CHAPTER 28

VACCINATION AND IMMUNOLOGY IN LARGE ANIMALS

Qaiser Akram*[1], Muhammad Younus[1], Muhammad Asif Idrees[1], Muhammad Ahsan Naeem[2], Waqas Ahmad[3] and Qamar Un Nissa[4]

[1]Department of Pathobiology, University College of Veterinary and Animal Sciences, Narowal, 51600, Pakistan
[2]Department of Basic Sciences, University College of Veterinary and Animal Sciences, Narowal, 51600, Pakistan
[3]Department of Clinical Sciences, University College of Veterinary and Animal Sciences, Narowal, 51600, Pakistan
[4]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, 54000, Pakistan
*Corresponding author: Qaiser.akram@uvas.edu.pk

INTRODUCTION

Pathogenic microbes pour major threat to both humans and animals while the protection against these pathogens is essential for their survival (Balloux and van Dorp 2017). Environmental opportunistic microbescan induce serious infections in them if no external protection is provided (Lanzas et al. 2020). However, to counter these diseases, both humans and animals are equipped with several defense mechanisms which offer instant protection against the assault by these pathogens (Hart 2011).

Innate immunity, a non-specific type, is the first resistance against any infection and its response is always prompt, dependent on macrophages and their secreted proteins *i.e.* cytokines that identify the conserved features of pathogens (Carrillo et al. 2017). It can be explained in better way when right after the birth, the gastrointestinal tract, skin and mucous membranes are inhabited by normal microbial flora in a symbiotic way (Belkaid and Hand 2014). These microorganisms are tolerated in these body parts and in this way provide a natural antibacterial defense mechanism by preventing the harmful microbial invasion (Belkaid and Hand 2014). In contrary, adaptive immunity, a specific type, is the most sophisticated form which is trained in learning any previous contact(s) with the pathogens and based on that it thrashes them on their re-infection (Deets and Vance 2021). So in other words, the immune system's learning from the previous exposureand responding the pathogen in a calculated way is known as 'effector memory' and its memorizing the contact for future exposure is known as 'central memory' (Deets and Vance 2021). Among the immune cells, lymphocytes harbor the immunological memory which is produced during delivering a response against infectious agent (Nicholson 2016). Moreover, the immunological responses are not merely restricted to infectious agents but also against harmless pollens and some therapeutic drugs and hence, induce allergic reaction (Marshall et al. 2018). Immune system is also responsible for immunological surveillance (scrutiny) by which it can detectthe neoplastic tissue changes and have potential to eliminate it (Ribatti 2017). Vaccine is the best external source that primes and boosts the adaptive immunity in host (Laupèze et al. 2021). The Fig. 1 below describes various features of an ideal vaccine. Any vaccine which is available currently or in future will be more reliable whose characters will be close to the features of ideal vaccine (Kamel et al. 2019).

History of Vaccines

In 1798, Edward Jenner published- *An Inquiry into the Causes and Effects of the VariolaeVaccinae*-in a booklet, a disease discovered in some of the western counties of England, particularly Gloucestershire, known by the name of Cow Pox (Jenner 1800). Strictly speaking, vaccination was not discovered by Jenner, instead, he was the first one who scientifically proved that immunization from disease can be overcome by targeted interference (Boylston 2013). It was actually the'Benjamin Jesty (1737–1816)' a dairy farmerfrom England who was vaccinated against smallpox after so many exposures (Boylston 2013).

The concept and the term *vaccination* was coined into the light spot about hundred years ago by Louis Pasteur (Gomes 2021). Pasteur inoculated in chickens with "stale" cultures of *Pasteurella multocida,* in 1878 (Guzman and Montoya 2018). At first, chickens developed sickness and later recovered so he re-inoculated them with *fresh* bacterial culture. This time, the chickens received the "stale" culture were recovered whereas, those that were not exposed to the stale culture were died. Pasteur's studies were in quite concordance with Jenner's published studies on smallpox and then in the honor of Jenner, he coined the term "vaccine" (Guzman and Montoya 2018).

William Smith Greenfield in the Great Britain and Pasteur along with Henri Thullier, Charles Chamberl as well as Pierre Paul Émile Roux in France had started developing vaccine against anthrax bacteria *i.e. Bacillus anthracis* in cow and sheep, in the early 1880s (Sternbach 2003). Following 10 years, the German analysts Friedrich Loffler and Paul Frosch identified the first filterable infectious agent of mammals *i.e.* Foot and Mouth Disease Virus (FMDV) (Wang and Liu 2020). Later, a heat-inactivated vaccine was developed which provided long-term immunity against this virus.

Immune sera were great discovery in the field of biological science and horses have a great contribution in understanding the basic immunological tools behind it (Kaufmann 2019). In a chain of experiments, Emile Roux and Alexandre Yersin, trailed by Emil von Behring (Nobel Prize winner in Medicine, 1901) and Shibasaburo Kitasato immunized horses for immune sera production against the diphtheria toxin (Cavaillon 2018). One morebreakthrough in the development of vaccine was the Marek's disease (MD) vaccine generation in 1970's. MD was the herpes-virus induced cancerous disease in chickens (Reddy et al. 2017).

How to cite this chapter: Akram Q, YounusM, Idrees MA, Naeem MA, Ahmad W and Nissa QU, 2022. Vaccination and immunology in large animals. In: Abbas RZ, Khan A, Liu P and Saleemi MK (eds), Animal Health Perspectives, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 2, pp: 223-229. https://doi.org/10.47278/book.ahp/2022.63

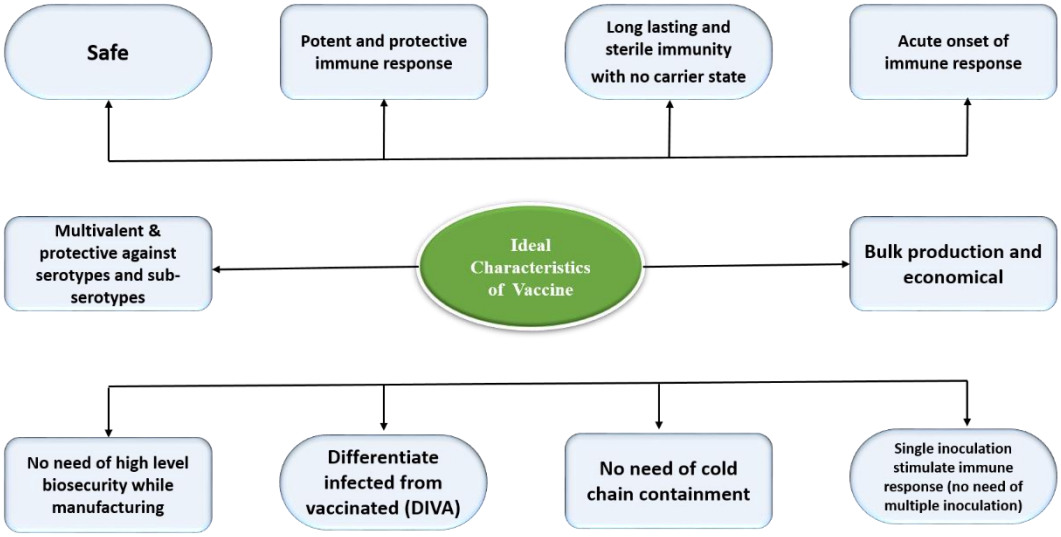


Fig. 1: Characteristic features of an ideal vaccine regarding its production, provision of protection and containment (Kamel et al. 2019).

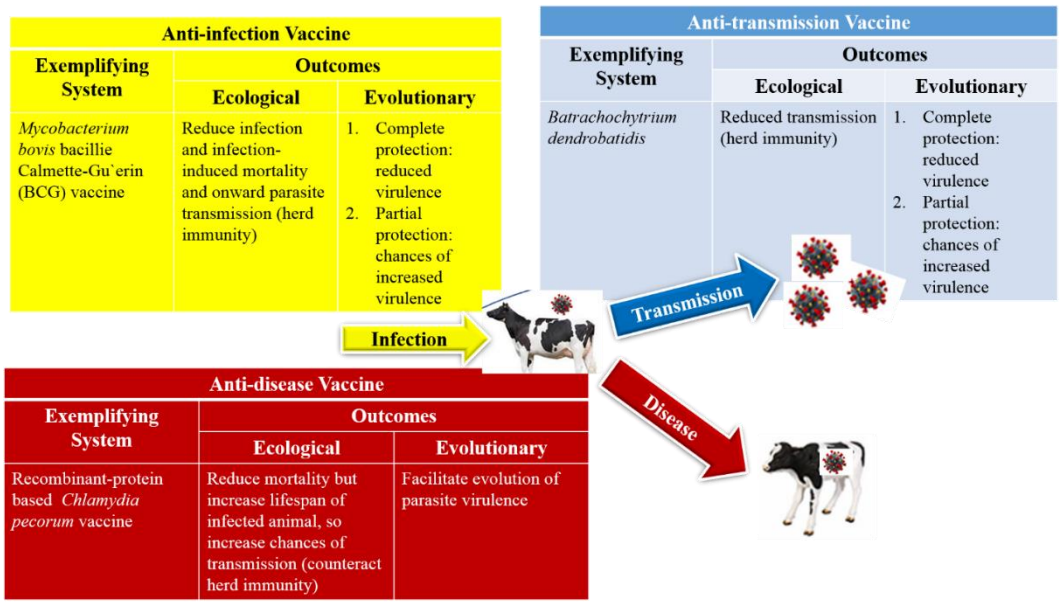


Fig. 2: Ecological and Evolutionary Outcomes of the Exemplifying System (Barnett and Civitello 2020): Categories of defective vaccines, such as anti-infective, anti-transmission and anti-disease lead to the production of phenotypic resistance strains in the vaccine species and ultimately impact the evolution of pathogen and epidemiology.

In between 1960 and 70, with the advent of various techniques in molecular biology, the establishment of recombinant vaccines' competition was at the top (Plotkin 2014). In 1981, a polypeptide vaccine synthesized biologically was considered the first published report (Skwarczynski and Toth 2016). FMD virus VP3 structural protein was cloned in prokaryotic plasmid and then transformed into *E. coli* protein expression strain. Six cattle and 2 swine were vaccinated with this purified protein. Neutralizing antibodies were produced and protected them against FMD virus challenge. This strategy helped in understanding the utilization of farm animals in the vaccine development (Guo et al. 2013). Molecular dynamic ranking was used by Kotecha and colleagues to calculatestability of FMD virus capsid. These calculations were then confirmed by X-ray crystallography (XRD) which showed improvement in *in vivo* (Vaccinating cattle) immunogenicity (Li et al. 2021). The Fig. 2 demonstrated below represents the impacts of flawed vaccines in pathogen's resistant phenotype emergence, transmission and epidemiology (Barnett and Civitello 2020).

Conventional Veterinary Vaccines

Historically, approach of empirical trial-and-error was used for veterinary vaccines development and its immunity mimics with immunity produced by natural infection (Doolan et al., 2014). Protection against a broad range of viral and bacterial pathogens was induced by traditional inactivated or killed vaccines. Inactivated, killed, toxoid and live-attenuated are the main conventional vaccines which are licensed to use. For the animal and public health improvement, these vaccines and their extensive use has contributed a lot. A disadvantage of conventional vaccine was its cost ineffective production and multiple booster doses for getting optimum immunity (Meeusen et al. 2007; Delany et al. 2014).

Moreover, *in vitro* cultured pathogen was used to induce whole-organism based vaccination. However, this strategy is suitable for pathogens with low immunogenic variability and not for those having high immunogenic variability. As highly immunogenic variability equips the pathogens for hijacking the

Table 1: Livestock vaccination schedule

Month	Large Animals especially Bovines	
	Up to 1 year	Adult
January	FMDV & ETV	HSV
February	-	FMDV & Anthrax
March	-	Theileria
April	-	BQ
May	FMDV & ETV	-
June	HSV	HSV
July	-	-
August	FMDV & ETV	HSV
September	-	FMDV & Anthrax
October	-	RP
November	-	-
December	HSV	HSV

*FMDV= Foot and Mouth Disease Virus, ETV= Enterotoxaemia, HSV= Bovine herpes virus: BQ= Black Quarter, RP= Rinder Pest

immune response (Doolan et al. 2014). Another lacking point in traditional vaccine is that its scheme to work is like immunity induced by natural infection. This is not as appropriate for many pathogens as this type of vaccine provides only suboptimal protection and with so many adverse effects of stimulated inflammatory reactions (Zepp 2010). For examples, a pathogen causing chronic disease can co-sustain with host for a longer period of time despite the presence of host immunity (Doolan et al. 2014).

Table 1 below shows vaccination schedule that is commonly followed throughout the year in large animal practice in the India and Pakistan (Singh and Borkotoky 2018).

Live-Attenuated Veterinary Vaccines

The passage of pathogen in an atypical host or cell weakens it and in this way, live attenuated vaccines are produced. This vaccine is then inoculated in its actual host expecting that the pathogen has lost its pathogenicity but retained its immunogenicity (Meeusen et al. 2007). However, practically such vaccines are not safe for so many pathogens and many get activated and induce the disease. Moreover, they cause many side effects, local inflammatory reactions and autoimmune disorders consequently may get back their virulence. Possible reasons could be their improper culture, passage and refrigerated preservation (Babiuk et al. 2003; Meeusen et al. 2007). Their benefit is that they don't need any adjuvant that can enhance their immunogenic potential as they retain their infecting and replicating ability in host cells.

The strategy associated with developing vaccines is quite intricate as it uses live cells and hence, difficult to optimize. These live vaccinations are hard to design due to the multifaceted macromolecular nature of pathogens. Live-attenuated vaccines are comparatively less hard to make than inactivated vaccines as they don't need adjuvant in their formulation with least downstream handling (van Gelder and Makoschey 2012). Attenuated vaccines were used by considering them as older technique; now-a-days, specified mutagenesis is employed to produce vaccine virus strains.

Immunologically characterized and safe vaccines are recombinant ones prepared by reverse vaccinology technique (Delany et al. 2014). The desired regions can be inserted or deleted (Indels) by using molecular techniques. Therefore, this approach can overcome the drawbacks of live-attenuated vaccines, representing a doable strategy.

Inactivated Veterinary Vaccines

Currently, killed viral strain or bacterial serotype are used and adjuvant them in aluminum hydroxide or oil to formulate inactivated vaccines (Meeusen et al. 2007). These are cost effective in production and stable in environmental conditions. Vaccine pathogens are normally cultured in bioreactors or roller bottles type cell culture and then killed/inactivated by chemical or physical treatments which can denature their proteins and damage their nucleic acids. As they lost their infective and replicative ability, so adjuvant(s) is added for improving their immunogenic potential (van Gelder and Makoschey 2012). Their safety profile is quite improved; however, their ability to provide long-term immunity is compromised (Cho et al. 2002). Many vaccines are unable to handle with the prevalent pathogenic strain of virus or bacteria, thus circulating field strain sample collection, pathogen isolation and culturing for vaccine production are necessary to combat new outbreaks (Meeusen et al. 2007).

Toxoids

These vaccines have bacterial toxins which are responsible for inducing disease. So, commercially formed inactivated/killed toxins (toxoids) are pooled with traditional adjuvants. The drawbacks of producing toxoids are; the amount produced of the toxin *in vitro* is erratic and for some toxins high level biosafety measures are required (Arimitsu et al. 2004). Recombinant toxoids can overcome such restrictions, by producing them in ample quantity with low reactive potential. For example, the production of recombinant *E. coli* toxins takes only 2–3 days using simple growth media. Formaldehyde is used for inactivation and requires least biosafety precautions because of the removal of the toxic domain of the protein (Moreira et al. 2016).

Conventional Subunit Vaccines

A specific part (genetic material or protein) of pathogen that can stimulate host's immune system is present in subunit vaccines (SV). If long chain carbohydrates which are present in the bacterial capsule are used as SV, then these are known as polysaccharide vaccines. However, these SVs are incapable to recruit T helper cells as this kind of immunity can only be recruited by some antigenic protein part which provides a protective immune response. Protein-polysaccharide-conjugate (covalently linked to a carrier protein) technology has been used to overcome the disadvantages of inactivated toxin (toxoid), such as; tetanus or diphtheria toxoids. By using a conjugate vaccine, the immune responses to the polysaccharides are dramatically improved (Dintzis et al., 1992). Virus-like particles (VLP) vaccines do not hold any replicative genetic material but permit antigenic presentation in a repetitive, ordered array just like the virion structure that only increase the immunogenicity (Jennings and Bachmann, 2008). VLPs can efficiently provoke both cell-mediated and humoral immune responses without necessitating an adjuvant. This is due to the close resemblance of molecular scaffolds of VLPs to the native viruses and the absence of genetic material. However, for commercially producing these vaccines, such approaches have yet to be employed (Liu et al. 2012).

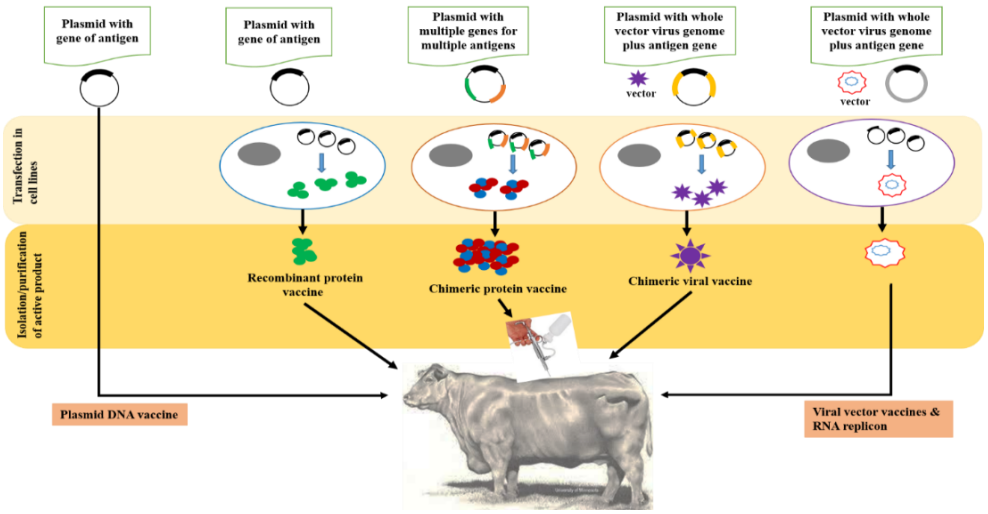


Fig. 3: Schematic diagram of novel recombinant vaccine technologies from their production to vaccination (Aida et al. 2021)

Biotechnology Applied to Next Generation Vaccine Development

Genomic analyses of pathogens and enhanced understanding of the mechanisms of pathogenesis have resulted in new antigen discovery and the development of recombinant veterinary vaccines. A large amount of draft and whole-genome sequencing of viruses, prokaryotes and eukaryotes pathogens have been performed (Pizza et al. 2000; Tettelin et al. 2000; Vasconcelos et al. 2005; Kremer et al. 2016). These advancements have also improved antigen discovery and the characterization of variability between viral pathogens, which typically contain fewer than ten genes, and eukaryotic pathogens, which often encode >10 000 genes (Cho et al. 2002; Aurrecoechea et al. 2007). The genome sequencing technologies and the approaches used to screen the genome and proteome of a pathogen have greatly improved the efficiency of antigen discovery (Seib et al. 2012) because relevant antigenic structures can identify and produce recombinant vaccines that contain only the antigen necessary to elicit protective immunity.

Genomic databases generally contain whole genome sequences and the complete repertoire of encoded proteins from which vaccine screening is possible (Bagnoli et al. 2011). Surface-exposed antigens, secreted proteins, and toxins are commonly viable vaccine candidates against bacterial infections (Ravipaty and Reilly 2010). However, further *in vivo* investigation of antigens is still necessary and desirable. Comparative genomic analysis software can be used to perform gene comparative analysis by basic sequence similarity searches. Sequence similarity algorithms facilitate the comparison of predicted coding sequences (ORFs) with known genes/proteins in public databases, and are commonly used to predict the degree of gene conservation among a bacterial population.

In silico analysis may also result in enhanced protein antigen qualities such as expression and solubility. As native gene sequences retain their own specific codon usage that reflects the composition of their respective genomic tRNA pools, gene sequences may be optimized for higher expression levels in any heterologous system (Bagnoli et al. 2011). One drawback of reverse vaccinology is that it cannot be used to predict polysaccharides or lipids, which are often included in vaccines as active compounds. Fig. 1 has shown a scheme of recombinant vaccine development strategies.

One negative aspect of reverse vaccinology is that it can't be helpful in anticipating lipids, which are usually associated with vaccinations as unique compounds. Fig. 3 represents the 6 unique techniques of various recombinant vaccines right from their generation/isolation or purification of antigens to the application of vaccination on animal (Aida et al. 2021). Starting from plasmid-DNA vaccines, the gene of interest (GOI) of the desired immunogen is incorporated inside the plasmid. This is used as an active ingredient to vaccinate the animal. Vaccine recipient's cells, the plasmid-DNA vaccine occupy the DNA encoding for the target immunogen is translated into protein of interest. The immunogen is then appeared from the cell, resultantly inciting an immune response (Aida et al. 2021). Recombinant chimeric and protein vaccines employ the similar methodology. Nevertheless, transfection of these plasmids is done in appropriate cell-lines for antigen protein expression. Then immunogen(s) is/are collected, filtered, and made into the final vaccine form (Aida et al. 2021). In case of chimeric viral vaccines, they use a plasmid with complete viral genome that is used as a carrier to transfer the gene of interest for the desired antigen. Like above the plasmid transfected in an appropriate cell-line for whole virus expression along with the integration of antigen. The virus is then collected and filtered, and formulated into a final vaccine form (Aida et al. 2021). Viral vectors use a virus that had been specifically made to express the required gene of interest. The vaccine will release the recombinant genes into the host cells. Genes of interest will be transcribed into the target antigen which will then be expressed and induce an immune response (Aida et al. 2021). Ribonucleic replicon vaccines use a RNA segment that codes the desired immunogens encapsulated in a vesicle carrier. Upon entering in the cell of host, the RNA is translated directly, which results in the expression of the antigen which is being targeted (Aida et al. 2021).

Vectored Vaccines

The usage of immunogen/quality movement system had worked with the improvement of new preventive and curative immunizer contender. To pass on guarded protein(s) to the immune plan, vector counter acting agent development uses a vector. These vectors are for the most part antigenic and can show various immunogenic effects. Recombinant vector inoculations are named live vector antibodies and naked

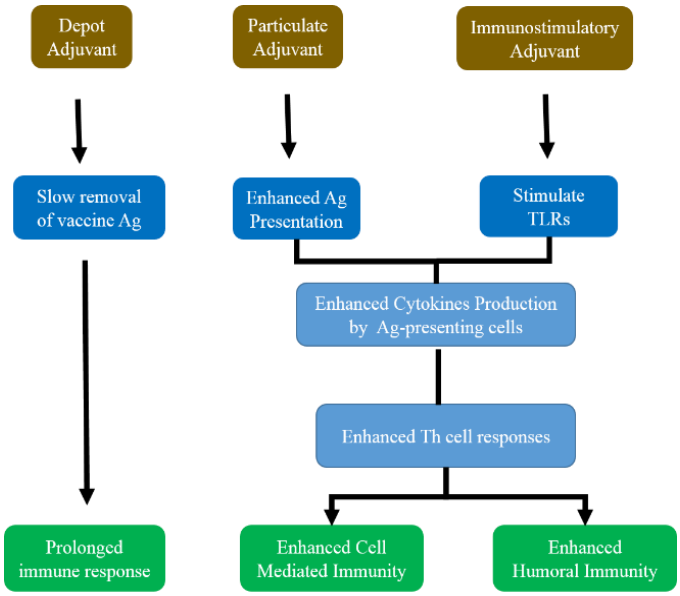
Deoxyribonucleic acid antibodies. Plant vaccinations are also vector antibodies that have basic capability in animal drugs.
Conventional live vectors are reduced organisms or contaminations that, just as prompting their own innate opposition, can similarly be used as for conveying the immunogens of other pathogens. For external characteristics, Poxviruses which join the fowl pox, canary pox and vaccinia diseases have been used as vectors successfully. Poxviruses can oblige a great deal of new characteristics and can pollute mammalian cells, achieving the announcement of tremendous measures of encoded protein. At the present time, the canary pox disease vector system has been applied as a phase for an extent of animal antibodies in opposition to FLV, WNV, EIV, Rabies contamination. BCG, which is the bacterial reduced vector, has been perused up for quite a while. Recombinant BCG provides gigantic ability for conveying a huge numeral of heterologic immunogens and is able to affect solid safety (Rizzi et al. 2012).
Using plants for assembling and passing on immunogen through sources of food is uncommonly profitable. The usage of transgenic plants shows an imaginative progression that has revealed novel streets in the inoculation ventures. In animal vaccinology, genetically modified plants can make and pass on immunogen through feed of animal (Shams 2005).

Nucleic Acid Vaccines

DNA vaccinations produce antigens in the genuine host. We can describe Deoxyribonucleic acid (or Ribonucleic acid) vaccination as "a plasmid consisting of a bacterial, viral or parasite which may be conveyed in cells of mammal or a quality inscribing a mammalian protein (non-microbial ailments). This nature is implanted into a plasmid close by reasonable genetic parts, for instance, powerful eukaryotic publicists for transcriptional control, a polyadenylation signal plan for consistent and convincing translation. The mRNA is translated after plasmid is transferred inside cells. The mRNA is consequently deciphered, achieving the host cell contraption making an immunogenic protein. The host safe structure sees the imparted proteins as new, and this can incite the headway of a humoral and cellular safe response.
Vaccination of veterinary side with stripped DNA which codes immunogens for virus' protection in various methods addresses an optimum framework for viral antibodies. Since it does not simply beat the effects produced with vector immunity and live vaccines yet also propel the acknowledgment of cytotoxic T cells after enunciation of the immunogens intracellularly (Meeusen et al. 2007).

Adjuvants for Recombinant Animal Vaccines

The development and use of adjuvants to inoculation (immunogens) pass on a couple of advantages, for instance, segment saving, extended sufficiency in the more established, and enlarging of the humoral or/and cell safe respond. Subdivisions of recombinant units are routinely favored over inactivated or live microorganisms; regardless, they usually are not so much capable of provoking immune response and need the extension of an adjuvant to accomplish cautious invulnerable responses (Soema et al. 2015). The impacts of immune modulation depend on the specific adjuvant used related with particular antigens. Types of adjuvants are presented below in the Fig 4 and designed by taking help from online source https://veteriankey.com/vaccines-and-their-production/#s0075.
A couple of adjuvants have been listed for use in animal inoculations, similar to mineral salts (aluminum) (Li and Cui 2014); emulsions (Montanide) (Peter et al. 2001; Miles et al. 2005) biodegradable polymeric micro-particles, and nanoparticles. Furthermore, the elective extent of adjuvants is depicted as "safe potentiators" as they apply ramifications for safe introduction (Ott et al. 2000). A couple of adjuvants act by confining antigens in locales, called as terminals, to give an extensive time frame of antigenic inclination. Along these lines, a couple of veterinary inoculations are as emulsions in oil. This for the most part more seasoned style advancement is, regardless, a solid philosophy that accomplishes a powerful combustible respond and slow antigen opportunity, this is what was not recombinant subunit vaccines. Rather than the solidly safe authorizing emulsion-type adjuvants, aluminum salt adjuvants are not good for prompting Th1 or cell-mediated invulnerable actions take place to any enormous degree; in any case, they are useful Th2 inducers, prompting elevated antibody titers in the vaccinated organism.



Depending upon size either, endocytosis or phagocytosis masks the particles. The foreign particles are either typified in nano particle's framework core or adsorbed upon the surface layer of the nanoparticles (Slütter et al. 2009). As of now, micro-particles from polymer have still not been fruitfully made as an immune response thing. Micro-particles overall redesign the acknowledgment of Th2-type, humoral obstruction, while nanoparticles advance Th1-based, cell-mediated safe responses (Li and Cui 2014).

Role of Reverse Vaccinology In animal Health Perspectives

The improvement of animal antibodies is a troublesome endeavor; however, reverse vaccinology is significantly reassuring as a part of animal vaccination progression. Basic breakthrough has been made in the space of vaccinology during the hour of genomics, and state of the art vaccinations are set to dynamically influence animal prosperity. We can assume significantly more progress in vaccinology and the improvement of new fruitful animal antibodies that safe the

host from compelling ailments just as against various diseases or continuous issues. Believe it or not, switch vaccinology is as of now being used in various bacterial, viral, and eukaryotic microorganisms and has been powerful in giving new antigens to the arrangement of novel vaccinations (Bagnoli et al. 2011; Buonaguro and Pulendran 2011). Furthermore, the limit of sensible arrangement to additionally foster contender immunogens can give extended confirmation against immunogenically factor organisms (Seib et al. 2012).

Now a day, a new breakthrough in the field of vaccinology is mRNA vaccines which are obvious by dozens of publications on pre-clinical and clinical data in the last 2 years. These vaccines are mostly used for cancer protection but they have also been designed for various infectious organisms *e.g.* Zika virus, influenza virus, Ebola virus, *Toxoplasma gondii* and *Streptococcus* spp. Thus, the coming time is the era of mRNA engineering in the field of vaccinology and all the basic and clinical research trial findings will be used in designing various transcriptional drugs.

REFERENCES

Aida V et al., 2021. Novel Vaccine Technologies in Veterinary Medicine: A Herald to Human Medicine Vaccines. Frontiers in Veterinary Science 8: 340.

Arimitsu H et al., 2004. Vaccination with recombinant whole heavy chain fragments of *Clostridium botulinum* Type C and D neurotoxins. Clinical and Diagnostic Laboratory Immunology 11 (3): 496-502.

Aurrecoechea C et al., 2007. ApiDB: Integrated resources for the apicomplexan bioinformatics resource centerNucleic Acids Research 35, 10.1093/nar/gkl880.

Babiuk et al., 2003.Induction of immune responses by DNA vaccines in large animals.Vaccine 21: 649-658.

Bagnoli F et al., 2011. Designing the next generation of vaccines for global public health. Omics 15 (9): 545-566.

Barnett KM and Civitello DJ, 2020. Ecological and Evolutionary Challenges for Wildlife Vaccination. Trends in Parasitology

Boylston A, 2013. The origins of vaccination: no inoculation, no vaccination. Journal of the Royal Society of Medicine 106(10):395-398.

Belkaid Y and Hand TW, 2014. Role of the microbiota in immunity and inflammation. Cell 157(1): 121-141.

Balloux F and van Dorp L, 2017. Q&A: What are pathogens, and what have they done to and for us? BMC Biology 15(1): 1-6.

Cavaillon JM, 2018. Historical links between toxinology and immunology. Pathogens and disease, 76(3), fty019.

Cho HW et al., 2002. Review of an inactivated vaccine against hantaviruses. Intervirology 45: 328-333.

Dintzis RZ et al., 1992. Rational design of conjugate vaccines. Pediatric Research 32: 376-385.

Deets KA and Vance RE, 2021. Inflammasomes and adaptive immune responses. Nature Immunology22(4): 412-422.

Delany I et al., 2014.Vaccines for the 21st century. EMBO Molecular Medicine 6: 708-720.

Doolan DL et al., 2014. Genome-based vaccine design: The promise for malaria and other infectious diseases. International Journal for Parasitology 44: 901-913.

Guo HC et al., 2013. Foot-and-mouth disease virus-like particles produced by a SUMO fusion protein system in Escherichia coli induce potent protective immune responses in guinea pigs, swine and cattle. Veterinary Research 44(1): 1-13.

Guzman E and Montoya M, 2018. Contributions of farm animals to immunology. Frontiers in Veterinary Science307.

Gomes MD, 2021. Louis Pasteur and Dom Pedro II engaged in rabies vaccine development. Journal of Preventive Medicine and Hygiene 62(1): E231.

Hart BL, 2011. Behavioural defences in animals against pathogens and parasites: parallels with the pillars of medicine in humans. Philosophical Transactions of the Royal Society B: Biological Sciences 366(1583): 3406-3417.

Jenner E, 1800. An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow pox. Printed for the author, by Sampson Low...; and sold by Law... and Murray and Hihghley.

Jennings GT and Bachmann MF, 2008. The coming of age of virus-like particle vaccines. Biological Chemistry 10.1515/BC.2008.064

Kremer FS et al., 2016. Draft genome of the *Leptospirainterrogans* strains, Acegua, RCA, Prea and Capivara, obtained from wildlife maintenance hosts and infected domestic animals. Memorias do Instituto Oswaldo Cruz 111: 280-283.

Kamel M et al., 2019. Foot-and-mouth disease vaccines: recent updates and future perspectives. Archives of Virology 164(6): 1501-1513.

Kaufmann SH, 2019. Immunology's coming of age. Frontiers in Immunology 10:684.

Liu F et al., 2012. Virus-like particles: Potential veterinary vaccine immunogens. Research in Veterinary Science 10.1016/j.rvsc.2011.10.018.

Li X et al., 2014. Aluminum hydroxide nanoparticles show a stronger vaccine adjuvant activity than traditional aluminum hydroxide microparticles. Journal of Controlled Release 173 (1): 148-157.

Li C et al., 2021. Molecular dynamics study on the stability of foot-and-mouth disease virus particle in salt solution. Molecular Simulation 47(13): 1104-1111

Lanzas C et al., 2020. On modelling environmentally transmitted pathogens. Interface Focus10(1): 20190056.

Laupèze B et al., 2021. Vaccination as a preventative measure contributing to immune fitness.Vaccines6(1): 1-10.

Marshall JS et al., 2018. An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology14(2):1-10.

Meeusen ENT et al., 2007. Current status of veterinary vaccines.Clinical Microbiology Reviews 20: 489-510.

Miles AP et al., 2005. Montanide® ISA 720 vaccines: Quality control of emulsions, stability of formulated antigens, and comparative immunogenicity of vaccine formulations. Vaccine 23: 2528-2537.

Moreira C et al., 2016. Protective potential of recombinant non-purified botulinum neurotoxin serotypes C and D. Anaerobe 40: 58-62.

Muñoz-Carrillo JL et al., 2018. Cytokine profiling plays a crucial role in activating immune system to clear infectious pathogens. In Immune response activation and immunomodulation. IntechOpen.

Nicholson LB 2016. The immune system. Essays in Biochemistry 60(3): 275-301.

Ott G et al., 2000. The adjuvant MF59: A 10-year perspective. Vaccine Adjuvants 42: 211-228.

Pizza M et al., 2000. Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. Science (New York.) 287: 1816-1820.

Peter K et al., 2001. Induction of a cytotoxic T-cell response to HIV-1 proteins with short synthetic peptides and human compatible adjuvants. Vaccine19: 4121-4129.

Plotkin S, 2014. History of vaccination. Proceedings of the National Academy of Sciences 111(34): 12283-12287.

Ravipaty S and Reilly JP, 2010. Comprehensive characterization of methicillin resistant *Staphylococcus aureus* subsp. *aureus* COL secretome by two-dimensional liquid chromatography and mass spectrometry. Molecular & Cellular Proteomics 9: 1898-1919.

Rizzi C et al., 2012. Vaccination with a BCG strain overexpressing Ag85B protects cattle against *Mycobacterium bovis* challenge. PLOS ONE 7: e51396, 10.1371/journal.pone.0051396

Reddy SM et al., 2017. Marek's disease vaccines: Current status, and strategies for improvement and development of vector vaccines. Veterinary Microbiology206:113-120.

Ribatti D, 2017. The concept of immune surveillance against tumors: The first theories. Oncotarget 8(4): 7175.

Singh RK and Borkotoky D, 2018. Vaccination schedule of Mithun, thotho and buffalo, In: Livestock vaccination and health record book. ICAR - National Research Centre on MithunPorba, Pfutsero – 797 107 Phek, Nagaland, India pp: 16.

Sternbach G, 2003. The history of anthrax. The Journal of Emergency Medicine 24(4): 463-467.

Shams H, 2005. Recent developments in veterinary vaccinology. Veterinary Journal 170: 289-299

Slütter B et al., 2009. Mechanistic study of the adjuvant effect of biodegradable nanoparticles in mucosal vaccination. Journal of Controlled Release 138: 113-121.

Seib K et al., 2012. Developing vaccines in the era of genomics: A decade of reverse vaccinology. Clinical Microbiology and Infection 10.1111/j.1469-0691.2012.03939.x

Soema PC et al., 2015. Current and next generation influenza vaccines: Formulation and production strategies. European Journal of Pharmaceutics and Biopharmaceutics 94: 251-263.

Skwarczynski M and Toth I, 2016. Peptide-based synthetic vaccines. Chemical Science7(2): 842-854.

Tettelin H et al., 2000. Complete genome sequence of *Neisseria meningitidis* serogroup B strain MC58. Science (New York, N.Y) 287: 1809-1815

Vasconcelos ATR et al., 2005. Swine and poultry pathogens: The complete genome sequences of two strains of *Mycoplasma hyopneumoniae* and a strain of *Mycoplasma synoviae.* Journal of Bacteriology 187: 5568-5577

Van Gelder P and Makoschey B, 2012.Production of viral vaccines for veterinary use.Berliner und MünchenerTierärztlicheWochenschrift125: 103-109.

Wang Y and Liu, M, 2020. The Causative Agent of FMD Disease. In: Shah Y, Abuelzein E, editors. Some RNA Viruses [Internet], London. IntechOpen.

Zepp F 2010. Principles of vaccine design—lessons from nature. Vaccine, 28: 14-24.