DOI:10.22059/IJVM.2023.360044.1005406 Iranian Journal of Veterinary Medicine Original Article

Online ISSN: 2252-0554

Overview of Future Infectious Bronchitis Disease Vaccines Development Methods

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Running title: Infectious Bronchitis vaccine development

Abstract

It is well known that vaccines are major health controlling tools in human and animal practices. There are long lists of diseases that have been controlled or even eradicated by vaccination all

over the world. Classic viral vaccines usually are composed of whole virus either live or inactivated and have been producing for many years however they have not been so much successful, especially in some persistent infections, fast-evolving viruses, complex and compound antigens, and emerging agents. Novel vaccine development technologies such as DNA, protein or viral vector vaccines revolutionize vaccine development and opened a wide range of routes for study and research in vaccine research and production vision. Most of traditional vaccines or even newly developed vaccines are based on new technologies, especially in the field of human diseases where cost and complications in production can be easily ignored but in animal health especially for commercial poultry production cost of development and simplicity, mass application of large scale production have been limiting items. In recent years in line with technology improvement and emerging novel and variants viruses from Infectious Bronchitis viruses that has been important poultry pathogens for years, significance of producing or setting up to produce novel vaccines has been highlighted. Here in this review, we will introduce some studies on novel vaccine development techniques and investigate the results of those vaccines in the protection of chickens and clinical outcomes.

Key words: Infectious bronchitis, , novel techniques, Variant, viral vector vaccines

Introduction

Infectious Bronchitis disease is a contagious viral disease with a high economic impact on the poultry industry from the first detection of it in North Dakota, USA by Schalk and Hawn,1931 has been distributed to different continents all over the world(Hajijafari Anaraki et al. 2022). Respiratory, kidney, and reproductive system are mostly affected by the virus. Economic losses are the consequence of high morbidity of the virus, weight loss, the condemnation at slaughterhouses and decreased egg production, and inner and/or outer egg quality. Nowadays control strategies for the disease are a combination of good biosecurity and most importantly vast vaccination in broiler and breeder flocks(De Wit, Swart and Fabri 2010b, Cavanagh 2005)

Infectious bronchitis disease is caused by a single-stranded enveloped RNA virus belonging to *Igacovirus* subgenus of *gammacorona* virus genus and *coronaviridae* family which is limited to the avian population. Approximately IB virus genome has 27 to 32 kb in length, the largest avian RNA virus. It encodes 4structural proteins including spike(S), Matrix(M), nucleocapsid(N) and envelop(E), interspaced by 3 and 5 accessory genes and at least 15 nonstructural proteins that are encoded by the first two-thirds of the genome. Spike protein and nucleocapsid protein were proposed to be immunomodulatory proteins in the virus. The most important virus protein is the glycoprotein Spike projecting from the surface of the virus responsible for bird immune system reaction and neutralizing antibody production in the chicken. 3400 nucleotides are what make

IBV S-protein(Beheshtian et al. 2020). Furin or its related enzymes cleaves spike protein into S1 520 at amino-terminal and S2 625 amino acids at the carboxyl-terminal in the Golgi complex of the host cell. Typically, S1- glycoprotein plays a major role in host cell receptor binding and membrane fusion via cell-to-cell and virus-to-cell interactions, S2 contributes to the fusion mechanism (Koch et al., 1990). A complication is present when the protein is very variable and has at least 3 hypervariable regions which are located at (positions 24–61 and 132–149 and also at 291–398 amino-acid residues) and are continuously evolving into new variants different from classic strains and natural or vaccinal protection against them cannot confront variant viruses.(Lee, Hilt and Jackwood 2003) Nucleocapsid protein attaches to the genome and causes the helical capsid complex

Important proteins in immunomodulation following virus infection or vaccination

As previously said S1 is hyper-variable unfortunately sequence comparisons of variants with vaccines failed to identify the site of gene responsible for protection induction. The highly conformational nature of S1 has complicated the antigenic characterization of S1 and whether cell-mediated immune or humoral responses are the main mechanisms of protection. Researchers have tried to map antibody-inducing sites and CMI response factors in S1 protein(Cavanagh *et al*. 1992, Wei *et al*. 2014, Ignjatovic, Gould and Sapats 2006, Ignjatovic and Galli 1995, Ignjatovic and Galli 1994) and to date 5 antigenic sites which all were conformation dependent

and responsible for virus neutralizing antibodies production were mapped within the hyper-variable region(HVR) of S1 at positions 24–61 and 132–149 in addition to outside the hyper-variable region at 291–398(Kant *et al.* 1992, Kusters *et al.* 1989, Moore, Jackwood and Hilt 1997). Because of this nature monoclonal antibodies are the main tool used in antigenic epitope recognition on S1.

The S2 also induces antibodies cross react in ELISA and cell mediated responses but not protective responses.[6,14] the two antigenic sites in N terminus of the S2 between 546-577 amino acids were reported to be immunodominant and causing cross reactive antibodies(Kusters *et al*. 1989)

The Nucleocapsid protein induces cross-reactive ELISA antibodies and also cell mediated immunity(Ignjatovic and Galli 1994); however, it not involved in protection. The carboxy-terminal portions of N (Seah, Yu and Kwang 2000)had B-cell and a region between 78–94 amino acid residues was mapped which induces a T-cell response in addition to protection(Jayaram, Youn and Collisson 2005) . Nucleocapsid protein functionally binds with the genomic gRNA to form a helical ribonucleoprotein complex (RNPC), thus aiding transcription, replication, translation, and packaging of the viral genome during the replication process. (J. Jayaram, S. Youn, and E. W. Collisson, 2005)

Being the RNA virus is a risk factor for fast and continues evolutions. Two important phenomena about shaping the genome of coronaviruses are mutation and recombination(Domingo and Holland 1997). It is difficult to define how IBV genome evolved, three major theories have been hypothesized as follows: 1) the lack of proofreading in RNA polymerase may lead to mistakes in genome which in turn causes mutation (deletions, insertions or point mutations of nucleotide). 2) Presence of multiple serotypes infections or use of different live attenuated vaccines leads to recombination and favors emergence of variants (Kusters *et al.* 1989). Mutations, in the hyper-variable region of S1, affect its subpopulation and make new viruses of different pathogenicity as well as virulence, in this regard quasispecies viruses are generated with mixture of multiple genetic mutants of the same strains(Nix *et al*. 2000).The most common regions in IBV genome for recombination are encoding regions of *nsp* 2, 3, and 16, plus the glycoprotein spike (Thor *et al*. 2011). 3)Other suggested factors are the presence of immunosuppressive agents like Marek's disease, infectious bursal disease, Chicken Anemia Virus, which affect the evolutionary dynamic of the IBV(Bande *et al*. 2015)

Control and vaccination strategies

Several IBV strains and variants, classified by both serotype and genotype has been detected. Some of them has limited geographical distribution (Italy 02; variant2) and some are globally

distributed, including M41,QX,.. (Valastro *et al.* 2016)as it was mentioned, IBV is controlled currently by vaccination with both live-attenuated and inactivated vaccines. (Motamed and Bashashati 2022, Motamed, Beshashati and Fallah 2021). Vaccination programs in one geographical area differ from other sites because vaccines typically induce restricted cross protection between strains. (De Wit, Swart and Fabri 2010a)live-attenuated vaccines are administered to Young chicks through sprays or drinking water. In older ages, Breeders and/or layers may then be boosted with either live or inactivated vaccines(de Wit, Cook and van der Heijden 2011). Ease of application favors Live-attenuated vaccines; however, the risk of reversion to virulence and breakdown limit the application. Thereafter, the molecular mechanism of attenuation has not been discovered yet however it is revealed that it happens only with few consensus level mutations so over passaging of the vaccine in the field provides reversion to virulence possibility (Oade *et al*. 2019).

Live attenuated vaccines: Infectious bronchitis virus is a pathogen of economic and welfare concern for the poultry industry globally. Today most effective controlling tool is vaccination(Motamed and Bashashati 2022). Live-attenuated vaccines are generated by serial passage of a virulent isolate in embryonated chicken eggs at least for 80 consensus passages until attenuation is achieved. Mechanism of the attenuation is unknown.(Motamed 2022) This is the most wildly use type of vaccine with an old history of production in addition to high benefits

there is some disadvantages such as: Reversion to virulence: even by efforts for decreasing virulence after more than 80-100 passages severe outbreaks in the farm may occur; or tissue damage which results in secondary bacterial infections or pathological disorders especially in day-old chick; Interference by Maternal Derived Antibodies; co- circulation of the vaccine virus and field viruses may lead to recombination events and emergence of new variants. To reduce problems associated with vaccine reversion, researchers explore the options of using reverse genetic technology to create vaccine virus that is potentially a pathogenic in the host, but capable of replication and inducing immune response(Y. S. Zhou, Y. Zhang, H. N. Wang et al.2013).Various clones of the virus: it was shown that some vaccine strains such as Ark weren't able to induce enough protection because of multiple virus subpopulations in a vaccine seed so protection was not reach into the optimum and chicks were still susceptible to the disease(de Wit *et al*. 2011). The ability of some ArkDPI-derived vaccine viruses to persist and be selected in vaccinated chick may lead to high frequency of Ark field viruses (Gholami et al. 2018). So persistence of the vaccine virus in field offers required materials for recombination with other circulating viruses or mutation resulting to increased pathogenesis (Ndegwa, Toro and van Santen 2014).

Mutations and recombination are contributed in the emergence of new variants following the intensive use of live, often multiple vaccines. Therefore attempts have been made over recent

years to develop new generation vaccines, such as subunit vaccines to allow the use of a part of protective antigen but enabling vaccination against different genotypes in the same vaccine (Ignjatovic *et al.* 2006).

Inactivated virus vaccines: Inactivated vaccines are used in combination with live or alone. Usually are administered to layer and breeder flocks at 12-18weeks of age and they can not replicate so there is not any possibility to revert to virulence, however limitations are present for example difficult and impractical administration especially in large settings, shorter immune duration with just antibody response not T-cell protection so in most cases a prime boost with live attenuated vaccine is needed, also elimination of the whole or parts of the carcass in slaughters because of the reactions in injection site can happen. Slow release of antigen and long lasting immunity throughout the laying period are achieved by intramuscular or subcutaneous injection of vaccines that incorporate an **adjuvant** together with IBV that has been inactivated.

Researchers took many approaches to design new vaccines against a pathogenic microorganism. These methods are dictated by the nature of infection mechanism, pathogen as well as practical factors about the use of it(Motamed 2022).figure 1 shows multiple methods of vaccine development which has been used against various pathogens.

In light of covid-19 which is classified in coronaviridae family and has a fast evolving nature, researchers have considered new generation vaccine approaches for confronting viral diseases. It

teach us that not always we can trust to live or inactivated vaccines but also we need to think about new methods with more flexible in manipulation or substitution and shorter time to reach to a new vaccine with new emerging strains. Continuous fast pace of development of vaccines, quality controls, represents a substitutional achievement that was impossible previously, strongly demonstrating the utility of modern technology vaccines in new emerging diseases.

- Pathogen outbreaks Considering this criteria a live attenuated vaccine usually takes at least 3to5 years to success in getting the official administration and distribution permission however according to studies, an emerged variant may persist not more than 4-5years in an area so it could be expect that neither a licensed variant vaccine which is now a bit different with the predominant variant after 5years nor classic vaccines are able to fight effectively against field viruses. The same thing is expected over protectotype vaccination that takes a long time and costs to be studied against variants. However nowadays protectotypes are considered as most effective vaccination method to make an optimum immune statue in a flock(De witt et al., 2011). Over the last years, lots of reports declares that 793/B-like and Mass-like-based vaccines combination seems to be the widest protection against heterologous (Awad *et al*. 2015b, Awad *et al*. 2015a, Habibi *et al*. 2017) strains, such as Variant 2 and QX (Franzo *et al*. 2017, Lisowska *et al*. 2017) and is commonly adopted in the most regions around the world(Jordan 2017),

industry have to develop rationally live vaccines. Past research has evaluated vaccines including the spike glycoprotein as DNA or by viral vectors (Song *et al*. 1998, Yan *et al*. 2016, Toro *et al*. 2014, Zhao *et al*. 2017a, Shirvani *et al*. 2018, Ellis *et al*. 2018). Spike is the main attachment factor and virus entry. And is as a main target in development of vaccines since the studies showed that it induces virus-neutralizing antibodies (Koch *et al.* 1990, Kant *et al*. 1992).Vaccines currently uses against SARS-CoV-2 aiming to induce neutralizing antibodies follow this method to deliver spike protein (Folegatti *et al.* 2020, Jackson, Roberts and Graham 2020). The vaccine offers a good degree of protection after multiple doses they can not stimulate complete protection in mild to moderate clinical disease or infection and replication of the SARS-CoV-2. (Ellis *et al.* 2018, De Wit *et al.* 2010a)If the industry is going to be ready to response the newly emerged viruses will have to develop and set up alternative techniques insuring efficient reaction in a right and fast manner

mRNA vaccines: mRNA vaccines have attracted considerable attention in recent years because they have the potential to accelerate vaccine development, improve safety and efficacy, and combat diseases which are not able to be prevented by other ways. mRNA is non-infectious, non-integrated and degraded by normal cellular processes shortly after injection, reducing the risk of toxicity and long-term side effects._Intracellular expression of antigen by mRNA may

result in strong T-cell responses typically seen with viral vector-based vaccines or replication-defective virus-based vaccines*(Gebre et al*. 2022). However, mRNA vaccines have the advantage that they do not induce vector-specific immunity and do not counteract pre-existing or newly developed vector immunity that can interfere with subsequent vaccinations *(Gebre et al*. 2022). In Late 2020 Moderna and Pfizers company lunched their new mRNA vaccine against covid-19.mRNA gene delivery system has numerous applications including cancer, vaccines and disease. Concept of this method was initially developed in 1990. mRNA is a delivery system which encodes antigen of a specific pathogen in host. Infected cells translate it and the antigen is recognized by the immune system. In order to increasing stability and ease of entrance usually mRNA is typically delivered in a lipid nanoparticle (LNP) without immune response to it allowing multiple use of LNP-mRNA. The simple and fast nature of assembling new sequences in mRNA systems in vaccine formula will make mRNA vaccines as pioneers in near future (Folegatti *et al*. 2020).

Two main limiting reasons that hindered the researching of novel IBV vaccines are considered. The first factor is cost. Poultry plants have a very small profit margin, so any extra cost seems to be significant. Classic live-attenuated and inactivated vaccines have a few costs per dose. Other standard recombinant vaccines are commonly used against poultry pathogens other than IBV even though they are expensive are still frequently used as a result of their ease of application

and good efficaciousness. If a new IBV vaccine can match those specifications, its cost would not be so impediment. The second limiting reason is method of application. Each vaccine could be applied in mass will be compatible for large scale

Vaccine development in viral vectors: The recombinant viral-vectored vaccines hold promises for commercial poultry industry. Adenovirus vector vaccines have also evolved to become promising vaccine platforms. Optimal adenovirus vaccine vector design involves selection of uncommon vector serotypes, and structural components of Ad vectors can be harnessed and modified to enhance tropism, efficient delivery, and optimal antigen expression. Ad vectors can be rapidly developed and produced on a commercial scale, and the potency and stability characteristics of the vector support single-shot vaccines that do not require cryopreservation. In spite that This technology does have limitations that include issue of preexisting immunity or maternally derived immunity that interferes with the live vector itself and reduces the uptake of the antigen by the antigen presenting cells and consequently the transgene expression as well as specific immune response.

The development of promoter vectors against multiple pathogens shows their flexibility and promise for current and future vaccine applications.

Vectors may be replicating or non replicatings viruses As yet, Fowl pox virus, Marek's disease virus, turkeys Herpes virus, Newcastle disease virus, and members of Retroviridae family have been most extensively used as expression vectors. Genes of antigenic proteins of Newcastle virus, infectious bursal disease virus (IBDV)(Darteil *et al*. 1995) , and (ILTV)(Vagnozzi *et al*. 2012) had been inserted into these systems and induced the appropriate immune reaction in chickens. someone attempted to insert S1 in these viruses(Toro *et al*. 2014) they all had different immune response to homologues challenge but do not meet the requirements of vaccination against IBV Specially mass application that is not a feasible work in a commercial setting. Adenoviral vectors which were widely used in covid-19 vaccine production and some of them reach into global consumption admissions (Mendonca *et al*. 2021) have efficient transduction in wide various cell types so can easily express inserted antigens accompanying by economic advantages of mass production of ad-vectored viruses by cell lines in serum free media and large bioreactors, simple chromatography separation techniques. The potency of human Ad-vectored vaccines for immunizing chickens was reported by stimulating immune responses in chickens following intramuscular injection(Zeshan *et al*. 2010) those ***adenoviruses were non-replicating,*** non-causing damages in tissues as well as tropism to different dividing and non-dividing cells which allows sustained antigen release then effective immune response and reduced problems associated with reversion to virulence or mutation. However lake of posttranslational modifications such as protein folding and glycosylation can alter epitope arrangement and affect

immunogenicity or vaccine efficacy. A recombinant adenovirus vaccine containing infectious bronchitis S1-glycoprotein showed a prominent antibody response and conferred 90–100% protection. Zeshan *et al*., 2010 had a study on developing human adenovirus- vector IB vaccine for using in ovo , they constructed a recombinant adenovirus expressing the S1 gene of nephropathogenic IBV (rAd-S1) and reported that in-ovo vaccination and then an intramuscular inoculation by rAd-S1 led to dramatic augmentation of cellular and humoral responses against homologous challenge and lesion and clinical signs were decreased. In a study, expressing N gene of IBV by a replication-defective human adenovirus was evaluated in SPF chickens by immune response and protective efficiency against challenge. Despite the recognized immunogenic, the N protein had not had any proliferative response to IBV in vaccinated chickens and no significant protection. Some researchers designed oral adenovirus vector vaccines to avoid neutralization of vectors by maternally derived or preexisting antibodies other advantages are ease of application and lower handling associated stress but they had o T-cell responses so complementary studies are needed to stimulate CMI.

A modified baculovirus BacMam virus which under the control of the mammalian promoter mediates expression is an emerged versatile and safe vector in the development of vaccines. In a study, an improved BacMam virus expressing S1 of IBV was generated. S1 glycoprotein was displayed on the baculovirus envelope that expressed in mammalian cells. The vaccine BV-Dual-

S1 elicited significant humoral and cell-mediated immunity in specific pathogen-free chickens. Protection rates of immunized chickens with BV-Dual-S1 reach to 83% comparing to 89% inactivated vaccine following challenge with IBV-M41(Zhang *et al*. 2014). Other vectors may replicate in bird body and have their specific effects: Shi *et al*. in 2011 showed a recombinant fowl pox virus vaccine expressing S1-IBVgene and chicken INF-γ gene [rFPV-IFNγS1] enhances humoral and cell-mediated immunity and protect birds against heterologous and homologous IBV challenge(Shi *et al*. 2011). In another study expression of -S1-gene with IL-18 in a fowl pox virus vector caused a significant increase in humoral immunity, CD4+, and CD8+ activity (Chen *et al*. 2017). Metapnemoviruses, Newcastle disease virus and duck enteritis viruses are other viral backbones for inserting S1 or S2 especially metapnemoviruses which can be massively used and replicate in respiratory system and may stimulate the head associated lymphoid tissue to a higher extent and producing high immune response.(Falchieri *et al*. 2013, Li *et al*. 2016, Toro *et al*. 2014, Zhao *et al.* 2017b)

Subunit and Peptide-Based Vaccines

Peptide subunit vaccines contain an antigenic portion of the pathogenwhich are amino acid short segments presented to the immune system. Often these peptides are synthetic and represent the immunostimulating antigen. S1- and N-gene epitopes has been used for making neutralizing antibodies as well as CTL, respectively. Some of these vaccines showed promising results in

protection challenges (Wei *et al*. 2014, Yang *et al*. 2009). A novel chimeric infectious bronchitis-
285 Newcastle disease (IB-ND) virus-like particles (VLPs) vaccine constructed from the, rF, rS and M IBV protein was designated. It stimulated humoral and cell mediated immunity and caused 100 protection against clinical signs and reduced virus shedding (Wu *et al*. 2019)

Immune response following administration of these vaccines must be enhanced by combining with factors such as cytokines, adjuvants. The second limitation is method of administration
290 which is commonly by injection that is not favored in large rearing settings and they are usually cost much higher than other methods of production. They may be expressed in E. coli, yeast, insect etc. (heterologous expression system). Today the majority of under investigation vaccines are based on purified subunit antigens or recombinant proteins
- Hepatitis B Virus (HBV) vaccine is one of the best recombinant protein vaccines currently
295 produced .A study has reported that synthetic peptide epitopes from S20 to S255 well reacted with polyclonal antibodies, demonstrating the potential use for poly-topic IB vaccines(Wang *et al*. 1995). some have focused for developing multiepitope peptide vaccines against a wide variety of IBV genotypes: Yang *et al.*(2009) have demonstrated an IBV multiple epitopic vaccine based on S1- and N-protein genes can cause remarkable cell-mediated and humoral
300 immune responses(Yang *et al*. 2009). The *Lactococcus lactis* bacterial system could deliver

peptide IBV vaccines orally and with mucosal immune response induction (Cao *et al*. 2012, Cao *et al*. 2013)

Plasmid DNA Vaccines

DNA vaccine does not involve a live vector and use plasmids to express the DNA of immunogenic portion of pathogen genome. No licensed DNA vaccine for poultry use is available. Mostly because of the route of administration as injection it can be overcome by in-ovo administration or oral route. A nanoparticle delivery system may protect the DNA from degradation by enzymes and enhancing mucosal responses. As DNA vaccines can be administrated in the presence of MDAs, they could poultry overcome challenges related to vaccination in early ages. Other advantages are ability to induce humoral and cell mediated immunity, possible expression of multiple epitopes, safety and lower cost production especially comparing with peptide vaccine, short production time is a valuable tool for confronting emergencies. They can be used in combination with adjuvants and cytokines(zuo et al.2021, ;Yang et al.2009),.

A DNA vaccine Based on Spike with Consensus Nucleotide Sequence was designed and developed by Zuo *et al*., 2021 (Zuo *et al*. 2021). After two time intramuscular injection of the

vaccine 85% protection was observed against challenge with M41 Infectious Bronchitis virus. The vaccine could stimulate both humoral and cell mediated immunity (Zuo *et al*. 2021).

A designated S1- DNA vaccine pDKArkS1-DP, based on Arkansas IBV was developed. *In ovo* Vaccination, followed by a live attenuated IB vaccine at 2-week later, caused high immune response and 100% protection against challenge. Whenever a cationic liposome carrier used, efficacy and protection of the DNA vaccine were tending to improve. Alternatives to improve the efficacy of that kind of vaccine is combination with specific adjuvants such as cytokines whether they are mono or poly-valent DNA vaccines encoding nucleocapsid or S1 or even membrane protein. Co-administration of a DNA vaccine encoding nucleocapsid or S-glycoprotein genes with IL-2 Chicken (GM-CSF); a liposome-encapsulated multiepitope DNA vaccine fromS1, S2, and N regions in intramuscular injection resulted in increased numbers of CD4+and CD8+cells, and a 80% protective immune response in immunized birds(Leyson *et al*. 2017, Jordan 2017)

Reverse Genetic Vaccines

A reverse genetic vaccine is a new technology for manipulating viral genes and production of a new virus from a classic one. For example a recombinant, BeauR-IBV vaccine was constructed by replacing the antigenic sites of S1 of Beau-IBV strain with

S1- from a pathogenic strain M41 and 4/91 strains(Armesto *et al*. 2011, Hodgson *et al*. 2004). Changes lead to protective responses without making the manipulated BeauR strain to be pathogenic. Reversion to virulence which is a weak point for live attenuated vaccines is abrogated and also it can be used in the presence of maternal immunity. Whether this vaccine generation is going to increase or reduce the mutation rate or selection pressure is not clearly understood(Zhou et al. 2013).

Previous researches have focused on developing an attenuated recombinant IBV (rIBV), a molecular clone of the highly attenuated Beaudette-CK strain. For S1 expressing of other heterologous genotypes. The rIBV as a vaccine backbone mimics natural infection, so can induce both local and systemic immune responses. Beau-R with S gene of 4/91 strain could achieve to 65% protection after homologue challenge (Keep *et al.* 2020, Keep *et al*. 2022b). The replication of rIBV Beau-R in host is highly limited and in cell culture is completely inhibited at natural chicken body temperature 41°C. There was a hypothesis that temperature sensitivity of the recombinant backbone is a desired character for production of live attenuated vaccines that are temperature sensitive and so restricted to cause virulent infection in chicken but having limited replication to induce immunity. Temperature sensitivity was not a new issue in virology and has been used for developing

some viral vaccines such as influenza.(Keep *et al*. 2022a, Martinez-Sobrido, Peersen and Nogales 2018) .

Post translational modifications in different expression system including yeast, bacteria, plant or baculovirus influences the outcome of the vaccine production. For example: An attempt with IBV vaccine on Vaccinia, could not produce enough antigen and then enough antibody responses which is probably because of poor replication of the designed vaccine in avian cells and maybe immune response of the mice to the vaccine that hindered the antigen presenting for IBV gene(Bande et al., 2015). Another attempt for developing a baculovirus based vaccine to produce the Korean KM91 strain S1-glycoprotein had just 50% immunity because of post translation modifications (Jung et al., 2022). The potato was choosed to express S1 of IBV by using cauliflower mosaic virus (35S) promotor gene (Zhou et al., 2004). The vaccine had promising results suggesting the method for food based IB vaccines. Application of Infectious bronchitis Beaudete virus as a background was a technology for new generation of vaccine was a successful method because of mimicking the virus replication cycle in host without virulence but providing a possibility for production of vaccine in cell culture especially in the Vero cell that is a licensed cell media to produce viral vaccines (keep et al., 20922b). The delivery method and route of administration in vaccination can affect immune

responses and kind of the MHC which responses. Live vaccines are administrated through water or spray. Inactivated vaccines are used via injection. The real is that when you can use a vaccine in poultry as mass application it is very useful and easy to use. Some designed vaccines were developed to be administrated via feed which is a very applicable route(Jordan 2017). A DNA vaccine expressing S1- protein has been used orally with an attenuated *Salmonella enterica* strain(Jiao et al., 2011). Mucosal immune responses were increased following oral or intranasal immunization *Lactococcus lactis* bacteria as a system to deliver vaccine, had effective immune response in mucosa (Peng et al., 2013).

Conclusion

The vision is that in the future an IBV vaccine must be used for broad protection against variable genotypes or induce strong protection in response to challenges with emerging viruses. Novel designed vaccines need to have the ability to escape maternal antibody effects, be easy to use, and fast to develop with cost-effectiveness considering fast and continuous evolution of the virus and the emergence of new variants that might not have cross-protection with the classic vaccines immunity (Motamed and Bashashati 2022, Motamed *et al*. 2021). In light of the novel technology, it is possible to develop vaccines that can reduce reversion to

virulence although inactivation by maternal antibodies especially following viral vector vaccine as well as live attenuated vaccines remains a major concern.

The recombinant vaccines such as plasmid vaccines and multi epitopic vaccines have the ability to deliver multiple antigens therefore inducing both humoral and cell-mediated immunity and also can be manipulated and be inserted by new genotypes in an established mechanism. Oral or occulonasal rout for administration by developing these vaccines in novel delivery techniques as nanoparticles or virus like particles (VLPs) are preferences of them. either DNA or protein vaccines are developed in now and future it should be keep in mind that the protection is not 100% and boosting with other kind of vaccines must be contributed. These novel vaccines may be used orally or mucosal but gaining best protection needs repetition of vaccination.

Conflict of interest

Hereby author declares that there is no conflict of interest.

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مروری آینده نگر بر روش های تولید واکسن علیه بیماری برونشیت عفونی

نجمه معتمد

بخش تحقیق و تولید واکسن های طیور، موسسه تحقیقات واکسن و سرم سازی، سازمان تحقیقات، آموزش و ترویج کشاورزی، کرج ایران

به خوبی شناخته شده است که واکسن ها ابزار اصلی کنترل سلامت در جوامع انسانی و دامی هستند. فهرست طولانی‌ای از بیماری‌هایی که در سراسر جهان با واکسیناسیون کنترل شده یا حتی ریشه‌کن شده‌اند وجود دارد. واکسن‌های ویروسی کلاسیک معمولاً از ویروس کامل زنده یا غیرفعال تشکیل شده‌اند و سال‌هاست که تولید می‌شوند، اما متاسفانه در برخی موارد به‌ویژه در عفونت‌های پایدار، ویروس‌های با رشد سریع، آنتی‌ژن‌های دارای ساختار پیچیده و کمپلکس و عوامل نوظهور چندان موفق نبوده‌اند. فن‌آوری‌های جدید توسعه واکسن مانند واکسن‌هایDNA ، پروتئین ساب یونیت یا واکسن‌های ناقل ویروسی، توسعه واکسن را متحول کردند و طیف وسیعی از راهها را برای مطالعه و تحقیق در تحقیقات تولید واکسن به روی دانشمندان باز نموده اند. بیشتر واکسن‌های سنتی یا حتی واکسن‌های جدید ساخته شده مبتنی بر فناوری‌های جدید هستند، به‌ویژه در زمینه بیماری‌های انسانی که می‌توان هزینه و خسارات تولید را به راحتی نادیده گرفت، اما در سلامت دامها به ویژه برای تولید تجاری طیور هزینه توسعه و سادگی کاربرد و روش استفاده آسان در سطح گله و امکان تولید در مقیاسهای بزرگ اقلام محدود کننده

محسوب می شده است. در سال‌های اخیر در راستای پیشرفت فناوری و ظهور ویروس‌های جدید و واریانتهای جدید از ویروس‌های برونشیت عفونی که سال‌ها پاتوژن مهم طیور بوده، اهمیت تولید، تحقیق یا توسعه تکنیک های جدید تولید واکسن بیش از پیش برجسته شده است. در این بررسی، ما برخی از مطالعات در مورد تکنیک‌های جدید ساخت واکسن برونشیت عفونی را معرفی می‌کنیم و نتایج آن واکسن‌ها را در حفاظت از جوجه‌ها و بروز علائم بالینی بیان می نماییم.

واژگان کلیدی: واکسن های mRNA، تکنیک های جدید، واریانت، وکتورهای ویروسی واکسن