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Veterinary Vaccine Development and its Role in One Health Approach: A Review

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Abstract: A vaccine is a biological preparation that provides active acquired immunity to a particular disease. Veterinary vaccines are important for protecting animal health, animal welfare, enabling efficient production of food animals to feed the mushrooming human population and public health by reducing or preventing transmission of zoonotic and food borne infections to people. The goal of vaccination is to induce long-lasting protective immune memory. Development of the earliest generation of vaccines, following on the example of Jenner, was to some extent empirical and involved the use of whole killed organisms, attenuated organisms or inactivated toxins and took place in the absence of any detailed understanding of how the vaccines worked. Vaccine development has become much more sophisticated with immunologists working closely with molecular biologists and chemical engineers to design and produce highly purified vaccines that are safe, consistently manufactured and effective. Beside the active vaccine itself, the excipients and residual manufacturing compounds are present or may be present in vaccine preparations. After production, to properly preserve, store, handle, ship and deliver vaccine supplies, it is essential to maintain cold chain from the manufacturer to the point of use, keeping temperatures within a precise range of values and avoiding temperature excursions or fluctuations. Much progress has been made in vaccine development in recent years; however, significant challenges remain. Increases in human and animal populations, with accompanying environmental degradation and globalized trade and travel, enhance opportunities for transfer of pathogens within and between species. Emerging zoonotic diseases of both food and companion animals are a major threat to public health. Rapid development of animal vaccines can play a key role in controlling emerging diseases. Veterinary vaccines reduce the need for antibiotics to treat infections in food producing and companion animals. Recently, vaccines have been developed to reduce the shedding of organisms that cause food borne diseases in people. One Health requires multidisciplinary efforts at global, national and local levels, for the sake of our planet, mankind and animals. 'One Health' concept of co-ordinated activity of those involved in human and animal health is cooperate with clinicians, researchers, agencies and governments working together for the benefit of domestic and wild animal and human health and the global environments.

Key words: Immunity · One Health · Public Health · Veterinary Vaccine

INTRODUCTION

A vaccine is a biological preparation that provides active acquired immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future [1, 2]. However, according to

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Palm and Medzhitov [3] report the magnitude, quality and duration of adaptive responses are highly influenced by the innate arm of the immune system, which is characterized by limited specificity and the absence of immunological memory.

According to Castellino [4], the goal of vaccination is to induce long-lasting protective immune memory. Veterinary vaccines have had and continue to have, a major role in protecting animal health and public health, reducing animal suffering, enabling efficient production of food animals to feed the burgeoning human population and greatly reducing the need for antibiotics to treat food and companion animals. Prominent examples include rabies vaccines and rinderpest vaccines. Rabies vaccines for domestic animals and wildlife have nearly eliminated human rabies in developed countries [5]. According to Lütticken *et al*. [6], vaccination is generally accepted as an adequate tool to control infectious diseases in man and animals. No real alternative exists for viral diseases of animals since there are no antiviral drugs suitable for widespread application in the field; moreover, there might be a restriction of the use of such drugs in humans in the future so as to avoid problems due to resistance. Therefore, the objective of this review paper was to highlight the veterinary vaccine development and its role in one health concern.

Historical Background of Vaccine Development: Prior to the introduction of vaccination with material from cases of cowpox (heterotypic immunisation), smallpox could be prevented by deliberate inoculation of smallpox virus, later referred to as variolation to distinguish it from smallpox vaccination [7]. One of the brightest chapters in the history of science is the impact of vaccines on health. Over 300 y have elapsed since the first vaccine was discovered [8]. Almost a century later, Louis Pasteur observed that inoculating chickens with a weakened culture of bacteria-built resistance to the disease [9].

According to Plotkin and Gilbert [10] report, in fact vaccine development has been based on rational choices ever since the mid-20th century, when immunology advanced to the point of distinguishing protection mediated by antibody and that mediated by lymphocytes and when passage in cell culture permitted the selection of attenuated mutants. One surprising aspect of non-infectious disease vaccine research [11]. Excitement in the field of tumor immunotherapy is being driven by several remarkable breakthroughs in recent years. Therapy with engineered T cells has also demonstrated remarkable tumor control and regression in human trials. Autologous cancer vaccines have recently demonstrated impressive prolongation of disease-free intervals and survival times in dogs with lymphoma [12].

As is the case in humans, there is a genetic predisposition in some animals, especially cats, dogs and horses, to develop allergic skin disease or atopic dermatitis in response to environmental allergens such as grass pollen, weeds, mold spores and house dust mites. So the most common treatment against atopic dermatitis is vaccination with an allergen extract to which the animal has been shown to react [13]. The science behind vaccines changed little until about 20 years ago when the first genetically engineered veterinary vaccines were developed and licensed. These vaccines were able to successfully control Aujeszky's disease in pigs [14]. Another example of a novel vaccine that is currently licensed is a vaccine that induces antibodies to gonadotropin releasing hormone to prevent the need to castrate male pigs [15].

One characteristic of veterinary vaccination is the DIVA ("differentiating infected from vaccinated animals") approach. The DIVA strategy is especially interesting for regulated control of diseases like foot-and-mouth disease, infectious bovine rhinotracheitis, pseudorabies and classical swine fever [16]. The first DIVA vaccines were known as marker vaccines. The term DIVA vaccine was coined in 1999 and the accompanying diagnostic tests were developed by J.T. van Oirschot [17]. Control or even eradication of viruses can be facilitated by a combination of vaccination and culling of persistently infected (PI) animals. PI animals represent the main source of virus in the field and their identification and elimination is the most important issue [18].

Differentiating infected from vaccinated animal tests work by testing for specific antigens which are present in the disease agent but not present in the vaccine. For instance, DIVA tests for FMD are being developed that detect proteins produced only in infected animals and not by vaccinated animals. In the DIVA vaccines for infectious bovine rhinotreicheitis (IBR) and Aujeszky's disease, a gene segment has been deleted in the vaccine virus. During testing, detection of this segment implies the animal was infected and not vaccinated. DIVA vaccines have also been developed that contain a 'marker' which is not present in the disease agent [19]. Nevertheless, conventional vaccines have reduced the prevalence of disease in enzootic areas; vaccination was used to reduce the spread of the disease, although the vaccinated were subsequently slaughtered to enable the rapid reestablishment of the FMD-free status of the country [20].

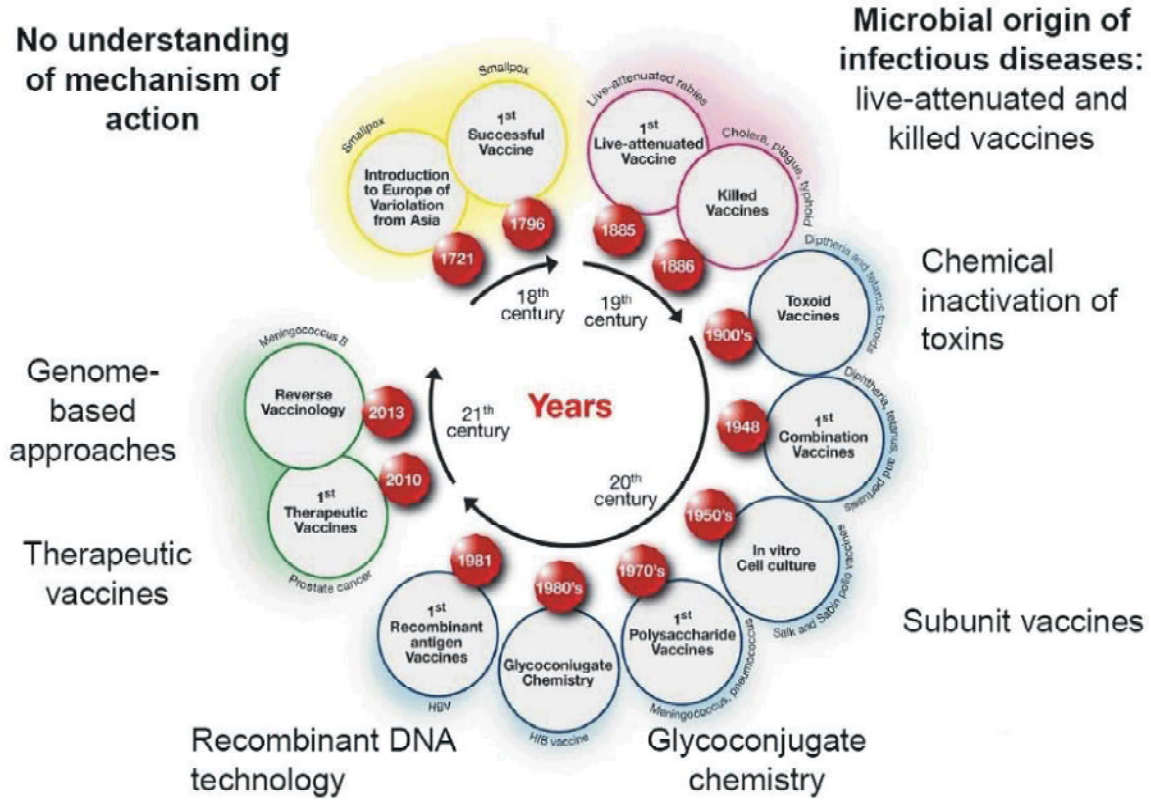

Fig. 1: History of vaccine development [24]

Vaccine Production, Types and its Components

Vaccine Production: The development of a new vaccine to the point of application for licensure is a complex, arduous and expensive process involving both public and private sector participants [21]. Vaccine development has become much more sophisticated with immunologists working closely with molecular biologists and chemical engineers to design and produce highly purified vaccines that are safe, consistently manufactured and effective [22].

Rational vaccine design depends on an understanding of the pathogenicity of the disease agent and of the host immunological response [23]. Generation of the antigen or identification of the causative organism is only the first step. The pathogenesis of the infection (how the organism produces the disease), what components of the organism are responsible for the manifestations of the disease (infectivity, virulence, pathogenicity) and which determine subsequent immunity and whether current techniques can be anticipated to produce a safe and effective immunizing agent all represent crucial questions [21].

Release and isolation of the antigen when once the production strain for each vaccine components has been selected, bulk vaccine production can begin [25]. The most basic technical requirement is the ability to consistently produce the organism (maintaining its immunogenicity) in the laboratory in sufficient quantities for study and, ultimately, for vaccine production. A reliable means must be found to measure immunity without exposure to disease [21].

Several of the newer approaches to vaccine development were reviewed including DNA vaccines [26], vaccines based on antigens expressed in viral vectors [27] and those developed through a process known as reverse vaccinology [28]. Interest continues in the use of transgenic animals and plants for the production of therapeutic agents and vaccines. Plant-based bioreactor systems offer several potential advantages over other production methods, with relatively low costs of cultivation, scale up and maintenance for vaccine manufacture. It is also suggested that the production of edible subunit-based recombinant vaccine proteins in the leaves, seeds or fruits would allow products to be easily stored and transported with limited refrigeration and would provide a means of oral administration that would need less effort and reduce the required technical training of medical and veterinary personnel [29].

Transport, Storage and Handling of Vaccines: After production, to properly preserve, store, handle, ship and deliver vaccine supplies, it is fundamental to maintain cold chain from the manufacturer to the point of use, keeping temperatures within a precise range of values and avoiding temperature excursions or fluctuations. Vaccines need, indeed, to be stored within a safe zone, namely, between 2 and 8°C, otherwise their quality is compromised and their potency cannot be restored [30]. Proper transport, storage and handling of vaccines are issues that are frequently overlooked when creating or implementing vaccine protocols. Between the time a vaccine leaves the manufacturer's plant and the time it is injected into an animal, there are many opportunities for inadvertent contamination or inactivation. By being aware of these potential "weak points" in a vaccine protocol, technicians can help ensure that vaccines are not rendered ineffective because of improper handling [31].

Vaccines are frequently transported in large animal practices and in small animal house-call practices. The cold chain must be maintained during transport. Vaccines should be kept in an insulated cooler. The temperature in the cooler should be monitored and logged immediately before and after transport. A layer of insulation should be tucked between the vaccine box and the ice packs to prevent direct contact, which could result in freezing temperatures in the vaccine vial. The cooler should be kept in the passenger cabin of the vehicle; temperatures in a trunk or truck bed could get too hot in summer or too cold in winter [32].

For lyophilized vaccines, only the diluent that is provided with the vaccine should be used [33]. Generally, diluents do not need to be refrigerated, but it is usually more convenient to keep them in the refrigerator with their corresponding vaccines. A new, sterile syringe and needle should always be used for drawing up and administering a vaccine. Vaccines should not be reconstituted or drawn up into the syringe until needed. Not only may the reconstituted vaccine be more temperature sensitive than the non-reconstituted vaccine, but there is also a risk of bacterial contamination and overgrowth if the syringe is left for a prolonged period. In addition, there is a risk of "mistaken identity" because many vaccines look similar in the syringe [34].

Challenges in Vaccine Production: A disadvantage of veterinary vaccines is that the potential financial returns are much less than for human vaccines. Veterinary vaccines have lower sales prices and smaller potential market value. Consequently, there is a lower investment in research and development for animal vaccines than human vaccines, although the range of hosts and pathogens are greater [5]. However, a number of pitfalls and challenges should be properly recognized to be addressed by future research. Moreover, some algorithms underlying novel data streams need to be refined in that, sometimes, do not exactly predict epidemic outbreaks [35].

Challenges to the introduction of a new vaccine: collection of sufficient information to allow national decision makers to make a rational decision on whether or not to support introduction of the new vaccine generation of acceptance by the population at whom the vaccine is targeted that the vaccine is safe and effective, practical issues related to introduction of the new vaccine into the routine immunization programme, financing introduction of the new vaccine [36]. New vaccines are generally more complex than the ones used in previous immunization programmes, more difficult to manufacture and hence more expensive. Vaccines costing $40–$50 a dose will not be used in developing countries. To facilitate the introduction of new vaccines in poor countries, GAVI subsidizes their cost in countries with an average national income of less than $1000, covering the difference between the contribution from the national vaccination programme and the costs charged by the manufacturer [37].

Up on Kaufmann *et al.* [38] result, a range of factors that can explain the shortcomings in vaccine delivery in developing countries: major disconnects between the overseas supply chain and the in-country supply chain, lack of coordination between procurement organizations and supply chain managers, insufficient storage and delivery capacity when large volumes of new vaccines are added to supplies of existing regimens; inadequate infrastructure for transport; poor maintenance of shipment and storage materials. Additionally, insufficiently trained staff and lack of career prospects for health professionals and funds for immunization activities at district level, failure to track available data on district immunization coverage and vaccine stock levels [39].

Types of Vaccines

Live-Attenuated Vaccines: Live attenuated vaccines are created by passage of viruses or bacteria in an unnatural host or cell. After multiple passages of the virus or bacterial strain in various media, the strain is administered to the natural host in the hope that random mutation has delivered a non-virulent and replicative infectious agent [40]. However, the strains that are present in most of the existing live attenuated bacterial vaccines are not highly protective. In addition, they have many drawbacks. For example, they cause local inflammation and other

unwanted reactions and they can revert to virulence [41]. Additional issues include the inability to effectively culture the bacteria or virus, the possibility of inducing an autoimmune response and the need for refrigerated storage. As the live attenuated organism can still infect target cells, these vaccines can replicate and induce both cellular and humoral immunity and, generally, do not require an adjuvant to be effective [42].

The reverse vaccinology approach to vaccine design can create recombinant vaccines that are generally safer and more immunologically defined than the traditional live-attenuated vaccines [24]. Therefore, this approach represents a viable strategy by which some of the drawbacks associated with live-attenuated vaccines can be overcome [43].

Inactivated Vaccines: Inactivated vaccines currently consist of bacterins of one or more bacterial species or serotypes, or killed viral strains formulated most often in an oil or aluminum hydroxide adjuvant [40]. Inactivated vaccines offer improved safety profiles but cannot provide effective long-term protection due to the destruction of the pathogen replication [44]. A large number of viral infections are caused by viruses that have multiple serotypes (e.g., bluetongue virus and influenza viruses). As a consequence, many of the existing viral vaccines are often unable to cope with the prevailing strains in the field and new vaccines have to be generated from field strains in response to new outbreaks [40]. Killed/inactivated vaccines are typically safer; however, they may be less effective than attenuated vaccines [45].

Toxoids: Vaccination is the best preventive measure available to control the diseases caused by bacterial toxins. The vaccines that are currently commercially produced consist of inactivated native toxins (toxoids) combined with conventional adjuvants, which, although efficient, present some production limitations. For example, the amount of toxin produced in vitro is unpredictable and some of the toxins are potent biological toxins that require high levels of biosafety [46]. The use of recombinant vaccines can overcome these limitations, since they can be produced efficiently in large amounts and usually present low reactogenicity and toxicity. As such, they represent promising alternatives to the current commercial vaccines. For example, the production of recombinant Escherichia coli toxins takes only 2-3 days using simple growth media and formaldehyde for inactivation. This production method does not require many biosafety precautions because the toxic domain of the protein can be removed [47].

Subunit Vaccines: Subunit vaccines contain short, specific proteins of a pathogen that are non-infectious because they lack the ability to replicate in the host. Protective antigens allow recombinant vaccines to be administered as safe, non-replicating vaccines. Cloning the gene coding for the antigen is often necessary to better characterize and produce the identified antigen. E. coli has been used extensively as a host for heterologous protein expression; however, this approach has some limitations relating to the yield, folding and post translational modifications of the recombinant protein [48].

An alternative host to *E. coli* is the methylotrophic yeast, Pichiapastoris. This yeast strain has emerged as a powerful and inexpensive expression system for the heterologous production of recombinant proteins that facilitates genetic modifications, allows the secretion of expressed proteins, permits post translational modifications and produces a high yield [49]. By incorporating more than one protein into a subunit vaccine, it is possible to invoke immunity to more than one strain or serotype of a bacteria or virus pathogen. The potential drawbacks of subunit vaccines are they offer only a moderate level of immunogenicity and require adjutants to generate robust immune responses [50].

Vectored Vaccines: The use of antigen/gene delivery systems has facilitated the development of novel prophylactic and therapeutic vaccine candidates. Vector vaccine technology uses a vector to deliver protective protein(s) to the immune system of the vaccinated host. These vectors are usually immunogenic and can display multiple antigens. Classical live vectors are attenuated bacteria or viruses that, in addition to inducing their own natural immunity, can also be used as carriers to express the immunogenic antigens of other pathogens. Poxviruses, which include the vaccinia, fowl pox and canary pox viruses, have been successfully used as vectors for exogenous genes [43]. The use of plants to produce and deliver immunogenic antigens via food sources is highly beneficial. The use of transgenic plants represents an innovative development that has opened new avenues in the vaccine industries. In veterinary vaccinology, transgenic plants can produce and deliver immunogenic antigens via animal feed [51].

DNA and RNA Vaccines: DNA vaccines induce antigen production in the host itself. DNA (or RNA) vaccine can be defined as a plasmid that contains a viral, bacterial, or parasite gene that can be expressed in mammalian cells or a gene encoding a mammalian protein

(non-infectious diseases). The gene of interest is inserted into a plasmid along with appropriate genetic elements such as strong eukaryotic promoters for transcriptional control, a polyadenylation signal sequence for stable and effective translation and a bacterial origin of replication. The plasmid is transfected into host cells and transcribed into mRNA, which is subsequently translated, resulting in the host cellular machinery producing an antigenic protein. The host immune system recognizes the expressed proteins as foreign and this can lead to the development of a cellular and humoral immune response [52].

Immunization of animals with naked DNA encoding protective viral antigens would, in many ways, represent an ideal procedure for viral vaccines because it not only overcomes the safety concerns associated with live vaccines and vector immunity but also promotes the induction of cytotoxic T cells after intracellular expression of the antigens [40].

Excipients (Components) in Vaccine: Beside the active vaccine itself, the excipients and residual manufacturing compounds are present or may be present in vaccine preparations. Chemicals commonly used in the production of vaccines include a suspending fluid (sterile water, saline, or fluids containing protein); preservatives and stabilizers (for example, albumin, phenols and glycine); and adjuvants or enhancers that help improve the vaccine's effectiveness. Aluminum salts or gels are added as adjuvants. Adjuvants are added to promote an earlier, more potent response and more persistent immune response to the vaccine; they allow for a lower vaccine dosage. Antibiotics are added to some vaccines to prevent the growth of bacteria during production and storage of the vaccine. Formaldehyde is used to inactivate bacterial products for toxoid vaccines. Formaldehyde is also used to inactivate unwanted viruses and kill bacteria that might contaminate the vaccine during production [53].

An adjuvant is defined as any compound that enhances the immune response against a vaccine antigen. The word ‘adjuvant’ comes from the Latin word ‘adjuvare’, means ‘help’ or ‘to enhance’, can be defined as any product or association of components that increases or modulates the humoral or cellular immune response against an antigen. In many cases, the antigen itself is very weakly immunogenic; therefore, an adjuvant is needed to intensify the immune response [54]. Thus, there are two distinct reasons to incorporate an adjuvant into a vaccine. First as adjuvants are currently used clinically to increase the response to a vaccine in the general population, increasing mean antibody titres and/or the fraction of subjects that become protectively immunized. The second reason is to achieve qualitative alteration of the immune response. For vaccines currently under development, adjuvants are increasingly used to promote types of immunity not effectively generated by the non-adjuvanted antigens [55].

Immunization in Animals

Routes of Immunization: Vaccines have traditionally been administered via intramuscular or subcutaneous injection. Administration of vaccine onto mucosal surfaces such as those in nasal passages, eyes, lungs and the gastrointestinal tract is an effective way of inducing mucosal immunity. It is important to emphasise that all mucosal sites are interconnected by a common mucosal immune system and that the administration of protective antigens at one primary site will stimulate antigen-specific lymphocytes which migrate and provide immunity at other mucosal sites, regardless of the site of induction [56]. Immunization via some of the routes favours the accumulation of effectors cells in certain compartments. For example, oral vaccination results in strongest immunity in the small intestinal tract, The observation that the various compartments of the mucosal immune system are in permanent contact with each other resulted in a wide variety of possible routes of immunization including oral, intranasal, rectal, vaginal and intraocular [57].

Recent developments in vaccine delivery have drawn on advances in nanotechnology and microencapsulation. Nano-vesicle technology is also suitable for a variety of non-parenteral routes of administration and has the additional benefit of helping to boost the host response to the vaccine [58].

Mechanism of Vaccine to Induce Active Immunity: The most effective licensed vaccines elicit long-term antigen-specific antibody responses by plasma cells in addition to the development of persisting T cell and B cell memory [59]. T lymphocytes play a central role in the generation of a protective immune response in many microbial infections. After immunization, dendritic cells take up microbial antigens and traffic to draining lymph nodes where they present processed antigens to naïve T cells. These naïve T cells are stimulated to proliferate and differentiate into effector and memory T cells. Activated, effector and memory T cells provide B cell help in the lymph nodes and traffic to sites of infection where they secrete anti-microbial cytokines and kill infected cells [60].

Antibody production is an efficient method used by the immune system to control many pathogens, including bacteria, toxins, as a memory response to many viruses. The presence or absence of antibodies in serum is frequently used to evaluate either exposure to a pathogen or evaluation of a response to a vaccine [61]. Memory cells confer immediate protection and generate secondary responses that are more rapid and of higher magnitude as compared to primary responses. In the B cell system, immediate protection is mediated by long-lived plasma cells that are present in the bone marrow and secrete antibodies in an antigen-independent fashion, thus maintaining constant amounts in serum and body fluids [62]; recall responses are mediated by memory B cells that rapidly proliferate and differentiate in response to antigenic stimulation generating a burst of plasma cells and a marked but transient elevation in serum antibodies [63].

Veterinary Vaccines on One Health Concern: The term 'One Medicine' was coined by Schwabe (1984) and focuses attention on the commonality of human and animal health. Schwabe states that there is no difference in paradigm between human and veterinary medicine and that both medicines have the same scientific foundations [64].

Domestic livestock, wildlife and humans share many similar pathogens. Pathogens of wild or domestic animal origin that can cause infections in humans are known as zoonotic organisms and the converse are termed as anthroponotic organisms. Seventy-seven percent of livestock pathogens and 91% of domestic carnivore pathogens are known to infect multiple hosts, including wildlife. Additionally, understanding wildlife and their role is a vital part of understanding the epidemiology and ecology of diseases. To do this, a multi-faceted approach combining capacity building and training, wildlife disease surveillance, wildlife–livestock interface and disease ecology studies, data and information sharing and outbreak investigation are needed [65].

How can we benefit most from 'One health'? Firstly, through the broad implications of closer cooperation between human and animal health sectors and recognising the linkages among humans, animals and the environment, Secondly, mainstreaming a 'One Health' approach should lead to better health for humans and animals and financial savings to society from such a closer cooperation between the sectors which could not be obtained if they worked in separation [66]. A key goal of the evolving One Health paradigm includes surveillance of infectious diseases in domestic and wild animals to anticipate emergence of new zoonoses and protect humans. To achieve this goal, it is essential that global resources be allocated for more effective disease surveillance and reporting schemes that incorporate environmental, human and veterinary health professionals [67].

Control of Zoonotic Diseases: Zoonoses is the word derived from Greek word "zoo" means animals and "noses" means diseases, the term coined and first used by Rudolf Wirchow who defined it for communicable diseases [68]. Zoonosis can be defined as transmission of disease between human and animals that happens due to interaction between these two populations. Zoonosis not only interrupts human health but it also affects wild life and livestock industry. Recently, more than 65% of emerging infectious diseases in humans have been reported to originate from zoonotic pathogens [69]. Zoonotic diseases can be divided into two categories depending on their mode of transmission. Vector-borne zoonotic infection is transmitted to humans via arthropods carrier and non-vector-borne diseases are transferred by contaminated food or direct contact [70].

Rabies is a fatal viral disease that affects all mammals including humans. Domestic dog is the main source of rabies for humans and livestock in developing countries [71]. Vaccines to control zoonotic diseases in food animals, companion animals and even wildlife have had a major impact on reducing the incidence of zoonotic diseases in people. When used optimally, vaccines prevent disease manifestations, reduce transmission of disease, decrease the need for pharmaceutical intervention and improve the health and welfare of animals, as well as indirectly protecting against zoonotic diseases of people [72].

Efficient Food Production: Veterinary vaccines are used in livestock and poultry to maintain animal health and to improve overall production. More efficient animal production and better access to high-quality protein are essential to feed the growing population. Vaccines that preserve animal health and improve production are important components in meeting this need [73]. Emerging and exotic animal diseases are a growing threat to human and animal health and jeopardize food security [74].

Control of Emerging and Re-Emerging Diseases: Two major categories of emerging infections-newly emerging and re-emerging infectious diseases-can be

defined, respectively, as diseases that are recognized in the human host for the first time; and diseases that historically have infected humans, but continue to appear in new locations or in drug-resistant forms, or that reappear after apparent control or elimination [75]. Facts and factors which have favoured the re-emergence of zoonotic pathogens in the last decades are as follows: increasing human population expanding into new area, a change in the behaviour of humans, including frequent and long-distance travel, globalisation of trade (for animal products), movement of wild and domestic animals over long distances, climate change that has allowed pathogens and vectors to survive in new areas [6]. Rapid development of animal vaccines can play a key role in controlling emerging diseases [5].

Reduction of Need of Antibiotics and Antibiotics Resistance: Increasingly widespread antimicrobial resistance among zoonotic bacteria is illustrating the limitations of antibiotic treatments in animals and effective vaccination of animals against zoonotic diseases caused by bacteria may help to solve the problem [6]. Antibiotic misuse in lower- and middle-income countries (LMICs) contributes to the development of antibiotic resistance that can disseminate globally. Strategies specific to LMICs that seek to reduce antibiotic misuse by humans, but simultaneously improve antibiotic access, have been proposed. However, most approaches to date have not considered the growing impact of animal and environmental reservoirs of antibiotic resistance, which threaten to exacerbate the antibiotic resistance crisis in LMICs [76].

Vaccines are a key component in the fight against anti-biotic resistance both directly and indirectly. By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics. However, even vaccines create against non-bacterial pathogens can also have an indirect effect on pathogenic bacteria by reducing complications associated to super infections that routinely require anti-biotic use [77]. Vaccines also contribute to the reduction of antibiotic usage through the establishment of herd immunity by halting. The levels of transmission of pathogenic bacteria to potentially susceptible individuals and therefore limiting the numbers of infections in the overall population [78, 79].

There is a growing appreciation for the role of vaccines in confronting the problem of antimicrobial resistance (AMR). Vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use and can reduce its impact by reducing the total number of cases. By reducing the number of pathogens that may be responsible for a particular clinical syndrome, vaccines can permit the use of narrower-spectrum antibiotics for empirical therapy. Any resistant infection prevented by vaccination is a case for which, by definition, the burden of AMR disease is reduced, the need for antibiotic therapy is eliminated and the risk of poor outcomes is avoided [80]. Veterinary vaccines reduce the need for antibiotics to treat infections in food producing and companion animals. There are increasing concerns related to antibiotic resistance associated with the extensive use of antibiotics in veterinary and human medicine [81]. Affordable and available vaccines reduce reliance on antibiotics for animal health [5].

Food Safety Vaccines: Keeping the costs of animal vaccines low will encourage more use of vaccines and less use of antibiotics. It will also enable the use of food safety vaccines that do not have an economic advantage for the producer or health advantage to the animal, but have important public health benefits [5]. Animal based protein consumption in LMICs is rapidly increasing due to economic development and intensive animal production systems are proliferating to meet these demands [82]. To meet with the increasing demand for food, the scale of world food production is increasing, as is the transport of animals and food products. At the same time, the contact of animals with the environment remains unchanged or, in the case of free-ranging animals, is even increasing. A number of microorganisms have established themselves in farmed animals, which although relatively harmless to animals are pathogenic to man [6].

Global food security will require the production of more food using resources including land more efficiently and with less waste. A significant proportion of diseases affect the safety of food supplies, in addition to or instead of, their effect on volume and quality of food products. Parasitological diseases including those caused by nematodes, trematodes, protozoa and ectoparasites, have widely differing effects on meat, milk and fibre production and many new technologies have been developed in order to prevent or treat them. Approaches to developing better control of parasites have included livestock breeding strategies, improved nutrition and management and the development of new drugs, diagnostic tests and vaccines [83]. Recently, vaccines have been developed to reduce the shedding of organisms that cause food borne diseases in people. Vaccines for E coli O157:H7 in cattle and Salmonella enteritidis in chickens are available. These vaccines typically do not improve the health of the

vaccinated animal, but they reduce the shedding of pathogens that may contaminate animal products for human consumption [5].

Control of Diseases of Companion Animals: The One Health paradigm for global health recognizes that most new human infectious diseases will emerge from animal reservoirs. Companion animals have been domesticated by humans and kept primarily for social benefit (i.e., companionship, showing) or utilitarian purposes (i.e., hunting, military, or police activity; support for blind or deaf persons; guarding; and herding). They might be bred or wild caught with the intention of keeping them in the domestic environment. In some cultures, certain companion animal species also provide a food source [84]. There is a spectrum of infectious diseases of dogs and cats that are shared by humans. Many of these are true zoonoses spread by direct contact between the species and others are vector-transmitted (e.g., fleas, ticks, flies and mosquitoes) diseases for which cats and dogs might act as reservoirs for the pathogen. Reverse zoonoses also occur in which disease is transmitted from the human reservoir to the dog or cat; the most contemporary examples are methicillin-resistant Staphylococcus aureus [85]. Vaccines for diseases of companion animals and horses have greatly enhanced the ability to keep animals in the household and to own horses. The human-animal bond that develops enriches the lives of both the animals and the people [5].

CONCLUSIONS AND RECOMMENDATION

Veterinary Vaccines are a group of biologics or biological preparations which provides long last acquired active immunity for a particular disease and considered to be the lifeline of the animal. The major goals of veterinary vaccines are to improve the health and welfare of companion animals, increase production of livestock in a cost-effective manner and prevent animal-to-human transmission from both domestic animals and wildlife. Due to the contemporary human–animal relationship is complex and profound, ranging from exploitation of livestock for food and international trade in animal species create interfaces between animals and humans, which lead in some instances, to disease emergence. 'One Health' concept of co-ordinated activity of those involved in human and animal health is cooperate with clinicians, researchers, agencies and governments working together for the benefit of domestic and wild animal and human health and the global environment. Based on above conclusions, the following recommendations are forwarded: As veterinary vaccines play a numerous role beyond animal health, hence it is crucial to check that individuals take delivery of the vaccine as per vaccine schedule. Governmental financial sponsorship (push and pull mechanisms) should be requisite due to potential financial returns are much less in veterinary vaccine and it resulted in lower investment in research and development for animal vaccines. Because of bounder-less interaction between animals and human, co-ordinated activity of government, human and animal health professionals should effort together for the benefit of animal and human health on “one world, one health principle”.

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