Standardization or tailorization of veterinary vaccines: a conscious endeavour against infectious disease of animals

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Summary. Protecting animals from infection is a major obligation of every veterinarian's work in order to preserve animal welfare while assuring human health. Highly infectious animal diseases can reduce the performances of food producing animals and may have a great economical impact on many industries. Some animal diseases can be transmitted to humans, and control of these types of diseases, is beneficial to public health. In the wild, animal populations reduced by disease can dramatically affect the ecological balance of an area. Vaccination is one part of an effective health program as it helps to prevent disease and, in most cases, is more cost-effective than treating sick animals. Veterinarians have succeeded in greatly reducing the incidence of important diseases by taking advantage from improved technologies in vaccines production and by planning vaccination schedules based on the different characteristics of available products. Today, veterinarians can recommend and plan to use vaccines designed for a specific herd or flock or class of animals and even for individual treatments.

Key words: vaccines, immunity, prevention, zoonoses.

Riassunto (Sviluppo e impiego consapevole dei vaccini veterinari nei confronti delle malattie infettive degli animali). I vaccini rappresentano uno strumento indispensabile per il controllo e l'eradicazione delle malattie infettive dell'uomo e degli animali. Di particolare rilievo risulta l'azione di prevenzione esplicata dalla vaccinazione degli animali nei confronti di devastanti malattie infettive del bestiame come afta, peste bovina, peste suina, blue tongue. Il pericolo di trasmissione all'uomo di zoonosi come la brucellosi e la rabbia è tenuto sotto controllo anche dalla vaccinazione degli animali. Il progresso delle conoscenze scientifiche e l'applicazione di moderne tecnologie hanno contribuito allo sviluppo di vaccini, saggi diagnostici e metodi di controllo e prevenzione sempre più sicuri ed efficaci. Di questi strumenti si avvale oggi, in maniera sempre più consapevole, il medico veterinario al fine di elaborare protocolli vaccinali da applicare per interventi di massa o per il trattamento individuale degli animali.

Parole chiave: vaccini, immunità, prevenzione, zoonosi.

VACCINES AND VACCINATION

Vaccines play an important role in the control of infectious diseases and in preventive health care programs for humans and animals. In particular, veterinary vaccines have been called the core products of animal health, and have contributed to the eradication or control of many of the most devastating diseases of livestock, poultry and pet animals, such as foot and mouth, rinderpest, classical swine fever, Newcastle disease, canine distemper and parvovirosis. In some instances, in the case of the use of flock specific vaccination to control established diseases, the amount of pharmaceutical treatments, such as antibiotics, can also be reduced. Moreover, veterinary vaccines are considered crucial tools in controlling infectious diseases such as brucellosis and rabies that can be transmitted from animals to man, and therefore, are of major concern for public health. The principle of vaccination has been established for more than two

hundred years. Early attempts to protect cattle from rinderpest using infected setons to prevent the disease, had started by Bernardo Ramazzini in 1711. By the end of that century, thin ropes wetted with nasal secretions from infected cattle were inserted in scissions made in the dewlap in order to induce a milder illness compared to the natural infection caused by rinderpest virus. Vaccination was the term firstly adopted by Edward Jenner for the process of inoculating humans with weakened or killed "immunogens" obtained from cowpox to prevent them from getting smallpox. In 1794 Jenner, provided the scientific demonstration that vaccination was an effective way of preventing smallpox. One hundred years later, Louis Pasteur who had built on his work on the basis of Jenner's one, adopted the name of vaccine as a generic term for the protective inoculation of any "immunogens" designed to stimulate an immune response to an infectious agent. By the end of 19th century, Pasteur

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had applied active immunization by using attenuated avian colera (whose causative agent has been designated Pasteurella from Pasteur's name) and anthrax cultures, and spinal cords from rabbits inoculated with rabies virus to actively immunize animals or humans against avian colera, anthrax and rabies. Since those early days, progress in the development of vaccines and in vaccination procedures have helped to prevent and in some cases eliminate diseases in humans, farm and companion animals. Although it was thought that mass eradication programs started after the World War II could have banished epidemics in humans and animals by the use of vaccines, infectious diseases remain a challenge. New diseases have emerged and old ones have reappeared. Moreover, these infections, more easily than in the past, can spread around the world favoured by factors such as the evolution of modern transportation and climatic conditions. In recent years, the biological and socio-economic impacts of animal diseases on human societies have had an extremely high profile, with the spread of diseases like BSE and foot and mouth among animal populations, as well as the transmission of diseases such as HIV, Ebola, SARS and Influenza from animal to humans. In human medicine, advanced technologies and new trend of modern vaccinology have greatly increased the role and the potential application of vaccines, such as in the case of anti-cancer and disease therapeuthic vaccines which are administered after the patient has already developed the disease. Historically, similar principles have been applied in veterinary vaccinology by manufacturing the so called autogenous/autologous (A/A) vaccines for animals.

PRELIMINARY REMARKS ON THE USE OF VACCINES IN ANIMALS

It should be recognized that "the perfect vaccine" has not been made yet, and that in general, the use of vaccines is variable, and using them without some specific knowledge of disease patterns and immunology makes their selection difficult. Whether these considerations are widely suspected as major causes for some reported deficiencies of human vaccines, they appear to be even more realistic as far as animals are concerned. Here, the accepted variability in the degree of immunogenicity, in addition to that unicum of biodiversities represented by the multiplicity of species, races, subpopulations and categories of animals, are factors largely acknowledged for the reduced capability of building a common immunity from vaccination, and explaining the reasons for vaccine failures frequently occurring among animals. Immunization is not a routine: the type of immune response that protects an animal against infectious diseases varies among pathogens and depends on the route of introduction and site of replication of those pathogens. Protection may result essentially from humoral (circulating antibodies) and cell-mediated immunity (sensitized T-lymphocytes). After the first exposure to an antigen, the cell-mediated immune system generally is actived in 4-6 days

whereas at least 14 days are necessary for an optimal response of the humoral immunity. The anamnestic response is the protective principle on which immunization is based: priming with and subsequent exposures to a specific antigen should result in a rapid and effective activation of the immune response mechanisms. In addition to these mechanisms, initial control of infection can be obtained by the immediate activation of the nonspecific immunity mediated by phagocytic cells such as granulocytes, macrophages, natural killer cells, and complement. This system is not directly affected by vaccination or previous exposure to an infectious agent. Vaccination performed through the same route of exposure and primary site of replication of a pathogen (intranasal administration of vaccines against respiratory infections) normally results in a faster and more effective stimulation of both systemic and local immunity.

THE ROLE OF THE VETERINARIAN

As veterinary medicine has advanced, prevention of disease has become a priority. Veterinarians have succeeded in greatly reducing the incidence of various infectious diseases by establishing vaccination protocols and educating animal owners and caretakers about the effective role of vaccines used under different health programs. A veterinarian who is familiar with the herd and the diseases in the area is the best counsel in making decisions concerning the use of vaccines. Vaccines should be used in accordance with principles of immunology to allow for maximum protection against disease. Factors that affect the immune response to vaccines should be considered prior to vaccine administration. Not all animals need every vaccine, and the complexity of the use of vaccines in the field is largely recognized. While vaccination of animals against diseases that occur very often is considered as a routine practice, there are others that may not warrant the expense of vaccination because the disease incidence in that herd and area may be very low. Vaccination protocols vary by farm and depend on general parameters such as the management system, the location of the farm, the consistency and history of the herd or of the flock, the geographic distribution of infectious agents most likely to be encountered. By contrast and whenever possible, vaccination of companion animals should be applied on an individual basis, and only for diseases for which there is an effective risk of exposure and disease.

GENERAL ASPECTS CONCERNING VACCINES AND THEIR USE

The multiplicity of target species, different husbandry conditions, the extension of the infected area, animal population density and the opportunity for exposure are among the most critical issues affecting risk of exposure to an infectious agent. Independent agentassociated variables, such as virulence, challenge dose, environmental stability, and mutation, influence

the outcome of infection but can be difficult to assess objectively. The pathogenesis of a specific microorganism may vary depending on the target species, as well as the prevalence of a disease in a geographical area and the epidemiology of different serotypes in different countries. Sometimes, the transient nature of diseases incidence, the agriculture-related economics and national differences in regulatory requirements (prohibition of the use of vaccination against a particular disease, such as foot and mouth and classical swine fever or limiting the type of vaccines used in vaccination programs to a particular strain or marker, such as gE-vaccines for Aujeszky disease and DIVA-Differentiating Infected from Vaccinated Animalsvaccines for avian influenza) increase the complexity in the choice and use of veterinary vaccines. A limited number of agents affect several species foot and mouth disease and rabies viruses, Clostridium, Leptospira and Brucella spp., Erysipelothrix rhusiopathiae. As a consequence, only a very limited number of vaccines can be administered to more than one species whereas different products tailored to a particular disease of each individual animal species represent the majority of customer needs. Moreover, different patterns of use (combined vaccines) and routes of administration depend on the management system, husbandry conditions, age, sex, breed susceptibility and category of the target animal species [1, 2]. Each antigen component of a vaccine is specific and cannot be substituted by any other antigen. The limited cross protection between strains, and the variety of pathogens causing diseases in each species, have resulted in the formulation of combination vaccines. Although it is possible to use the same vaccine formulation in several species, more often the formulation has to be specifically adapted for each target species. Number of antigens contained in multiple-antigens vaccines is a point for concern: the more components are combined in a single dose of vaccine, the more likely they are to interfere each others [3]. Vaccination and immunization of very young animals is also a specific problem. Maternal antibodies acquired through colostrum at birth protect animals during their early age but only last for a limited variable time and while present, can block the immune response to a vaccine. Determining the optimum time for vaccination of mother (potential risk of using vaccines in pregnant animals) and age for vaccination of offspring (the level of maternal antibodies should not interfere with the antigenic components of the vaccine) is of crucial importance in order to balance the risks and benefits inherent to both interventions. Onset, duration of immunity and revaccination are crucial points in assessing the validity of vaccination programs [4]. Protection cannot be expected until the immune response is complete (onset of immunity), and if the length of time between vaccination and exposure to an infectious agent has been longer than the protection afforded by the vaccine (duration of immunity). Incomplete protection can be expected if a vaccine does not contain the proper strains or serotypes of microorganism required to stimulate protective immunity. Finally, there are additional pathogens present

in the environment that are not commercially available in vaccines.

VACCINE SELECTION

Core vaccines are generally considered as immunological medicinal products which should be used to vaccinate against infectious diseases characterized by ubiquitous nature, seriousness and potential as zoonosis. By contrast, non-core vaccines should be administered only on the basis of a realistic evaluation of all risk factors, including vaccine efficacy and safety. Veterinarians can determine which type of vaccine should be used by understanding the different characteristics of available products, balancing risks and benefits, and tailoring vaccination schedules to individual circumstances.

Basically, veterinary vaccines can be grouped in the two major classes of live and killed products. Live bacterial or viral vaccines are attenuated in order to prevent the development of the disease when replicate in the host body. The majority are viral vaccines and usually are administered in small quantities. One injection is generally sufficient to stimulate a fast and effective immune response. Killed vaccines are obtained following inactivation of the pathogens without impairing their immunogenic properties. Adjuvants, such as metallic salts, mineral oils or plant extracts are normally added to killed vaccines and more than one injection is needed to stimulate a protective immune response. The last decades have witnessed an explosion in methodologies for exploring the basis of virulence (attenuation) and for improved methods in vaccine production and delivery. Protective antigens (epitopes) can now be identified with great precision. Through recombinant-DNA technology it may be possible to manipulate pathogens in order to improve their safety (reduction in viral virulence) while preserving or even increasing the immunogenic properties [5, 6]. The choice of a vaccine, whether living or attenuated, is based on several factors: if the risk of a disease is high and the risk of adverse reaction is low, veterinary vaccinologists have generally favored live products because of their greater ability to mobilize the elements of the immune system, the need for a single injection, more enduring immunity and their relatively low cost. In certain instances, mainly in cases of viruses with multiple serotypes, and those whose genomes can integrate into host cell genomes, inactivated vaccines are generally preferred. A special class includes A/A vaccines (primarily bacterial and inactivated) whose current classification is commonly based on the concept of strain /antigen specificy associated with targeted treatment of a rectricted number of animals.

AVAILABILITY OF VETERINARY VACCINES

The decision to produce a vaccine is normally based upon the severity or economic impact of the target disease, the capacity of a vaccine to prevent infection or disease and the availability of methods to evaluate safety and efficacy. The directions for use provided by the

manufacturer are recommended on the basis of experimental evidence the manufacturer collected to support approval of its product by government agencies in order to assure their safety and efficacy. Recently, some concern regarding availability of immunological medicinal products against pathogens largely distributed in the environment but not commercially available as veterinary vaccines, has been raised by several interested parties. It appears that due to the increased cost of developing, producing and marketing a veterinary vaccine afforded by producers to comply with more recent EU legislation [7], there would be a sort of reluctance to develop new products where financial returns were unlikely to justify the cost of seeking authorisation, particularly for minor uses or minor species (MUMS is the acronymus currently adopted to designate these two categories). As a point to overcome a series of practical difficulties, current market is experiencing a renewed interest in A/A vaccines [8]. Manufacturing of A/A vaccines has a long tradition in veterinary medicine. These are immunologicals manufactured from pathogens from an animal or animals from the same holding, inactivated and used for the active immunization of this animal or animals from the same holding. The need for such vaccines was caused by the difficulties to establish efficient treatments of some infectious diseases in flocks of almost all species of farm animals. Today the renewed interest in A/A vaccines is mainly related to the problem of mutations and genetic variations which may not be addressed by fixed strain vaccines or in cases when intensive diagnostic and molecular workup of isolates have shown there is a need for different antigens. New technologies, today, facilitate science-based selection of isolate and manufacture of AA vaccines. Originally, A/A vaccines were used for therapeutic purposes. At present, they are often implemented into veterinary schedules for herd/flock/individual treatment and used to further limit the spread of infectious "emergent" diseases (for which there are no vaccines), and diseases affecting MUMS. As a matter of fact, the concept of strain/antigen specificity associated with targeted treatment inherent to A/A vaccines, enable veterinarians to consider their use in quite a large variety of epidemiological circumstances where lack of conventional vaccines or efficacy of vaccines (antigenic variation occurs that is outside the spectrum of protection afforded by

commercially available vaccines) are considered as an objective issue. In addition, and in contrast to conventional vaccines which are considered exclusively as a preventive tool against infectious diseases, A/A vaccines have historically been used to treat "ongoing" infections. Although the limited scientific value of these products and the poor investigations of the effector mechanisms involved are widely recognized, their use is still claimed in conditions where disorders in the immune system are suspected. Furthermore, the use of herd/flock/individual vaccines has been claimed to provide significant advantages in reducing the use of antibiotics, in responding to new epidemiological situation, and in general, in improving animal health in live stock husbandry. Today a more appropriate definition of A/A vaccines is indeed, the one that takes into account their historical tradition, and practical use such as stable or herd specific vaccines, custom(...ized) vaccines, therapeutic vaccines, pharma-vaccines, vaccines used for biological therapy, etc. In any case, the use of A/A vaccines should be subordinated to a justification for the specific use and to a risk/benefit analysis. The following are examples of vaccines which several interested parties have been indicated as primary needs against major target animal diseases. Helminth parasites vaccines are required for cattle, sheep and goats. Shortage of contagious agalactia, clostridiosis salmonellosis, (S. abortus ovis), staphylococcosis, blue tongue and contagious ectima vaccines has been identified for sheep and goats. Clostridiosis, pasteurellosis, salmonellosis and circovirosis type 2 vaccines are generally missing for pigs, as well as, in some countries, combined vaccines based on different strains (primarily USA and EU strains) of porcine reproductive and respiratory sindrome virus. Equine viral arteritis and West Nile vaccines are sought necessary for horses. Vaccines against clostridiosis, coccidiosis, hemorrhagic enteritis and Newcastle disease are needed for turkeys, while vaccines against coccidiosis, salmonellosis and Newcastle disease are urgent for ratites. Efficacious avian influenza vaccines for chickens and turkeys are urgently requested. Vaccines against clostridiosis and coccidiosis are sought necessary for rabbits.

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