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Editorial

From the first to the latest vaccines in Veterinary Medicine

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The branch of Immunology dealing with the investigation and development of vaccines is called Vaccinology. This latter is actually an eminently practical tool strongly related, not only to Human Medicine but also to Veterinary Medicine. Its interest relies mainly upon the usefulness of vaccines in the prevention and control of infectious diseases. In addition, the latest vaccines, developed according to the newest advanced technologies, allow their use also for the treatment of different disorders, for instance, against allergic diseases and neoplastic processes [1]. Even so, some of them, such as allergy vaccines, which are based usually on natural allergen extracts, often have a low efficacy nowadays [2].

As in human diseases, vaccination has become the cheapest and most effective method in controlling animal infectious diseases and, sometimes, the only one in case of being viral diseases. A major role in the development of modern livestock farming has been assigned to vaccines, because these products clearly improve the animal health and efficiency and have a significant impact for the Public Health in the case of the protection against diseases being common to humans and animals (zoonoses). Moreover, vaccines minimize the use of hormones and drugs as antibiotics, as well as the presence of residues, thus latter being one of the main highlight topics at present. Even it can be emphasized the fact that vaccines can aid in animal welfare because their application does not cause great controversies, to such an extent that animal welfare organisations all support this practice.

Vaccinology is going through a stage of large achievements in all fields, as a result of the implementation of Biotechnology and of the knowledge arisen from Bioinformatics, Genomics, Immunology, Microbiology and Molecular Biology. From these sciences, innovative concepts such as genetic vaccines (DNA and RNA) reverse vaccinology or recombinant subunit and non-replicant viral vectors among others have been derived. These new approaches attain unknown areas until

recently, both in human and animal medicines, as for instance allergies, cancer, chronic diseases, emerging or re-emerging infectious diseases.

From an economic point of view, the global market of vaccines covering products against all kind of species has been boosted especially in food producer domestic animals because of the increasing interests in food safety and zoonotic diseases, this latter area currently accounting for more than 58% of all human infectious diseases. Based on an annual growth expectation of 8.8% in market values for vaccines, an expenditure is estimated to be around 19 billion dollars in 2019, an amount which is increased until 22 billion dollars according to some calculations. The worldwide market of animal vaccines is so important that constitutes about a quarter of global intake in Animal Health.

During most of the 20th century, vaccine production followed the guidelines given by Pasteur at the end of the previous century, based on the isolation and characterization of the organism. However, the emergence of the recombinant DNA technology, the chemical conjugation of proteins and polysaccharides, and the novel adjuvants have involved a major advance in the development of vaccines. Genetic engineering allows to isolate and modify organism genomes in order to achieve more and more accurate antigens capable of increasing the efficacy and safety of vaccines while, at the same time, enables their industrial production. In addition, progress made in Basic Microbiology, Parasitology, Genetics, Immunology and Bioinformatics during the last decades allows for novel designs to be used against infectious or parasitic diseases as well as against reproduction disorders or chronic tumour diseases. An additional revulsive derives from the -omic techniques (mainly Genomics, Proteomics and Transcriptomics), which have become key tools also in the development of newer vaccines. From the point of view of Vaccinology, the entire bacterial genome is a great gene reservoir codifying possible antigens that can be selected and then tested as vaccine candidates. Genome sequencing of pathogen organisms, which was begun in 1995 with that of *Glässerella parasuis* [3], covers at present more than 100,000 organisms, many of which are of veterinary concern and many more are being sequenced all over the world, in such a way that most of the pathogens being important for animal health are included.

Both the recombinant and the chimerical viruses are the result of a manipulation of the viral genome. The name “recombinant virus” is reserved for a genetically modified virus (with the purpose of being used as vector that expresses a subunit gene or a interesting antigen previously inserted on it, such for instance Baculovirus, Adenovirus, Poxvirus or Herpesvirus) that carries inserted gene sequences from other viral or non-viral species. As main advantages, a faint infection, with the induction of an immune response to the expression product of the interesting gene from the pathogen organism [4] can be observed, but also the recombinant vector is critical for the antigen presentation to the antigen-presenting cells, and the subsequent induction of the immune system [5].

Currently, there is a great number of vaccines bases on DNA viral vectors, such as Poxvirus and Herpesvirus mainly, already enabled for their commercialization [6]. Among other viral vectores already evaluated or in evaluation process, based on RNA viruses, Venezuelan equine encephalitis, Newcastle disease or feline foaming viruses, or other DNA viruses, including Adenovirus, Herpesvirus and Poxvirus, can be cited. Avian smallpox and canrypox viruses have been mainly used as vector in the expression of vaccine proteins to equine influenza and feline leukemia viruses [7,8], while turkey herpesvirus has been used to Gumboro disease and human adenoviruses and deficient replicant viruses to foot-and-mouth diseas vaccines [9].

Genome sequencing and in silico analysis are essential for the selection of suitable genes. When sequencing is concluded, potential open reading frames (ORFs) are identified and used for the search in databases of homologies with genes having a known function in other organisms. Thus, respective functions are adscribed to the ORFs and then bioinformatic study allows to allocate a function to each gene. In this sense, softwares as BLAST [10], enable the study of virulence genes and predict key data, such as cell location, molecular weight, topology, isoelectric point or solubility.

Cell location is one of the first conditions for a particular protein is considered a suitable antigen. In fact, the proteins being only present into bacterial cytoplasm are not good targets while, by contrast, those being secreted of associated to surface are more accessible to antibdoy binding and are therefore regarded as potential targets for immune system. Several bioinformatic methods (InterPro Scan, SignalP 3.0 or Prediction Protein) are available nowadays in order to study secreted or surface-associated proteins.

An "ideal vaccine" is that capable of inducing an effective and long-lasting immunity against to the greatest number of organisms possible, of an easy administration, which is not affected by maternal antibodies and does not give rise to carrier animals. In addition it must be capable of enabling the differentiation between vaccinated and infected animals, also allowing a collective therapy [11]. It must be recognised that the goal of an ideal vaccine has not been achieved in all these aspects until now and the use of a certain vaccine is sometimes conducted without an enough knowledge about the pathological pattern and the immune response developed by the host. When vaccines are destined to production animals, they must also be inexpensive, stable, suitable for mass vaccination and capable of inducing an immune response allowing its differentiation from that triggers by natural infection, thus affording its use both in control and eradication of animal diseases. Furthermore, a vaccine must be developed in such a way that the antigen can be released effectively in order to the antigen-presenting cells can digest it and secrete cytokines. In addition, a vaccine must boost both B and T cells and generate a great amount of memory cells. It must also boost Th and effector cells so the individual variations in the CMH-II polymorphisms are minimized.

As main problems, variability in immunogenicity, along with the biodiversity due to the variety of species, breeds and categories of animales to which vaccines are addressed, represent well-known aspects that impair the induction of a common immunity and therefore account for vaccine failures. As other factors, those directly depending on the organism, such as infective dose, virulence degree, environmental stability, mutation rate, can also influence the vaccine successful. On the other hand, pathogenesis can vary according to the host, the prevalence of a given disease in a specific geographical area and the epidemiology of the different serovars implied in it, also hampering vaccination programmes. National and economic differences in regulatory standards, for instance, the ban of vaccines to a particular disease, as happens for foot-and-mouth disease or classical swine fever, or the restriction of vaccines available in control programmes, can even increase the complexity in the choice of vaccine type and usage in animals.

Moreover, it should be considered that some organisms compromise several animal species but only a limited number of vaccines can be administered to more than one; in this respect, most of vaccines are manufactured against both a certain disease and a given species. There are different usage patterns and routes of administration depending on management system, the conditions of animal housing, age, sex, breed susceptibility and species towards which vaccine are directed [12]. Because of the scarce cross-protection between strains and the large variety of organisms causing disease in each animal species, the formulation of mixed vaccines becomes essential, containing

more than an immunogen belonging to a defined organism or to several different pathogens. The amount of immunogens included in a multiple vaccine need to be given careful consideration because the more components are combined in a single dose, the more likely that interferences among them occur [13].

In the very young animals, vaccination raises specific problems. For instance, maternal antibodies protect the offspring during the first weeks of life, blocking the immune response induced against vaccines. For this reason, it is necessary to know the drop in antibody curve (that in animals with epitheliochorial placenta is about two months old) for ascertaining the optimal vaccination time. Because of that, a common strategy is to vaccinate pregnant mothers so that colostral antibodies protect newborn animals; however, it is not always the case because in some vaccines there is no interference (for instance, with *Glässerella parasuis*). The duration of immunity and boosters become critical points in vaccination programmes in companion and producing animals [14].

In the case of food producing animals, vaccination protocols can vary according to the farm depending on helath state, management system, location, medical history, geographical spread of usual pathogens and other epidemiologic circumstances. However, the concept of particular patient is used with pets and vaccination is carried out as completely layered calendars with variations in accordance with the type of vaccine to be applied, when the supply of products is diverse. In some production species, such as poultry or pigs, there are standardized vaccinations schedules, which are occasionally modified if there are health alerts because of the emergence of not routinely regarded diseases.

Conventional or classic vacines are grouped in two main types: live attenuated and killed attenuated vaccines (or bacterins). The first ones prevent the disease when organisms replicate in the host without causing the virulent disorder or develop a faint disorder, easily overcame by the defenses of animal. Only one inoculation is often enough to boost an effective immune response. However, killed vaccines are gotten after the inactivation of the vaccine organism, although it preserves its immunogenic properties. In these cases, immunity adjuvants incorporated at two doses often separated two or three weeks are usually necessary. In Veterinary Medicine, a very used type of vaccines, derived from the use of killed vaccines. They are autogenous vaccines or autovaccines, which were managed from isolates obtained from a given herd, previously identified and characterized for a sole use in this herd. Its efectiveness has been proven in many disorders, such for instance those caused by *Staphylococcus* and *Streptococcus* genera or by *Escherichia coli*.

Concerning the lastest and most modern vaccines, as it has been already cited above, several forms have been developed. As a consequence of the insight of the immune response and the molecular biology techniques, a lot of protein antigens causing a protective response were identified at the middle of the past century. So, subunit vaccines were manufactured and they were formulated on the basis of antigen subunits including different nature molecules such as lipoproteins, proteins, polysaccharides, proteins, polysaccharides, mixtures of polysaccharides and proteins, microbial fractions, toxoides…, coming from natural preparations or purified by means of biotechnological action. These vaccines mean the first significant innovation in veterinary vaccinology field. As advantages of vaccine subunits over the attenuated live or the inactivated vaccines, is the capacity to induce a strong humoral immune response, but the cellular response is poor altough it can be improved by using adjuvants. In addition, they are safe and can be used along with other subunit vaccines, although their effectiveness depends on the protective immunity. On the other hand,

subunit vaccines can be expensive to produce and can require the use of adjuvants to boost the immune response.

Other kind of vaccines obtained from crude or purified products (toxins) containing antigens capable of inducing an protective immune response are toxoids or anatoxins. Good examples of toxoids are the toxins produced by some species of clostridia, as *Clostridium perfringens* type A, B, C and D, *C. septicum*, *C. chauvoei*, *C. sordelli*, *C. novyi* type D, *C. tetani*… In addition, the *Mannheymia haemolytica* leucotoxin, the *Actinobacillus pleuropneumoniae* Apx I, II and III and the dermonecrotic toxin *Pasteurella multocida* type D can be crude or purified subunits. In these cases, the usual lack of cellular immunogenicity makes necessary the addition of adjuvants, some of whose types can change the orientation of the immune response.

Other choice of production of animal vaccines involves the obtention of synthetic peptides (peptidic vaccines) including antigenic determinants of interest against animal pathogens. When these peptides have a smaller size than 15 amino acids, the conjugation with carrier proteins in the form of conjugated vaccines is advised. Among the wide variety of resources, liposomes, red blood cells… can be included. As examples of this type of vaccines, those against foot-and-mooth disease and classical swine fever can be listed.

DNA vaccines were implemented at the beginning of 90s thanks to the advances in. molecular biology. So, it can be proven that the injection of DNA sequences in animals triggers an immune response to the codifying protein [15,16]. This discover provided important advanges in relation the use of conventional live vaccines, because they are safer, allow to vaccinate against different antigens in a sole inoculation, are cheap and are not conditioned by the cool chain, althoug their effectiveness vary substantially according the methodology used. These vaccines are based in the use of bacterial plasmids codifying antigens being capable of inducing a specific immune response after its inoculation in the suitable hosts [17].

Conflict of interest

The authors declare no conflicts of interest in this article.

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