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VETERINARY VACCINOLOGY

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ABSTRACT

Veterinary vaccinology is a very interesting and rapidly developing field. In fact veterinary vaccines are not only used for the prevention of infectious diseases in the animal health sector, but also help to solve problems of public health, to reduce detrimental environmental impact of the use of some veterinary drugs and prevent the emergence of resistance of micro-organisms or parasites. After a short introduction, this paper will deal with the use of vaccines for animal health and welfare, including new developments in the veterinary field such as marker vaccines and vectored vaccines, the special case of equine influenza-inactivated vaccines and the use of veterinary vaccines in public health. The conclusions will analyze the reasons as to why develop veterinary vaccines and the obstacles to their development. © 1999 Académie des sciences/ Editions scientifiques et médicales Elsevier SAS

RÉSUMÉ

La vaccinologie vétérinaire est un secteur en plein développement et d'un profond intérêt. Les vaccins vétérinaires ne sont pas seulement utilisés pour prémevenir (rarement traiter) les maladies infectieuses des animaux mais également dans beaucoup d'autres domaines comme celui de la santé publique et pour diminuer les conséquences néfastes pour l'environnement qui peuvent résulter de l'emploi de certains médicaments vétérinaires. Enfin, l'utilisation de certains vaccins permet de pallier l'émergence de résistances bactériennes ou parasitaires a certains de ces médicaments. Après une brève introduction qui définit le marché du vaccin vétérinaire et les différences qui peuvent exister entre le marché des différentes espèces animales domestiques, cette contribution se propose de décrire les principales nouveautés dans le secteur, comme celle des vaccins marqués et des vaccins vectorisés dans le cadre de la santé et du bien-être animal. Le cas particulier des vaccins inactivés destinés a prévenir la grippe équine sera par la suite évoqué ainsi que la répercussion des vaccins vétérinaires en santé publique. Les conclusions seront consacrées a une analyse des raisons en faveur du développement des vaccins vétérinaires ainsi que celles qui font obstacle a pareil développement.

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Introduction

Veterinary vaccinology is a newly defined scientific discipline. The reasons for considering veterinary vaccinology as a new scientific discipline are many fold:

- the approach of vaccinology is multidisciplinary including immunology, epidemiology, microbiology, virology, parasitology, reproductive physiology, veterinary clinical sciences, etc.;
- veterinary vaccinology covers a broad scope of objectives; molecular biology has had a strong impact on veterinary vaccinology, bringing new insights and broadening the perspectives;
- the market for veterinary vaccines differs markedly from the human one.

Moreover, veterinary vaccinology often provides the opportunity to test new developments in the field of vaccinology. When defining the goal for a vaccine one must nowadays consider the impact of the vaccine, either simply the prevention or the reduction of the clinical signs associated with an infection for instance, or the prevention or reduction of the infection itself in order to hamper the spreading of infectious agents (epidemiological purposes).

Veterinary vaccines are not only used in the animal health sector itself but also for other purposes such as improvement of public health, reduction of environmental impact of other veterinary drugs, improvement of animal welfare, control of animal pests, etc.

This contribution will try to give an overview of the present developments and future trends in veterinary vaccinology.

One must always keep in mind that in the veterinary field there are two major categories of species: food producing ones considered basically as economic goods such as cattle, pigs and poultry, and pets such as dogs, cats and horses. The market of veterinary vaccines will be strongly influenced accordingly.

The market of veterinary vaccine

The world market for veterinary vaccines was estimated in 1993 to be at 1.8 million US dollars gross [1] and consists of about 20% of the market for all animal health products; this represents approximately 5% of the value of the pharmaceutical (human and veterinary use) market. The size of the veterinary vaccine market is equivalent to the size of the market for human vaccines [2]. However, the market for veterinary vaccines covers the existence of approximately 160 different vaccinal agents as compared to approximately 30 for human use. The number of vaccines is therefore higher, resulting in a much lower turn-over per product. To conclude, the role of veterinary vaccines within veterinary medicinal products is very important, but veterinary vaccines suffer from several drawbacks:

- the markets are often small;
- the markets are heterogeneous between different countries especially for food-producing animals;

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- those products are highly specific; many species are potential targets;
- many different conditions are involved.

Nevertheless one must always keep in mind that in the absence of broad spectrum antivirals, vaccination is often the only means of preventing or curing viral infections

Marker vaccines used for epidemiological purposes

In veterinary medicine, sanitary authorities may either choose to vaccinate against a disease as a method of prevention or decide to eliminate the infection using slaughtering programmes either on large scale or on a case by case basis. In some cases such as African swine fever in the complete absence of a vaccine, there is still no other choice than to eliminate the infection as quickly as possible by slaughtering and destruction of the carcasses.

On top of that, in the field of veterinary viral vaccines, most of the previous vaccines were only developed to prevent clinical signs of the disease without paying too much attention to their epidemiological impact on impeding wild virus excretion and spreading after subsequent field infection.

Major changes are nevertheless foreseen owing to changes in public opinion, slaughtering policies being less and less popular (animal welfare concern) and the availability of marker vaccines.

Marker vaccines are vaccines that can be used within the framework of an elimination programme because they allow us to distinguish between animals that are infected and those that are simply vaccinated. Marker vaccines are either obtained by the deletion of a gene coding for a non-essential protein of the infectious agent (until now viruses) or are sub-unit vaccines. They must always be associated with a companion diagnostic test allowing the distinction between infection and vaccination. In the case of a deletion the marker property is always linked to the deleted protein; in the case of a sub-unit vaccine several possibilities may exist. Nevertheless for harmonisation purposes a choice should be made. The marker is always negative since a positive marker such as that linked to the insertion of a gene coding for a foreign protein is useless since it will only tell that the animal has been vaccinated but not if it has been infected. Marker vaccines have been developed for Aujeszky's disease virus infection of the pig (often called pseudorabies) (gE deletion), classical swine fever (pestivirus infection of the pig; E2 subunit vaccine) and infectious bovine rhinotracheitis (herpesvirus infection of cattle; gE deletion or gD subunit). One of the best example is infectious bovine rhinotracheitis (IBR) caused by bovine herpesvirus 1 [3]. Previous IBR vaccines were mainly developed to prevent clinical consequences of wild virus infection. Infectious bovine rhinotracheitis be- longs to the list B of the Office international des epizooties and this infection can therefore impede international trades if it is implemented in some national elimination programmes. In western Europe most countries have chosen or are forced to implement a programme of infectious bovine rhinotracheitis elimination. Infectious bovine rhinotracheitis virus, like other herpesviruses, remains latent after infection. Unfortunately, the wild virus can establish latency in already vaccinated animals either with an inactivated vaccine or with an attenuated one. Conversely an animal remains a latent carrier of a wild virus if it is vaccinated after field

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infection. Moreover, so far all the attenuated strains of infectious bovine rhinotracheitis virus remain latent after vaccination, even the gE deleted ones and can be reactivated later on [4]. Therefore, in areas where cattle are vaccinated with either an inactivated or an attenuated conventional vaccine, one cannot distinguish between animals either vaccinated or infected, whilst in areas where vaccination is non-authorised, all animals that are seropositive against IBR virus must be considered as infected. If an elimination programme is implemented in a vaccination area, all seropositive animals, either vaccinated or infected, must be eliminated from the herds. As a matter of fact, in a vaccinated area, a serologically positive animal may be either:

- vaccinated;
- infected;
- vaccinated and infected;
- infected and vaccinated.

Unfortunately due to vaccination programmes against clinical disease, some western European countries show a high prevalence of seropositive animals (60-70%).

This has led to the use of marker vaccines. The protein chosen as a marker must show several characteristics:

- be non-essential (in order to be able to produce the vaccine);
- not be a major immunogen (in order to maintain vaccine efficacy);
- give a long living serological response when present (to be a marker);
- be present in all the wild strains so far studied;
- induce a serological response in already vaccinated animals.

In this case, whenever an animal is seropositive against the deleted protein, even after vaccination, it is infected and must be eliminated.

Vectored vaccines

Vectored vaccines are vaccines consisting of an attenuated infectious agent able to multiply in the target animal and harbouring foreign gene(s) of interest. The vector itself may be an immunogenic component of the vaccine.

Some of the vector may be 'suicide' vectors; that is to say that they only undergo one multiplication cycle in the target host without producing progeny.

The best example of this kind of vaccine in the veterinary field is the use of a vaccinia-rabies recombinant vaccine for the control and elimination of wildlife rabies [5].

The recombinant vaccinia-rabies glycoprotein virus (VRG) has been tested for efficacy and safety in the fox [6, 7]. The duration of protection conferred by VRG, a minimum of 12 months in cubs and 18 months in adult animals, corresponds to the length of protection required for fox vaccination in the field owing to the high turnover of the fox population. The efficacy of VRG contained in a machine-made baiting system has been tested and shown to be effective.

VRG was shown to be non-pathogenic in the fox what- ever the inoculation dose or route of administration. No transmission of immunising amounts of VRG was found to occur in adults or

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young foxes, with the exception of one adult fox bitten by another freshly vaccinated one. VRG only multiplies locally.

The influence of vaccination with VRG on the onset of the disease and on the delay before death in foxes previously infected with wild rabies virus, has been investigated. The results show that 'early' and 'late' death phenomena occur as a consequence of interactions between oral vaccination with VRG and rabies infection, but preclude the risk of the emergence of asymptomatic carriers of wild-rabies virus after vaccination.

Field trials with baits have shown that several non-target wildlife species compete with foxes for bait consumption. It must also be taken into account that, within the ortho- poxvirus group, the vaccinia virus has a wide range of host species. In fact, bait uptake monitoring and tetracycline (biomarker included within the bait) detection controls, performed after vaccination campaigns, proved that mustelids, wild boars (*Sus scrofa*) and domestic carnivores may ingest the vaccine baits. Moreover, a significant proportion of the baits are partly eaten by small mammals. It was therefore important to verify the safety of VRG for non-target species (both domestic and wild).

Several non-target wild species have been chosen for testing in Europe because of their opportunistic feeding behaviours and their presence in the areas where the vaccine must be distributed, including the wild boar, Eurasian badger (*Meles meles*) and several micromammals. No clinical signs of rabies and/or pox infected lesions were observed in the vaccinated animals during the observation period (28 days minimum after vaccination).

Taking into account all the available experimental data concerning the safety of the VRG for target and non-target species and its efficacy in foxes, limited field trials of fox vaccination with the recombinant virus were authorised first by the Belgian and then by the French public health authorities. The last trial of deliberate release of the VRG on a 2 200 km^2 area of southern Belgium was intended to test the feasibility of rabies elimination on a large area. The 25 000 baits containing VRG and tetracycline as a bio- marker were dropped by helicopter on three occasions (November 1989, April 1990 and October 1990). After the third phase of vaccination, 81% of inspected foxes were tetracycline positive. Only one rabid fox was recorded, at the periphery of the baited area, and this was tetracycline negative. Despite the dramatic decrease in the number of rabid foxes recorded after vaccine-bait distribution, the efficacy of the vaccination campaign remains difficult to evaluate because systematic collection of foxes is not logistically feasible. Nevertheless, because notification of cases of rabies in cattle and sheep is mandatory in Belgium, the incidence of rabies in livestock provides a reliable indicator of the prevalence of rabies in the wild. No case of livestock rabies has been recorded in the study zone since the second phase of vaccination. On this occasion, we have also investigated the economics of the vaccine-bait dispersal programme. The average yearly cost of rabies in Belgium (1980--1989), including post- exposure treatments of humans, animal diagnosis, compensation to farmers for the culling of infected livestock and the culling of wild foxes, was estimated to be 400 000 Euros per 10 000 km^2, or 88 000 Euros per year for the area under study. These figures did not include the cost of vaccination of domestic animals nor the salaries of civil servants. In comparison we estimate the overall expenditure during the three campaigns of vaccine-bait distribution to be 118 000 Euros. Because vaccination following elimination can in principle be interrupted or subsequently limited to the borders of the vaccinated zone, long-term maintenance of a rabies-free area by peripheral vaccination with VRG is economically justifiable [8, 9].

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The use of VRG has now been extended to all the contaminated areas in Belgium and the Grand Duchy of Luxembourg as well as to large areas in France. Rabies is approaching the stage of elimination in these three countries [10).

The quasi elimination of rabies in Belgium has already had other beneficial effects besides the improvement of animal health. First, the number of human post-exposure treatments has decreased in proportion to the decrease in rabies incidence in animals (mainly cattle). Second, the diminution in rabies incidence in wildlife has had a beneficial effect on the survival of threatened wild species, such as the Eurasian badger in the contaminated area. Estimation of the badger population in the treated area shows a gradual increase in numbers.

The same approach (baiting system) has been used in order to control the wild red fox population in Australia, where this introduced, non-indigenous species is consid- ered as being a pest [11].

The case of equine influenza

Horses are peculiar animals in the sense that they rep- resent the only domestic species behaving like man; that is to say free to circulate from one country to another, even from one continent to another, without necessarily being quarantined, provided they are duly vaccinated against equine influenza 15 d before travel at the latest. Equine influenza belongs to list B of the Office international des epizooties.

Equine influenza has remained among the main acute contagious respiratory diseases of horses worldwide. Equine influenza is represented by two subtypes: influenza Nequine 2 virus (H3N8) which is the most important cause of respiratory disease in the horse, and influenza Nequine 1 virus (H7N7) which is still circulating subclinically but is almost considered as extinct.

However, a divergence in the evolution of Nequine 2 (H3N8) viruses has occurred since 1987 and two families of virus are now circulating. These were designated European-like and American-like, although representatives of both families have been isolated in both continents [12]. There is increasing evidence from field studies that antigenic drift in the gene coding for haemagglutinin (HA), which is the major surface protein of these influenza A strains, eventually renders vaccine strains obsolete and is likely to compromise vaccine efficacy [13, 14]. In fact, the more the vaccine strain is related to field viruses, the more the vaccine can protect against field virus excretion and circulation, which is the ultimate goal. A formal reporting mechanism on antigenic/genetic drift or shift of equine influenza viruses and a vaccine strain selection system have been set up, so that vaccine manufacturers and regulatory authorities are informed of the potential need to update vaccine virus strains. An expert surveillance panel, including representatives from three WHO reference laboratories and from three OIE reference laboratories, reviews every year the epidemiological and virological information and make recommendations about suitable vaccine strains. These recommendations are published annually by the OIE in its bulletin (OIE, 1996). As antigenic drift in equine influenza occurs at a slower rate than in human influenza, it is considered that a regular update of the strains could be necessary every 3-5 years. What is even more important is the fact that the development of effective vaccines can now be facilitated by the availability of reliable in vitro assays such as:

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- single radial diffusion (SRO) to measure vaccine bulk antigen content in terms of haemagglutinin (HA) content;
- single radial haemolysis (SRH} to measure serological responses.

For in-process controls, SRD provides a reliable method of measuring haemagglutinin content of equine influenza bulk antigens, although it cannot be used on final adjuvanted products [15], while SRH is a sensitive and reproducible method for measuring antibody to haemagglutinin. Moreover, the European Agency for the Evaluation of Medicinal Products (EMEA) based in London has taken the initiative to shorten the procedure of strain replacement in equine influenza vaccines when required according to epidemiological circumstances in case of an antigenic shift. This will allow us not only to accelerate the procedure but also to reduce the number of animals necessary for vaccine development and control in accordance with the three Rs rules (reduction, replacement, refinement) [16].

New equine influenza antigenic variants to be used in vaccine production could be obtained by selection of appropriate reassortants as already carried out for human influenza vaccines.

Veterinary vaccines and animal health and welfare

As already mentioned, the public concern for animal welfare is increasing, leading to the establishment and implementation of the three Rs rule [17].

The value of animal models for veterinary vaccines is not to be ignored, particularly since one has access to target animal models which are often more relevant than the laboratory ones, especially for challenge/protection studies. Immune protection involves complex immunological phenomena and processes. It is particularly true whenever cellular immunity plays a crucial role because it is still easier to measure antibody responses than cellular ones in vitro.

Nevertheless the trend is to replace animal models by in vitro systems whenever possible. The problem of the replacement of the in vivo model by in vitro ones is further impeded in Europe by the necessity to comply with Pharmacopoeia monographs where the use of laboratory and/or target animals is often requested. As far as the use of veterinary vaccines itself is concerned the benefit for animal welfare is obvious. Vaccines unlike therapeutic treatments are the best way to avoid animal suffering since they prevent disease. Furthermore, due to the short life time of many categories of food-producing animals, the vaccine must only be administered once in contrast to treatments which generally necessitate repeated interventions. Nevertheless, there is still room for improvement by developing less reactogenic adjuvanted vaccines. Another area of animal health improvement is the use of vaccines for immunocastration of male pigs to avoid boar taint, instead of surgical castration. The use of vaccines in animal production systems is also often more environment friendly since it reduces the use of chemicals. Of special interest is the anti-tick vaccine developed in Australia based on a cryptic intestinal antigen [18].

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Veterinary vaccines and public health

In developed countries, due to overproduction, the public concern for food security has been replaced by a major concern for food safety. This concern has overwhelmingly increased after the mad cow crisis. People are concerned with food poisoning, the presence of drug residues following treatment of food-producing animals and the possible bacterial transfer of resistance to antibiotics from animal to man.

Veterinary vaccines may help to solve many of those problems. The best example of a veterinary vaccine used for public health purposes is the vaccination of wildlife against rabies; the primary goal is not to protect wildlife species from rabies but indirectly to avoid human exposure and contamination as well.

Being considered as products working by natural mechanisms, vaccines, except for some of their excipients, do not need to have an MRL (maximum residue limit) determination associated with a withdrawal period. In fact, since vaccine prevention works after a lag period the use of vaccines intrinsically contains a withdrawal period. Veterinary vaccines can also be used to prevent food poisoning as exemplified by the 'in ovo' [19] vaccination of poultry against salmonellosis, in order to decrease carcass contamination. Vaccines against sheep cysticercosis have been experimentally developed (20] leading to the possible control of bovine cysticercosis in order to prevent Taenia saginata taeniosis in man.

Last but not least, bacterial resistance to antibiotics is an emerging problem for both animal and public health sectors. Several antibacterial vaccines used in veterinary medicine disappeared after the second world war, being replaced by antibiotics. The resistance to antibiotics in the animal health sector with possible implications (although rarely) for human health as well as the resistance of several parasites to anthelmintics may lead to the reappearance or the appearance of antibacterial and antiparasitic vaccines. Even if other pathways such as selection of food-producing animals for genetic resistance may be followed, the story of Marek's disease in chicken shows us that vaccines are often the more economical way to procure an animal's resistance to pathogens.

Conclusions

In conclusion, one may ask the question as to why we develop veterinary vaccines and where we stand? The reasons for developing veterinary vaccines are many fold:

- to protect animal health;
- to improve animal welfare; to protect public health;
- to protect consumers of the products of food- producing animals;
- to better protect the environment;
- to avoid the emergence of pathogen resistance to available drugs.

Even if the reasons for developing veterinary vaccines are many, there are also many obstacles to their development:

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- scientific obstacles (e.g. African swine fever, many anti-parasitic vaccines);
- poor investment return for the companies involved in this business;
- the existence of so-called minor species as targets;
- the existence of conditions of minor importance in so-called 'major' species;
- the existence of conditions of minor importance in so-called 'minor' species;
- the existence of interdiction due to animal health regulation;
- regulatory requirements for vaccines registration.

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