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ORIGINAL ARTICLE

Traditional and Recent Approaches for the Development of Animal Vaccines. A Review

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ABSTRACT
Objective: To show new trends in the field of vaccinology and spread awareness among population regarding vaccination of animals and successfully controlling spread of diseases
Study Design: This is a review study for the development of animal vaccines and was conducted from September, 2021 to June, 2022 at IMBB Department, The University of Lahore, Lahore, Pakistan. Review of Literature was collected on traditional and recent approaches for the development of veterinary vaccines and gathered for the awareness among the field of veterinary vaccinology.
Methodology: Animals provide food and clothing in addition to other value-added products. Changes in diet and lifestyle have increased the consumption and the use of animal products. Infectious diseases in animals are a major threat to global animal health and its welfare; their effective control is crucial for agronomic health, for safeguarding food security and also alleviating rural poverty. Development of vaccines has led to increased production of healthy poultry, livestock, and fish. Animal production increases have alleviated food insecurity. Before year 2000, most veterinary vaccines were from inactivated organisms that were formulated with an oil-based adjuvant or live attenuated vaccines.
Results: The discovery of antigen/gene delivery systems has facilitated the development of novel prophylactic and therapeutic veterinary vaccines. Uses several bioinformatics algorithms to predict antigen localization and it has been successfully applied to immunize against many veterinary diseases. Vectors and pathogens that may lead to emergent diseases in animals. Preventing transmission of emerging infectious diseases at the animal–human interface is critically important for protecting the world population from epizootics and pandemics. Hence, there is a need to develop new vaccines to prevent diseases in animals. An area of veterinary vaccination that needs more research and discussion is vaccine interference. The phrase itself is ambiguous and might mean either a condition in which immunization against one disease may weaken the protective immunity established by immunization against another, or a circumstance in which the presence of maternally derived antibodies prevent immunization in newborn animals.
Practical implication: This study will provide awareness among community about veterinary vaccines and will develop a disease-free state for pets.Vetrinary vaccines not only prevent diseases in animals but also stops their spread among humans.
Conclusion: This review examines some of the main topics that have emerged in the veterinary vaccine field with the use of modern biotechnology techniques. In addition, development of effective vaccines has led to healthier companion animals. However, challenges remain including climate change that has led to enhancement in vectors and pathogens that may lead to emergent diseases in animals. Preventing transmission of emerging infectious diseases at the animal–human interface is critically important for protecting the world population from epizootics and pandemics. Hence, there is a need to develop new vaccines to prevent diseases in animals.
Keywords: Vaccines, Toxin, Immunization, Antibodies, Antigen, Host.

INTRODUCTION
A vaccine is a biological substance designed to protect humans from infections caused by bacteria and viruses. The terms vaccine and vaccination are derived from Variolae vaccinae (smallpox of the cow), and devised by Edward Jenner in 1799[1,3]. The administration of vaccine is called vaccination. Vaccination is an effective way to prevent diseases in various animals. The first animal vaccine against fowl cholera was invented by Louis Pasteur in 1879[1]. Study of vaccine is known as vaccinology, which has provided several effective

vaccines in both livestock and other animals that have significantly reduced the effects of some important diseases. Vaccine comprises of two types Conventional vaccine and Modern vaccine[2].

Conventional Vaccine also known as Traditional vaccine are the most important and commonly used animal vaccine; it consists of Live attenuated vaccine, Inactivated or Killed vaccine, and Toxoid vaccine. The live attenuated vaccine uses a weakened form of the germ that causes a disease, provides strong protection against pathogens in the field of vaccine science. They are an efficient and traditional way of immunizing animals. They are highly immunogenic and less safe than inactivated vaccines. A killed/inactivated vaccine is a vaccine in which viral particles, bacteria, or other pathogens are grown in culture and then killed to destroy their ability to cause disease. They are safer than usual, but may not be as effective as attenuated vaccine[3]. Toxoid vaccines use toxins (harmful products) produced by disease-causing bacteria. They create immunity against the parts of the bacteria that cause disease, rather than against the bacteria themselves[4].

Modern vaccine as very useful now a days in the treatment of various diseases in biological systems. They comprise of three types Recombinant sub-unit vaccine, DNA vaccine and viral vectored vaccine. A recombinant subunit vaccine consists of at least one viral antigen that can be produced in a heterologous expression system. Subunit vaccines consist of a small number of virus particles that induce protective immunity in patients[2,4]. Recombinant subunit vaccines are much safer than live attenuated or inactivated vaccines. Subunit vaccines are an effective and inexpensive way to prevent health problems. DNA vaccine technology is based on intramuscular or intradermal injection of a DNA plasmid encoding the G protein. Plasmids injected in this way integrate host cells and encode immunogenic proteins. DNA vaccines can be adjuvanted to improve their efficacy[4,5]. DNA vaccine afford advantages over conventional vaccine including ease of production, stability, and transport at room temperature, decreased likelihood of replication interference. viral vectored vaccine use virus which is harmless and modified version and can be very helpful in curing disease, it is most common way of making efficient vaccine against viral diseases[5].

Effective routes for vaccination are intramuscular or subcutaneous injection even though oral routes were also proven effective in recent studies. Injecting vaccine in these parts of animal will trigger the absorption and thus fast and effective action of vaccine against pathogens in biological systems[6]. Animal vaccination schedule is to be followed for proper immunization against different diseases and they may require booster shots, Black Quarter disease is given to animals age 6 months and above and booster shots are given annually in epidemic areas.[6,7]. Vaccine market has proven to be very effective in recent years when proper awareness is provided to all farm owners to vaccinate their animals. The main key players manufacturing veterinary vaccine are Zoetis, Elanco, etc. SARS-COVID 19 was firstly identified in bats and was transmitted to human but no cases in animals were reported later on in 2020 at Belarus cases were reported in Minks which were farm Animals. Transmission of COVID-19 cases were reported from humans to pet animals[7]

Vaccination techniques have diversified from last few years and a modernization in techniques are observed ,but many problems are also faced during their production, maintenance of cold chain of vaccine is very difficult as they are exported from advance countries to third world countries, traditional values encountered the production of vaccine in villages, political reasons have also proven discouraging use of animal vaccine ,nevertheless use of veterinary vaccine without sufficient trials is effecting the immunization of animals from diseases [8]

Significance of Study: Current study will be a gem in the field of veterinary vaccines which have compiled the literature hidden in the areas of veterinary vaccinology thus less animal suffering, enable efficient food animal production to feed the world's expanding population, and significantly reduce the need for antibiotics to treat both food and companion animals. Animal welfare and public health will both be benefited greatly from the use of veterinary vaccines.

Research Gap: Modern technologies used for developing vaccines are not practically explained and less work is yet done on veterinary vaccines, due to lack of literature fewer modern tools and techniques used by industries for processing vaccines and hence low therapeutic doses provided to animals for controlling of diseases.

Rationale of Study: This Review discusses traditional and recent approaches in the development of animal vaccines, shows new trends in the field of vaccinology and spread awareness among population regarding vaccination of animals and successfully controlling spread of diseases.

Chronological order of Animal Vaccine

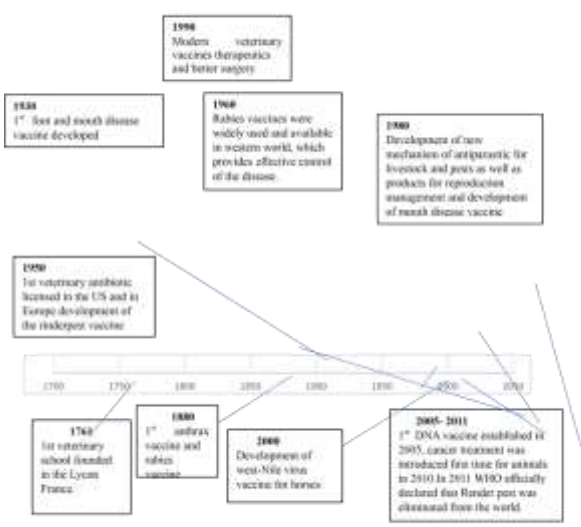

Fig 1: Chronological order of Animal Vaccine background

Conventional Vaccine: These are also known as traditional vaccine. Conventional vaccine can provide protection against a variety of bacterial and viral diseases. The majority of certified veterinary vaccine are traditional vaccine. The widespread use of these vaccinations has contributed significantly to improving animal and public health. These vaccines usually contain organisms or proteins (antigens) that because inactivated diseases produced by pathogens that mimic infectious pathogens. They strengthen the immune system and prepare it to react more quickly and efficiently if the body is re-exposed to infectious pathogens in the future. Vaccine design of these relies on simulating immunity elicited by natural exposure[9]. This is insufficient for many infections, and robust long-term protection necessitates the induction of immunity above and beyond normal biological immunity while reducing the negative consequences of increasing the inflammatory response. The pathogen can stay with the host forever even in chronic infections when there is a host-mediated anti-pathogen immune response[3]. The types of conventional vaccine are summarized in Table-1.

Table-1: Types of conventional vaccine:

Types of Conventional vaccine	Salient Features
Live-attenuated Vaccine	Live Attenuated vaccines are highly immunogenic, capable of producing a persistent, protective immune response with just one dose (in the absence of maternally produced antibodies), and are currently thought to be quite safe. Every vaccination approved for oral or intranasal delivery has been live attenuated vaccine.
Inactivated (killed)Vaccine	Due of the elimination of the pathogen replication, inactivated vaccines have favorable safety profiles but are unable to deliver long-lasting protection. Many inactivated vaccines cannot keep up with the prevalent field strains; periodically, new vaccinations need to be produced from field strains with new outbreaks.
Toxoid Vaccine	Made from selected toxins (proteins) that are sufficiently weakened (detoxified) to be able to induce a humoral (antibody) immune response. Multiple doses may be required and an adjuvant is usually required. A high level of biosafety is required.

Live-attenuated Vaccine: Live attenuated vaccine (LAVs) has existed since the 1950s and are made from pathogens that have been attenuated in the laboratory, such as viruses and bacteria. They grow in vaccinated animals, but because they are weak, they cause little or no illness. It is designed to elicit a humoral and cell-mediated immune response that mimics natural infections but cannot cause disease. In the absence of maternal antibodies, attenuated vaccine is highly immunogenic and can induce a sustained protective immune response with a single dose and are now considered very safe. It is extremely rare and non-existent with current manufacturing techniques for attenuated vaccine to return to the state that causes toxic diseases. Live attenuated vaccine is available for oral and intranasal administration. Even in the freeze-dried state, it is necessary to store and handle it while paying attention to the temperature. Vaccine doses should be administered or discarded within 1 hour after reconstitution[10]

Preparation and Production of Live attenuated Vaccine: Killed Vaccine: Inactivated / Killed vaccine are composed of whole virus and / or part of bacteria and are grown in culture and then killed by physical (heat, radiation) and chemical (usually formalin) methods. Increase, Pathogen particles cannot be destroyed and proliferate, but are recognized by the immune system and retain sufficient integrity to elicit an adaptive immune response. In the fractionated vaccine, the organism is further processed to purify only the components contained in the vaccine (such as the pneumococcal polysaccharide capsule). Inactivated vaccine are not effective and cannot replicate, so multiple doses are always required. The immune response usually occurs after the second or third dose instead of the first. The immune response resembles that of a natural infection, with an emphasis on humoral immunity and little or no cell-mediated immunity[11].

Toxoid Vaccine: Toxoid vaccine are made from toxins (proteins) that are sufficiently weakened (detoxified) and can elicit an immune response in the form of humoral (antibody) antibodies. Toxins are derived from toxins produced by bacteria (such as tetanus and diphtheria). Toxins enter the bloodstream and are the main cause of symptoms of the disease. Toxins made of proteins are neutralized to induce immunity. Use of H. toxoid as a vaccine antigen. Toxoid is an adjuvant that is adsorbed on aluminum or calcium salts and works to strengthen the immune response. Toxoid vaccinations do not have the same immune response as attenuated viral vaccine, and protection may require repeated initial doses given back-to-back (especially for very large and small breeds). Depending on the risk factors of the individual patient, re-vaccination (booster) may be required several times a year[4].

Modern Vaccine: Over the last 25 years, the field of veterinary vaccination has seen many significant technological advances. Modern vaccine technology is leading a new era by enabling more opportunities to treat the condition with more accurate vaccine after traditional vaccine. These include recombinant subunit vaccine, DNA vaccine and vector-based vaccine. These vaccines aim to provide farmers, business owners and healthcare professionals with safer and more effective alternatives to current vaccine technology. It also has the added benefit of being easy and stable to manage. In fact, many of the latest vaccine technologies have been used commercially for the first time in veterinary medicine and are currently interested in a one-health approach to humans, animals and the environment, and veterinary vaccine are important in promoting human well-being.[12].

Modern vaccines have proved to be very Safer and more efficacious vaccines. They are longer-lasting vaccines that provide immunity and are vaccines that avoid maternal inhibitory antibodies. These vaccines will increase immunogenicity and stability, which will increase the global vaccination rate. Millions of animals in less developed nations suffer from illnesses that can be avoided with modern vaccination. Advances in genetic engineering have enabled to pinpoint the antigens that trigger clinical immunity. Using modern methods in the field of vaccinology are the main sources of hope for new vaccination techniques[13]. The types of modern vaccine are shown in Table-2.

Table 2: Types of Modern Vaccine

Types of Modern Vaccine	Salient Features
Recombinant subunit Vaccine	These Vaccine utilize an extremely complex process of recombinant DNA engineering instead of an adjuvant. Possibility for cost-efficient. Primarily humoral immune response; Need of adjuvant. Subunit vaccines include Protein, Peptides and DNA.
DNA vaccine	A DNA vaccine is a type of vaccine that transfects a specific antigen-coding DNA sequence into the cells of an organism as a mechanism to induce an immune response. Long term persistence of immunogen. They are very safe to use, coast efficient and relatively stable. Refrigeration of vaccine is not required.
Vectored-based Vaccine	Induce both cellular and humoral immune responses. Induction of T and B cell immune response. Viral vectors allow for efficient infection of target cells.

Recombinant subunit Vaccine: Recombinant subunit vaccinations lack the ability to proliferate in the host, they employ a brief, non-infectious pathogen protein. The protective antigen enables the administration of the recombinant vaccination as a secure, non-replicating vaccine. To manufacture the discovered antigen, gene cloning for the antigen is frequently necessary[12].Antigen expression in a heterologous system improves the safety of both producers and users, as no toxic or partially toxic microorganism is required to induce immunity. Subunit vaccine also have the advantage of incorporating the protein in its most natural state, allowing proper protein folding and conformation epitope reconstitution. By incorporating multiple proteins into a subunit vaccine, it is possible to induce immunity against multiple strains or serotypes of bacterial or viral pathogens. These vaccine are cheaper, easier to manufacture, and more stable than vaccine that contain whole viruses and bacteria[9]

DNA Vaccine: DNA vaccine use viral and bacterial genes to stimulate the immune system. When a patient receives a DNA vaccine, intracellular mechanisms produce viral or bacterial proteins that the immune system recognizes as foreign. The immune system, like other vaccine, recognizes bacteria and viruses in the future and hopefully prevents the disease. DNA vaccine are based on plasmids' capacity to express vaccination antigens in host tissues, particularly muscle cells and cutaneous epithelium, while being regulated by the proper eukaryotic promoters. Recombinant plasmid DNA may often be produced at a low cost and is stable enough to do without the need of cold chains. However, the level of protective immunity elicited by DNA vaccination is frequently poor until a sizable quantity of DNA is administered, and recombinant protein vaccine are very costly[9].

Viral Vectored Vaccine: A vaccination that delivers genetic material encoding for a desired antigen into the recipient's host cells is known as a viral vector vaccine. Viral vector vaccine use a modified version of a different virus as a vector to deliver protection. Antigen delivery systems have assisted in the creation of novel therapeutic and preventative vaccinated animals. The immune system of a recipient of a vector vaccination receives a protective protein through the vector. These vectors may often display a variety of antigens and are immunogenic. Vector vaccine from plants have a lot of potential for veterinarians. Traditional live vectors are attenuated bacteria or viruses that may be utilized as carriers to express other pathogens' immunogenic antigens while also triggering their own innate immunity. Extrinsic genes have been successfully inserted into vaccinia, fowl pox, and canary pox viruses. When poxviruses infect mammalian cells, they can integrate a significant number of foreign genes, which leads to the production of a significant number of encoded proteins[14]

Table 3: Vaccination Schedule for Animals and Immunity developing time:

Names of Diseases	Age	Booster dose	Subsequent dose
Hemorrhagic Septicemia	6 months and above them	Not-required	in endemic areas.
Rabies	Immediately after the suspected bite.	4th day	7, 14, 28 and 90 days after first dose.
Anthrax	4-months and above	Not required	In endemic areas.
Brucellosis	4-8 months of age (Only female calves)	Not required	Once in a lifetime
Foot and Mouth Disease (FMD)	4 months and above	1 month after first dose	Six months
Black Quarter (BQ)	4-8 months of age	Not required	Actually-in epidemic areas
Theileriosis	3 months of age and above	Not required	Once in a lifetime, only required for crossbred and exotic cattle.
IBR	3 months and above	1 month after first dose	Six months

SARS COVID-19 in animals and its vaccination policies: The severe acute respiratory syndrome coronavirus 2 (SARS covid-19), which was initially discovered in bats, which are the cause of the continuing global pandemic of coronavirus illness 2019 (COVID-19). New wave is given name of SARS-CoV-2. The new virus was discovered in a December 2019 incident in Wuhan, China, but attempts to contain it failed and spread worldwide. The World Health Organization (WHO) proclaimed a pandemic on March 11, 2020, and a public health emergency of worldwide significance on January 30, 2020.Infested by bat-eating humans on February 27, 2022, these pandemic has become one of the deadliest in history, with more than 434 million cases and 5.94 million deaths[15]. Vaccine against Covid-19 have been developed for humans, but the government has not yet developed vaccine for animals. Therefore, there are new reports of cases of Covid-19 in animals. COVID-19 infection has been reported in animals worldwide[16].The majority of these animals were infected with COVID-19 after exposure to COVID-19-positive individuals, such as owners, caregiver, or someone else in the immediate vicinity. Not all animals susceptible to this disease are known yet. Infections have been reported in big cats, otters, non-human primates, binturongs, honeybees, fishing cats, hyena zoos and animal shelters. Mink farms and wild white-tailed deer can be found in several states of the United States. Coronavirus is a family of viruses that includes a wide variety of viruses. Some coronaviruses infect humans, while others infect cattle, camels and bats. Coronaviruses that infect only animals, such as coronaviruses in cats and dogs, do not infect humans[17].

Mink and SARS-COVID-19: SARS-COVID-19 has been found in mink on farms in several countries, including the United States, where increased respiratory illness and death from mink have been observed. However, some infected mink looks healthy. SARS-CoV-2 is most likely spread by infected mink workers on the farm. Once brought to the farm, the virus can spread not only to mink but also to other livestock (dogs, cats). SARS-CoV-2 was found infected with wild mink, and the escaped mink was found near an affected farm in Utah. Therefore, vaccine against Covid-19 should be developed to prevent animals from becoming infected with the virus, as the virus can become a carrier of the virus and infect others. Therefore, Covid vaccination of animals is essential to prevent the spread of this deadly virus[18].

Graphical representation of Covid-19 Cases among animals: COVID-19 case reported among animals are shown in Fig-9.

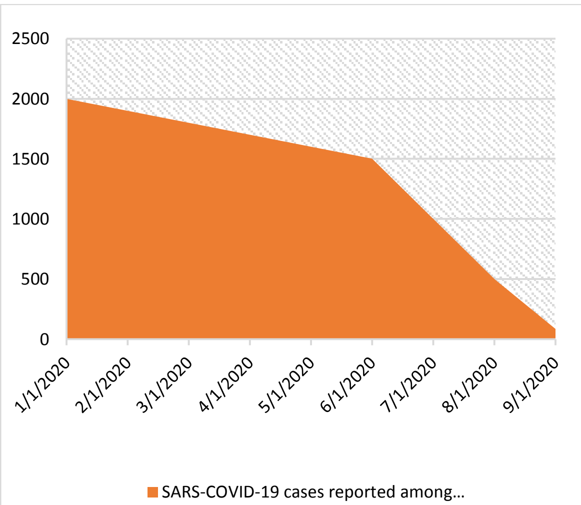

Fig-2: SARS-COVID-19 cases reported among animals 2020

RESULTS

The discovery of antigen/gene delivery systems has facilitated the development of novel prophylactic and therapeutic veterinary vaccines. Uses several bioinformatics algorithms to predict antigen localization and it has been successfully applied to immunize against many veterinary diseases. Vectors and pathogens that may lead to emergent diseases in animals. Preventing transmission of emerging infectious diseases at the animal–human interface is critically important for protecting the world population from epizootics and pandemics. Hence, there is a need to develop new vaccines to prevent diseases in animals. An area of veterinary vaccination that needs more research and discussion is vaccine interference. The phrase itself is ambiguous and might mean either a condition in which immunization against one disease may weaken the protective immunity established by immunization against another, or a circumstance in which the presence of maternally derived antibodies prevent immunization in newborn animals.

CONCLUSION

Veterinary vaccines are the one of the greatest animal and public health innovation Animal vaccination is proved to be very effective way of building immunization of livestock, or wildlife. The use of vaccines can be traced back to 18th century. Since then, much advancement has been made in the development of vaccines but is still much work to be done. The field of vaccinology has moved from the traditional method of vaccine development, where an organism had to be cultured, attenuated or killed before it could become effective vaccine candidate. With advancing recombinant DNA technology and it is now possible to develop safe, cost effective and reliable vaccines e.g. subunit, DNA, RNA and vectored vaccines. Progress in the development of each of these vaccines has had to contend with multiple challenges, not as regard to the underlying scientific concepts but also in terms of the logistics constrains of mass production, storage, distribution and mass vaccination. In addition to this, there is a dire need or demand to develop effective and safe vaccines against important diseases and controlling new and re-emerging pathogens.

Table 4: Abbreviations:

SARS	Severe acute respiratory syndrome
WHO	World Health Organization
DNA	Deoxy ribonucleic acid
LAVs	Live attenuated Vaccines
BVD	Bovine Viral Diarrhea
PRRS	Pig Reproductive and Respiratory Disease Syndrome
ILT	Infectious Laryngeal Tracheitis
APCs	Antigen-Presenting Cells
MHC	Major Histocompatibility Complex
WNV	West Nile Virus
IgA	Immunoglobulin A

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