted with an inactivated NDV vaccine, a superior protective antibody-mediated immunity was observed, indicating that these DNA vaccines can be used to improve the effectiveness of inactivated NDV vaccines [40]. Nanoparticles may, as well, improve the effectiveness of DNA vaccinations [41]. Nanoparticles made of dextran and spermines were utilized to encapsulate a DNA vaccine encoding NDV F and HN proteins. Although there was no significant difference between the HI antibodies titer acquired from patients vaccinated with the naked DNA vaccine and the HI antibody titer obtained when the nano encapsulated vaccine was delivered in-vivo, an improvement in HI antibody titer was seen [41]. Additionally, vaccination of SPF chickens with a DNA vaccine encapsulated in chitosan encodes the NDV F gene and results in increased mucosal and systemic humoral and cell-mediated responses [42]. Therefore, the DNA vaccine may be a secure alternative vaccination platform that may be used to combat the ND issues that are now prevalent. The capacity of these vaccines to produce CD4+ and CD8+ immunological responses and their high level of safety are two of their most important strengths. However, due to low immunogenicity and a high manufacturing cost, they cannot be suitable for mass administration. In addition, when administered without any delivery vehicle, the nuclease cells can quickly degrade the vaccine before they can reach their ultimate destination. Despite this, some limitations may be circumvented by utilizing adjuvants and a delivery vehicle [43,44].

Development of Viral Vector Vaccines

Utilizing recombinant viral vector vaccines is one of the most promising ways to battle infections that are significant to the veterinary industry. The vaccinia virus, the fowl pox virus, and the herpes virus of turkeys are the three most frequently utilized vectors in poultry [45]. Vaccinia viruses have a very high capacity for expressing foreign genes due to the large double-stranded DNA genomes that make up their genomes. They are highly immunogenic and can induce a robust inflammatory response from the innate immune system through the activation of TLRs. Using chicken embryo fibroblast cells; they can be readily mass-propagated. So, they are utilized to deliver genes against cancer and other disorders. Since the early 1990s, recombinant vaccinia virus expressing the F gene from NDV strain Italian has protected birds against virulent NDV. However, because of this vector's limitations, such as its sensitivity to preexisting immunity against the vector, its use in administering ND vaccines is quite restricted [46]. These vaccines are created by substituting the thymidine kinase gene with NDV F, HN, or F and HN. It has been shown that recombinant fowl pox vectored ND vaccines induce protective immunity against the virulent NDV challenge in chickens [47]. The key advantage of using this fowl pox vectored vaccine is that it does not result in the induction of postvaccinal respiratory reactions in hens that have already been immunized against fowl pox. Nevertheless, on the other hand, the presence of antibodies against the anti-fowl pox virus in chickens that have been vaccinated poses a substantial threat to the efficiency of this vector. Also, young birds should not be vaccinated with this vaccine because it can cause complications for them.

Interestingly, this deficiency may be remedied by using a recombinant herpes virus vector vaccine, which can be employed in embryos 18 days old and chicks one day old [48]. It can stay latent in the vaccinated chicken for a lengthy period, which is why it produces a cell-mediated and humoral immune response that is potent and long-lasting. Due to the fact that it replicates in a manner that is somewhat related to cells, the efficiency with which it delivers genes is not adversely affected by the presence of preexisting immunity directed against the backbone vector. This is because of how it replicates, which is in a manner that is connected with other cells [48]. Because it has all of these characteristics, the vector is an excellent choice for delivering NDV immunogens. It has been demonstrated that recombinant HVT that expresses the NDV F glycoprotein may protect chickens between 95 and 100 percent around four weeks after they have been vaccinated in vivo or subcutaneously [49]. Thus, immunization against virulent ND using HVT vectors remains a potential strategy for disease prevention in poultry.

Avian paramyxovirus-3 is another viral vector to deliver NDV vaccinations (APMV-3). This virus has been shown to reproduce very well in chickens, turkeys, and even cell culture [50]. In addition, the virus has been demonstrated to be significantly attenuated in chicken, with an ICPI value lower than that of most lentogenic NDV isolates [50]. Significantly, pre-existing

immunity to NDV does not affect its effectiveness as a vaccine vector. As a result, APMV-3 is a viable viral vector that may infect chickens without generating clinical illness. Kumar et al., recently developed recombinant APMV-3 vaccines with either NDV F or HN [51]. When these vaccines were administered to immunize 2-week-old chicken, NDV-specific cellular and humoral immune responses were detected, which protected against virulent NDV challenge, it is worth noting, however, that expressing NDV F or HN in the APMV-3 backbone causes the chimeric viruses to replicate slower than the wild type APMV-3. However, APMV-3 is still considered to be an effective and safe avirulent vaccination vector in chickens.

Development of Virus like Particles (VLP) vaccine

Viral-like particles, also known as VLPs, are assemblies of viral structural proteins that lack a genome and are instead made up of repeated surface structures. These VLPs function as pathogen-associated molecular patterns that are capable of provoking a robust immune response [52]. They are physically remarkably similar to viruses but are replication incompetent, giving them a very safe vaccination platform [53]. ND VLPs was first produced a few years ago when the M protein was expressed in conjunction with the NP and viral surface glycoproteins (F and HN) [54, 55]. Furthermore, co expression of the NDV F protein with the avian influenza M1 protein resulted in the production of VLPs in a baculovirus expression system [54]. In the preceding experiments, the VLPs not only effectively incorporated the surface glycoproteins, but the proteins' structural conformation and biological functions, such as F, and HN, were unaffected. Furthermore, immunizing mice or chickens with the VLPs elicited significant immune responses comparable to those elicited by an equal dose of inactivated ND vaccines [56]. NDVLPs are distinguished from other VLP systems by many distinguishing characteristics. To begin with, the protein ratio in the VLPs is quite close to that of the wild-type virus. Second, unlike other VLPs, which are released with efficiencies ranging from 10-50%, NDVLPs were demonstrated to be released from avian cells with an efficiency of 84%, making them the VLPs with the most significant known release efficiency [55]. Furthermore, utilizing proven viral purification techniques, the ND VLPs may be readily concentrated and purified to be free of any cell content contamination. Unfortunately, creating a high number of VLPs for a large-scale vaccination trial may be difficult, mainly if platforms other than baculovirus expression systems are employed. Furthermore, since VLPs cannot reproduce in vaccinated hosts, they must be supplied individually, in high amounts, and with adjuvants to induce a successful immune response [57]. Despite these obstacles, VLPs remain promising safe vaccination platforms that are gaining prominence in the management of NDV.

Nanoparticle Vaccines

The technology of the nano vaccine can encapsulate viral particles or effective antigens into nanoparticles that resemble viruses. To boost the vaccination's antigenicity and immunogenicity, the developed nanoparticle vaccine displays antigens on the surface of the particles or encloses antigens inside the particles themselves [58,59]. Generally speaking, there are two ways to boost the antigenicity of nanoparticle vaccinations. The first strategy is to display antigens on the surfaces of particles, such as nano-gold or silver, polymers, and other inorganic matter, or self-assembled ferritin, VLPs, chitosan, and other organic matter, to enhance immune cells' capacity to identify the antigen. Antigens are loaded onto the surfaces of nanoparticles or coupled with self-assembled proteins to create nanoparticles [60]. Kankio et al.'s study combined ferritin nanoparticles with boiling sequence to assemble double nanoparticle vaccines. Immunization results showed that the bivalently assembled nanoparticle vaccine could induce broad humoral immunity, with levels of neutralizing antibodies higher than the single-assembled nanoparticle vaccine [61]. Nanovaccines increase the level of CD4+ T cells, thus providing complete protection against the virus [62]. Overall, these results suggest that nanoparticles are an excellent way to improve the immunogenicity of small immunogenic proteins or small-molecule epitopes and to load more than one protein.

The second method is encapsulating single or multiple antigens in particles using liposomes. These particles are then transported into cells via the endocytosis mechanism of cells, using a double-layer structure of lipids as a carrier. This method improves the efficacy of cell processing and antigen presentation. For this purpose, the purified proteins of the virus were enclosed inside the liposome structure and then entered into the cell. After the liposome enters, protection against the virus is created [63,64]. For example, the use of surfactant nanoparticles as an adjuvant and their administration to animals can lead to the creation of comprehensive protection against the virus [65]. Because studies on the protective mechanism of vaccines have shown that lipid bilayer nanoparticles with a negative charge can effectively mediate endocytosis after binding with pulmonary surfactant protein in the alveoli, cGAMP could effectively activate the downstream STING pathway and stimulate the pulmonary epithelial cells to secrete cytokines, thereby increasing the immune response of the body to T/B cells that are produced by vaccines. This would result in an improved immune response [65]. Notably, it was found that CD8+ T cells played a significant part in the cross-immunoprotection that was induced by the vaccination. Therefore, for specific adjuvants or antigens that play a direct function in cells, lipid encapsulation may enable effective transmission into cells via the endocytosis process to boost the vaccine's immunological effect. This is done to improve the efficacy of the immune response [65].

Development of NDV Reverse Genetics-Based Vaccines

The major shortcoming of traditional genotype II-based NDV vaccines is their failure to prevent the shedding of heterologous pathogenic NDV even when clinical protection is obtained. Although several mechanisms may work in this postvaccination shedding of virulent NDV, genotype mismatch between the vaccine and challenge strains is considered a crucial component. According to experiments, virus shedding may be significantly decreased when birds are immunized with vaccines similar to the challenge strains. As a result, the current emphasis in the battle against ND is on developing so-called genotype-matched NDV vaccines. Reverse genetics, the recovery of a recombinant virus from its cloned cDNA, is the most recent technique for producing

genotype-matched live attenuated ND vaccines [66]. Since the F protein cleavage site is the major virulence determinant of NDV, whose amino acid composition clearly distinguishes virulent (polybasic) from avirulent (monobasic) strains, reverse genetics can be used to generate genotype-matched ND vaccine by modifying the cleavage site of the prevalent virulent NDV from polybasic to monobasic Using this method, Xiao et al. genetically modified the F cleavage site of a highly virulent NDV circulating in Indonesia [67]. They demonstrated that it completely lost virulence and induced a superb protective immunity that significantly reduced virus shedding after challenge with a highly virulent wild-type genotype VII NDV isolate. Other research employed a virulent NDV strain JS/5 as the foundation for developing a genotype-matched vaccination against genotype VII NDV. By changing the virus's F cleavage site from polybasic to monobasic, the rescued virus lost its virulent phenotype but retained its tropism in chicken embryonated eggs and induced protective immunity, resulting in a significant reduction in challenge virus shedding compared to the conventional LaSota vaccine. As a result, reverse genetics is a promising approach for rapidly developing stably attenuated genotype-matched vaccines against virulent NDV. Another critical use of this technique is the development of marker NDV vaccines capable of distinguishing vaccinated from diseased animals (DIVA). These DIVA vaccinations are an excellent tool for long-term ND elimination in poultry [68]. Another important use of this technology is the production of marker NDV vaccines capable of discriminating between vaccinated and sick animals (DIVA). These DIVA immunizations are a good strategy for ND eradication in poultry over the long run [68]. Because of the high cost of sequencing and other molecular biology services, creating vaccines based on reverse genetics is presently not a viable option. However, given the expanding number of companies specializing in gene synthesis, it is expected that the pricing of these vaccines will fall dramatically in the not-too-distant future. Given the unique properties of these vaccines, such as strong protective efficiency, genetic stability, and homogeneity with the most frequent NDV strains, it is fair to expect that they will become more widely accessible in a range of countries in the not-too-distant future.

ADJUVANTS

Adjuvants are essential in vaccine research because they raise antibody titters and breadth and improve T-cell immune responses, especially in subunit and inactivated vaccines. **Adjuvants** are antigens injected into the body to boost the body's immune response to antigens. Adjuvants' modes of action may include a mix of processes such as depot building, production of cytokines and chemokines, immune cell recruitment, augmentation of antigen absorption and presentation, and encouragement of antigen transport to draining lymph nodes [69]. Adjuvants include interferon pathway activators Poly I:C and cGAMP, cytokines including interferon and interleukin, and bacterial structural components flagellin and lipopolysaccharide (LPS) along with immunoregulatory oligonucleotide sCPG and synthetic chemical substances that play a role in immunological enhancement [70]. suitable adjuvants should be selected according to the vaccine strategy and type of desired immune response activation [71]. Assess the vaccine's capacity to protect against heterologous strains Choosing the correct adjuvant may significantly boost vaccination effectiveness.

CONCLUDING REMARKS

A good NDV vaccination is one that not only avoids clinical sickness but also decreases or eliminates viral shedding and raises the amount of the virulent virus necessary to produce infection [72]. Unfortunately, the presently available inactivated and lived attenuated NDV vaccines can only prevent clinical illness but not viral shedding, particularly after heterologous virus challenge [24]. Nonetheless, they have been the foundation of ND control for more than six decades because to their "disease prevention capacity" and low manufacturing costs. But, the hunt for better alternatives continues, leading to the development of innovative vaccination platforms based on recombinant DNA technology. VLPs and DNA vaccines are noted for their excellent safety among these new vaccines, however they are unfortunately not immunogenic. The existence of maternally generated antibodies against the vector has a major impact on the protective effectiveness of recombinant viral vectored NDV vaccinations. So far, the most promising vaccines against virulent NDV infection in poultry are reverse genetically produced recombinant genotype-matched live attenuated vaccine candidates. They are logically intended to meet the requirements of a great NDV vaccine because they particularly target the prevalent genotype in a certain location. These vaccinations are expected to outperform all presently available NDV vaccines in the near future.

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