Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

VETERINARY VACCINES FOR ANIMAL AND PUBLIC HEALTH

P.P. Pastoret, P. Jones

Institute for Animal Health, Compton Laboratory, Compton, Newbury, Berks, RG20 7NN, United Kingdom

ABSTRACT

Vaccination is without doubt the most useful single measure available to prevent animal infectious diseases. The advantages of vaccination are numerous. It is the only available method to prevent, or sometimes cure, viral animal infections in the absence of broad spectrum antivirals and avoids the alternative of mass slaughtering of livestock.

Antibiotic or anthelmintic resistance, and the problem of pharmaceutical residues, promote the use of vaccines rather than chemotherapy. Vaccines are environmentally friendly and increase animal welfare by preventing suffering from disease resulting from treatment for a cure which may result in antibiotic resistance and pharmaceutical residues in food. For the management of livestock health vaccines are the best tool to achieve sustainability.

Veterinary vaccines cannot only be used to protect animal health but also human health from zoonotic infections through animal vaccination as exemplified by wildlife vaccination against rabies. In animal health the focus is now on animal infections rather than on animal diseases. Vaccines should be designed to prevent infection rather than to prevent clinical signs of disease and should, wherever possible, produce sterile immunity.

Available technologies allow us to design "marker" vaccines together with their companion diagnostic tests which permit the distinction between vaccinated and infected animals even if the latter were previously vaccinated. Examples will be given of foot-and-mouth disease, classical swine fever, and herpesvirus infections of livestock such as pseudorabies or infectious bovine rhinotracheitis where carrier state or latency remain an issue after vaccination.

.

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

Introduction

Smallpox was the first viral infection to be eradicated worldwide. This remarkable success was due to several factors including the availability of an efficacious vaccine, namely vaccinia, and the absence of a wildlife reservoir. According to the World Health Organisation (WHO) eradication of human poliomyelitis and measles may be possible in the same manner.

The only animal virus disease which currently shares the same characteristics is rinderpest; there are several efficacious vaccines already available and the infection seems to be a dead-end if transmitted to susceptible wild species. Other animal viral infections do not share the same characteristics, either due to the lack of an efficacious vaccine (African swine fever) or to the existence of wildlife reservoirs such as the wild boar (*Sus scrofa*) for classical swine fever, the African buffalo (*Syncerus caffer*) for foot-and-mouth disease, bats for lyssavirus infections, etc.

These diseases are more prone to a regional elimination than to complete eradication worldwide. Two methods are used to eliminate an animal viral infection, either vaccination or the strict application of hygienic measures including "stamping out" and incineration, or an integration of both methods.

Public opinion is increasingly concerned about stamping out, even when necessary, such as when dealing with emerging zoonosis, such as Nipah virus infection of pigs in Malaysia. On the other hand, generalised vaccination (foot-and-mouth disease, classical swine fever, etc.) may be discontinued despite its efficacy, for macro-economical reasons. The solution may come from the use of marker vaccines associated with companion diagnostic tests which allow a distinction between infected animals and those which have been vaccinated, using serological examination, such as for pseudorabies in pigs and infectious bovine rhinotracheitis. Some diseases, such as rabies, may raise questions despite the success of fox vaccination campaigns and the progressive elimination of terrestrial wildlife rabies in Europe. The existence of a permanently potential wildlife reservoir in bats is a threat, taking into consideration the variability of RNA viruses (quasi-species).

This paper will focus not only on viral infections of animals for which no broad range pharmaceuticals exist, vaccines or slaughtering being the only alternatives, but also on bacterial infections because of the emergence of antibiotic resistance and the increase in food-poisoning in humans.

When discussing the control of infections in animals it is necessary to consider different situations, including true eradication (i.e. smallpox), regional elimination or, more often, merely control.

Eradication means the complete elimination of the infection/disease worldwide; as mentioned, only one disease has been eradicated so far, smallpox. A similar simian infection still prevails. The only animal disease which may be eradicated in the same way, because it possesses the same characteristics necessary for eradication, is rinderpest. According to Fenner, the characteristics of the disease which permitted the eradication of smallpox were:

1.that it was an important and "serious" disease;

2.the absence of sub-clinical infection or silent excretion;

3.the animals were not contagious during the incubation or prodromic periods;

4.the absence of asymptomatic carriers or recurrent access of excretion or disease;

5.one virus serotype;

6.the availability of an efficacious and stable vaccine;

7.seasonal incidence;

8.no alternative reservoir.

The other 15 important animal diseases in OIE List A (OIE, 1982) do not exhibit all these characteristics.

OIE LIST A DISEASES

-Foot-and-mouth disease

-Vesicular stomatitis

-Swine vesicular disease

-Rinderpest

-Peste des petits ruminants

-Contagious bovine pleuropneumonia

-Lumpy skin disease

-Rift valley fever

-Bluetongue

-Sheep pox and goat pox

-African horse sickness ;

-African swine fever

-Classical swine fever (hog cholera)

-Highly pathogenic avian influenza

-Newcastle disease

The OIE List A diseases are defined as highly contagious animal diseases which are particularly damaging to the national or regional economy. Some of them are zoonotic (Rift Valley fever, Newcastle disease), but this characteristic is not necessarily required for them to belong to List A.

As an example, foot-and-mouth disease has a reservoir in wildlife, the african buffalo (*Syncerus caffer*), and therefore eradication is impeded in the short term. The elimination of an animal viral disease must take into account the biologica an epidemiological characteristics of the

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

infection, the available control methods an e emergence of new vaccination technologies such as marker vaccines.

A Plea for Veterinary Vaccines

Why should we develop veterinary vaccines? The reasons are manifold:

1.to protect animal health;

2.to improve animal welfare;

3.to protect public health;

4.to protect consumers from the products from food-producing animals;

5.to protect the environment and biodiversity;

6.to avoid the emergence of pathogens resistant to available drugs;

7.to promote sustainable agriculture and animal production.

Unfortunately, even though the reasons for developing veterinary vaccines are many, there are still many obstacles to their development:

1.scientific obstacles (e.g. African swine fever, many anti-parasitic vaccines);

2.poor investment return for the companies involved in vaccine development and production;

3.the existence of so-called "minor" species as targets;

4.the existence of conditions of minor importance in so-called "major" species;

5.the existence of conditions of minor importance in so-called "minor" species (the worse case scenario);

6.the existence of interdiction due to animal health regulations;

7.regulatory requirements for vaccine registration.

This contribution will illustrate the role of veterinary vaccines in animal health and welfare and discuss their potential impact on public health.

Eradication of Rinderpest

Morbilliviruses have infected animals and man since the time of early civilisations, 5,000 to 6,000 years ago. These civilisations presented, for the first time, large populations of susceptible animals and people, a fact which guaranteed the presence of young naive individuals in sufficient numbers; this is a prerequisite for the persistence of such fragile agents as morbilliviruses which provoke a very short infection and produce a life-long sterile immunity.

The epizootic of rinderpest in 376-386AD was the first to be formally recognised in historical documents. This epizootic spread from Eastern Europe, devastated Flanders and terminated in

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

Italy. The expansion of rinderpest was always encouraged by wars, civil troubles and natural calamity. These disorders provoked migration within a country or across boundaries. In Africa transhumance (the seasonal movement of livestock) contributed to the dissemination of the disease. In Europe rinderpest was the major plague of cattle up to the end of the 19,h century when it was eliminated. Unfortunately in 1920 there was an accidental outbreak of rinderpest in Belgium. An infected zebu herd coming from India to Brazil, through the harbour of Antwerp, reintroduced the disease. These animals stayed approximately 15 days in quarantine where they contaminated American beef cattle which were afterwards sent to the markets of Brussels and Ghent.

In Ghent these cattle contaminated others from Germany which were afterwards sent all over the country thus propagating the disease and initiating many secondary outbreaks. The disease was only recognised after three weeks despite the death of seven zebus in Antwerp. Prophylactic measures (slaughtering, sequestration, disinfection) were applied and the disease was eliminated after approximately five months (August 1920 to January 1921). The reintroduction of rinderpest into continental Europe highlighted the necessity for international collaboration to combat the major contagious diseases of domestic and wild animals. Worried because of the extension of rinderpest to Belgium, France organised an international meeting to co-ordinate measures to contain contagious diseases of domestic animals worldwide. This meeting resulted in the creation of the Office International des Epizooties (OIE). Following the pioneer work of Walter Plowright in East Africa, systematic vaccination of cattle using an attenuated strain of rinderpest virus will most probably lead to the eradication of rinderpest; it will be the first animal disease to be eradicated and only the second one following the eradication of smallpox. New recombinant vaccines are now available. The main problem which remains is the circulation of hypovirulent strains in East Africa, mainly in Kenya, and the coexistence of a similar disease in small ruminants (peste des petits ruminants); once the problem of rinderpest is solved the same strategy may be applied to the eradication of peste des petits ruminants.

The mode of transmission of rinderpest is direct and cattle are the only reservoir of the infection. Wild artiodactyls are highly susceptible to the infection and develop a fatal disease which may contribute to virus dissemination but this constitutes a deadend infection. The struggle to eradicate rinderpest is, therefore, limited to domestic cattle and the best tool for eradication is vaccination.

Marker Vaccines and Companion Diagnostic Tests

In animal health the alternatives are to vaccinate animals to prevent disease or attempt to eliminate infection through strict application of sanitary measures such as the slaughtering of infected and in-contact animals. For diseases for which vaccines do not exist (e.g. African swine fever), and particularly for zoonoses (e.g. Nipah virus infection of pigs), the systematic slaughtering of animals is, at present, the only available solution. This will not be acceptable in the near future. Diagnosis of infection is of paramount importance. Diagnosis can be direct through the detection of the infectious agent using immunological or molecular technologies; a good example is the detection of persistently infected cattle with bovine viral diarrhoea (BVD)

virus. Polymerase chain reaction (PCR) is generally considered as being highly sensitive. However, this involves the use of specialised laboratories and obtaining a diagnosis is often too slow.

Other diagnostic methods are indirect since they are based upon the detection of specific antibodies against the suspected infectious agent. These methods do not give immediate results since they depend upon the synthesis of antibodies by the animal after infection or vaccination. Indirect methods also do not generally distinguish between the humoral immune response resulting either from an infection or a vaccination.

This problem can be overcome by the use of marker vaccines and companion diagnostic tests. There are two types of systems used; these are either based on the detection of a serological response against a protein, the gene for which has been deleted in the vaccine strain (either only one deletion or a sub-unit vaccine), or on the detection of the serological response towards non-structural proteins (purified vaccines). In the case of the deletion of a gene coding for a non-essential protein the marker characteristic is always linked to the deleted protein; in the case of sub-unit vaccines (e.g. protein E2 of classical swine fever virus) the choice of the marker may be linked to several other proteins. To standardise tests a choice must be made (e.g. protein gE of Pseudorabies virus). In the first type of marker vaccines, the marker must always be negative since a positive marker, for instance through the insertion of a gene coding for a foreign protein, is not suitable; it will only demonstrate that an animal has been vaccinated but not whether the animal was also infected. Due to their capacity to detect infected animals, either vaccinated or not, marker vaccines must always be associated with a companion diagnostic test which can be used during a prophylactic campaign to eliminate infection. If marker vaccines are used in such a situation they must have an epidemiological impact.

Vaccines which have been developed to prevent animal disease were mainly designed to prevent clinical signs without realising the epidemiological impact of vaccination on the excretion of wild virus following infection and on its dissemination and circulation. There can be a problem if virus multiplication is inhibited to the point that the infection does not induce the synthesis of specific antibodies, which may be detected in diagnostic tests.

The attitude of the general public towards mass slaughtering of infected or in-contact animals is changing. A better alternative is the "vaccination for life" (i.e. vaccination which allows animals to be kept alive rather than slaughtered). Marker vaccines may help to solve this problem if they show the required characteristics. Unfortunately most of the available companion diagnostic tests can only be used for herd certification and not for individual certification.

Marker Vaccines with one Deletion : The example of Pseudorabies and Infectious bovine Rhinotracheitis

Pseudorabies in pigs and infectious bovine rhinotracheitis are two infections caused by herpesviruses which become latent in an animal even when it has already been vaccinated. The first marker vaccine was available for pseudorabies infection in pigs due to the existence of an

attenuated strain of pseudorabies virus developed by Bartha in Hungary (1961), which was spontaneously deleted in the gE glycoprotein. Analogous vaccines were developed subsequently for infectious bovine rhinotracheitis. Vaccination against infectious bovine rhinotracheitis is a good example of the application of marker vaccines. Original vaccines against infectious bovine rhinotracheitis were designed to prevent clinical signs of the disease after infection of the animal with a wild virus. Infectious bovine rhinotracheitis belongs to list B of OIE and the infection may have a detrimental impact on the international exchange of animals for countries, particularly within the European Union, which wish to eliminate the infection.

In the European Union several countries have a programme of infectious bovine rhinotracheitis elimination. The herpesvirus responsible for infectious bovine rhinotracheitis becomes latent after infection, regardless of whether the animal is vaccinated or not. Wild virus can become latent in vaccinated animals whether an inactivated or an attenuated vaccine is used and animals remain latent carriers, even if vaccinated after the infection with a wild virus. Moreover, attenuated vaccine strains become latent after vaccination and this includes gE deleted strains. As a consequence, in an area where animals are vaccinated with a conventional (non-deleted) vaccine, either attenuated or inactivated, it is impossible to distinguish between vaccinated or infected cattle; in an area where vaccination is prohibited, all animals serologically positive to infectious bovine rhinotracheitis virus must be considered as potentially infected and latent carriers of a wild virus. If an elimination programme is initiated in an area where animals are vaccinated with conventional vaccine (undeleted), all the seropositive animals must be eliminated from the herd. In fact in those circumstances an animal can either be:

1.vaccinated;

2.infected;

3.vaccinated then infected;

4.infected then vaccinated.

A solution may come from the use of a marked/deleted vaccine. The deleted protein in the vaccine strain must show the following characteristics:

1.be a structural protein (inactivated vaccines);

2.be non-essential in order to be able to produce the vaccine;

3.not be an essential protective immunogen in order to still have an effective vaccine;

4.induce a significant and long-lasting humoral immune response in order to be used (when deleted) as a marker;

5.be present in all wild virus strains;

6.induce a humoral immune response in vaccinated animals when infected.

If a marker vaccine is used, whenever an animal is seropositive towards the deleted protein, it must be seen as infected and eliminated.

The gD protein of herpesviruses, which is a major protective immunogen, cannot be deleted but may be used to develop sub-unit vaccines.

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

The main problem with marker vaccines against infectious bovine rhinotracheitis is their epidemiological impact. This must involve their ability to prevent virus circulation when used as part of an elimination programme.

Vaccines capable of inducing a sterile immunity are not currently available. Vaccination schedules must be more stringent than those used at present, designed for the protection against clinical signs; vaccination must be repeated. Vaccination schedules must be associated with strict health measures. For an elimination campaign, epidemiological protection must prevent the excretion of wild virus by naïve animals and prevent re-excretion by latently infected animals. Attenuated vaccines produced with identical strains, deleted or not, are more efficacious than their inactivated counterparts.

The efficacy of repeated vaccination using an inactivated gE negative vaccine has been studied in field conditions in the Netherlands. The study showed a significantly reduced incidence of seroconversion against wild virus in the vaccinated group compared to the placebo-injected control animals. Wild virus circulation without being completely restricted was nevertheless significantly reduced. The attenuated gE negative marker vaccine reduced transmission of wild virus from infected cattle to naïve animals and in some circumstances even prevented transmission. A field experiment confirmed these results and demonstrated that the intramuscular administration of an attenuated gE negative vaccine reduced the incidence of seroconversion against gE and therefore virus circulation in vaccinated herds as compared to control.

Vaccination against Classical Swine fever and Sub-Unit Vaccines

Classical swine fever caused by a pestivirus is a serious disease belonging to the OIE list A.

An elimination programme is in place within the European Union; vaccination using conventional vaccines is prohibited and a slaughter policy is in place. This policy is challenged by the existence of a strong antigenic relationship with other pestiviruses such as the virus responsible for bovine viral diarrhoea (BVDZMD) which impedes serological diagnosis, the insidious circulation of hypovirulent strains and the presence of a wild reservoir, the wild boar (*Sus scrofa*) in continental Europe.

Classical, conventional, vaccines with a well-proven efficacy prevented the emergence of asymptomatic carriers when they had sufficient potency. Attenuated vaccines were more efficacious than their inactivated counterparts. They contributed to the elimination of the disease, but they had a disadvantage in creating serologically positive animals; this was not acceptable if a slaughtering policy was to be applied. The solution for countries which prohibit vaccination but are still facing recunent episodes of classical swine fever may come from the use of sub-unit vaccines.

Sub-unit vaccines have recently been obtained by the expression of the E2 major immunogen of classical swine fever virus in a baculovirus system, in vaccinia or pseudorabies virus (El).

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

The baculovirus expression system produced vaccines which allow the distinction between infected or vaccinated animals. These vaccines were evaluated and accepted by the European Medicinal Evaluation Agency (EMEA); they require the existence of reliable companion diagnostic tests which detect the presence of specific antibodies directed against other major immunogens of classical swine fever virus, not present in the sub-unit vaccine such as NS2 protein, a conserved protein. Independent experiments do not confirm the expectations. Unfortunately inactivated vaccines are not sufficiently efficacious from the epidemiological standpoint as compared to previous classically attenuated vaccines. Moreover, companion diagnostic tests currently available are not reliable and therefore limit the possibility of the use of these sub-unit vaccines in the field. This is worrying since it seems difficult in Europe to eliminate classical swine fever completely without vaccination, particularly since public opinion is strongly hostile to slaughtering policies.

Vaccination against Foot-and-Mouth Disease and Purified Vaccines

Foot-and-mouth disease was first scientifically described during the Renaissance period. Since the 17th century there have been many accurate descriptions of this highly transmissible disease which became more important after the elimination of rinderpest in Europe. Prophylactic measures taken against rinderpest, a directly transmitted contagious infection, were not efficacious against foot-and-mouth disease.

Elimination of foot-and-mouth disease in continental Europe required the mass vaccination of cattle and pigs in some countries. Preventive vaccination has been prohibited in the European Union since 1991. This prohibition ended a 30-year period of vaccination and consequently allowed the progressive appearance of completely naïve cattle herds. This is particularly detrimental when the disease is accidentally reintroduced. Since the prohibition of vaccination a contingency plan has evolved which is mainly based upon information and the training of the partners concerned. The cost of the two schemes (vaccination or information/training) has been estimated in France before (in 1990) and after (in 1992) the prohibition of vaccination on the basis of an equal efficacy postulate; prohibition of vaccination is a far less costly policy. To overcome the risks linked to the complete susceptibility of European livestock, concentrated antigen vaccine banks have been established and there is now the prospect of using marker vaccines in case of an emergency.

In fact, and when a highly purified vaccine has been used, then whenever an animal is seropositive against non-structural proteins coded by the virus (NSP) in an ELISA diagnostic test it can be determined that it has been infected by a wild virus. During foot-and-mouth virus multiplication the NSP are synthesised at the same level as structural proteins (cleaved polyprotein). The NSP are only produced when virus multiplication occurs and are not contained within extracellular virions used to produce purified inactivated vaccines. To remove contaminating NSP during vaccine production, vaccines must be submitted to a purification procedure to ensure that they only contain structural proteins before formulation. Unfortunately

the companion diagnostic tests currently available only allow the certification of the absence of contamination at herd level but not at an individual level.

In case a policy of vaccination for life is considered to control foot-and-mouth disease outbreaks, it must be possible to distinguish between emergency and preventive vaccines. In the case of an emergency vaccination, early onset of protection is important, whereas in case of preventive vaccination, the duration of the protection is the main goal.

Equine Influenza as a Special Case

A similar approach to foot-and-mouth disease has been applied to equine influenza in a different context. When determining real time duration of protection with equine influenza inactivated vaccines, it is useful to have a diagnostic tool which allows the exclusion of intercurrent infection of the experimental animals with a wild influenza virus. A diagnostic test has been developed by the group of Jennifer Mumford at Newmarket in the U.K.; it is based on the serological response against a non-structural protein coded by the virus.

Animal Vaccination for Public Health

In developed countries, partly as a result of overproduction, public concern for food security has been replaced by a major concern about food safety. This concern has increased following the BSE outbreak. People are concerned about food poisoning, the presence of drug residues following treatment of food-producing animals and the possible transfer of antibiotic resistance from bacteria causing disease in livestock to those which affect 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 was not to protect wildlife species from rabies but to prevent human exposure and the disease in the human population.

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 be used to prevent food poisoning as demonstrated by the "in ovo" vaccination of poultry against salmonellosis, in order to decrease carcass contamination. Vaccines against sheep cysticercosis have been developed experimentally and may lead to the development of similar vaccines to control bovine cysticercosis and thus *Taenia saginata* infestation in humans.

Bacterial resistance to antibiotics is an emerging problem for both the animal and public health sectors. Several antibacterial vaccines used in veterinary medicine disappeared after the second world war, and were 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 the selection of food-producing animals for genetic resistance to disease are followed, the story of Marek's disease in chickens demonstrates that vaccines are often more economical to procure an animal's resistance to pathogens.

Elimination of Terrestrial Rabies in Europe with a Vectored Vaccine

Elimination of terrestrial rabies is predicted in continental Europe thanks to the use of a recombinant vaccinia-rabies vaccine. Through the systematic vaccination of the European wildlife reservoir, the fox (*Vulpes vulpes*) rabies was eliminated from Belgium and other European countries. The nucleid acid sequencing of rabies virus strains allowed the identification of the source of recontamination of the country in 1994 and a molecular approach allowed the identification in a rather simple manner of the origin (vampire bats or terrestrial) of human infection in Mexico and the demonstration that the ancestors of lyssaviruses are bat lyssaviruses.

The fact that bats are potential sources of short or long term « spillover » of lyssaviruses transmissible by a terrestrial mammal after adaptation poses a problem that cannot be solved since one cannot exclude the re-emergence of terrestrial rabies from an aerial source.

Prevention of Food Poisoning – Impact of Animal Vaccination on the Safety of the Food Chain

Recent news releases have revealed that the U.S. budget will focus on food safety and veterinary vaccines mainly to safeguard the U.S. food supply against possible terrorist threats. Among the food poisoning threats bacteria such as *Salmonella* are of paramount importance. Salmonellosis is a collective description of a group of diseases caused by bacteria of the genus *Salmonella*, with clinical signs which range from severe enteric fever to mild gastro-enteritis. There are more than 2,400 serotypes of *Salmonella*, differentiated by o (somatic) and h (flagella) antigens. All serotypes are pathogenic for man, animals or both. One of the characteristics of *Salmonella* is that different serotypes vary in the range of animals that they can infect and cause disease. For example, S. *typhimurium* and S. *enteriditis* have a very broad host range and infections with these serotypes have been associated with virtually all warm-blooded animals. Other serotypes have a more limited host range and this has been interchangeably referred to as host-specificity, host-restriction or host-adaptation. The highly host-specific serotypes only cause disease in phylogenetically closely related host species, for example S. *typhi* only infects humans, S. *abortus-ovis* only infects sheep and goats, while S. *gallinarum* only infects poultry. Other serotypes are predominantly associated with disease in one species but may also infect a limited number of other host species. For example, S. *dublin* is usually associated with cattle and S.

choleraesuis with pigs, but natural infection by these serotypes may occur in other animals, including humans.

Salmonellosis as a disease of humans, cattle, sheep, pigs and poultry is manifested clinically by one of three major syndromes: a peracute systemic infection, an acute enteritis or a chronic enteritis. Salmonellas may also be carried by animals in the absence of clinical signs and this is probably the normal situation in poultry and pigs infected with serotypes other than S. *pullorum/gallinarum* and S. *choleraesuis* respectively. The "host-adapted" serotype for pigs, S. *choleraesuis*, has virtually disappeared from most of Europe although still prevalent in other parts of the world, including the U.S.A.

It is accepted that *Salmonella* gastro-enteritis in humans is a zoonotic disease, mainly contracted by consuming large numbers of salmonellae in food of animal origin, or foods contaminated with animal products or foods in which salmonellae have proliferated.

The cycle of infection between man and animals is called the "Salmonella cycle". Infections in the human population are usually associated with the consumption of animal products such as eggs, milk and dairy products. Infections in farm animals are usually caused by animal-to-animal contact or contaminated feed. It is further complicated by the spread of disease by wild animals such as rats, birds and insects and by the recycling of animal products and wastes from one animal species to another. An understanding of salmonellosis and the eventual solution to the problem may only arise from a study of the disease in many animal species and the manner in which the bacteria responsible contaminate the environment, pass from one animal to another, cause disease in some and colonise others in the absence of disease.

The main source of infection for the human population is animal products and the principle sources of infection for domesticated livestock are other animals of the same species and contaminated feed. Although over 2,400 serotypes of *Salmonella* have been identified, most human and animal disease is caused by just a few of these. The most significant serotypes involved change over time for usually quite unknown reasons, although some such as S. *typhimurium* always seem to be present in a variety of species. It is currently impossible to predict when and why a serotype or phagetype will decline in prominence, either as a result of natural causes or control measures, or when a new serotype is likely to rise in importance, and whether it will be a greater or lesser threat to human and animal health. This highlights the importance of research to understand the host, bacterial or environmental factors involved

Control of salmonellosis as an example

Control of salmonellosis and prevention of food poisoning in the human population depends on: (i) reduction of disease and carriage of salmonellae in farm animals; (ii) improvements in slaughterhouse hygiene, (iii) prevention of cross-contamination of animal products, (iv) decontamination of processed foods and (v) improvements in food preparation and storage. It may also eventually be possible to produce vaccines for the prevention of food poisoning in humans.

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

In farm animals prevention depends upon: (i) sourcing feed free from salmonellae or decontamination of feed; (ii) reduction of contamination during rearing and transport; (iii) detection of carriers and infected herds/flocks; (iv) competitive-exclusion, i.e. e use of harmless bacteria to inhibit the growth of salmonellae in the gut of animals; (v) effective vaccination and, eventually (vi) the development of herds an oc s which are resistant to disease and colonisation.

Improvements have already been made in treating animal feed to remove salmonellae and in preventing re-contamination of treated feed. Detection of infected her s an flocks is also possible, although it mainly relies on isolation of the organism. It is si not possible, however, to detect animals which are carriers of salmonellae in t e absence of clinical signs, which is a prerequisite for the elimination of infection from chronically infected herds. .

The prevention of salmonellosis by vaccination of humans (against typhoid an paratyphoid) and animals has been possible for over 100 years, usually with limite success. Vaccination presents a number of problems, particularly since the disease may be caused by a large number of serotypes in both humans and animals. It ,s a necessary to produce vaccines which protect against disease and colonisation and the problem is made more difficult because animals are often infected within the first few days of life before traditional vaccines can be administered or induce an active immunity. This is particularly true of cattle and poultry - the possibilities for pigs are more optimistic. There are also problems with the use of attenuated vaccines in food-producing animals when the vaccine may still be present when the animals are slaughtered for consumption. It is, however, likely that live vaccine strains will be needed to provide good immunity. In addition to the requirements discussed above, such vaccines sh ould: (i) be demonstrably avirulent in all possible host species, including immune-compromised and wild animals; (ii) protect against all serotypes; (iii) protect against disease and colonisation; (iv) have no or minimal adverse reactions - this has been a problem with killed vaccines which may cause hypersensitivity reactions and with some live vaccines which may retain the ability to produce systemic reactions and diarrhoea; (v) not revert to a virulent form and (vi) be readily differentiated from wild-type strains - otherwise investigations of the epidemiology of the disease will be compromised.

The success of vaccination, particularly in farm animals, has been limited by a lack of understanding of the immune response to *Salmonella* infection. Although previous infection produces a limited protection, the mechanisms involved in domestic animals, compared to humans or experiment rodent models remain relatively unexplored. However, recent advances in our understanding of the pathogenesis of disease, colonisation and the development of protective immunity makes the development of safe, effective vaccines a possibility.

With this improved knowledge of pathogenesis it should now be possible to design live vaccine strains capable of invading and inducing an effective immunity and yet lacking the genes responsible for the induction of enteropathogenic responses which have been a possible side effect of current vaccine candidates. Further knowledge of the basis of host specificity is still required before they can be made effective against all serotypes.

In particular, mechanisms used by salmonellae to invade the intestinal mucosa and cause diarrhoea are known and the genes responsible have been described. Deletion of these genes from candidate live vaccine strains renders them avirulent and unable to cause diarrhoea.

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

It has long been known that some individuals in a population are more resistant to some infections than others and resistance to systemic salmonellosis in laboratory mice (under the control of the *Ity* or *Nramp gene*) was described more than 30 years ago. More recently it has been shown that resistance to invasive *Salmonella* infection in poultry is mediated by a single, autosomal, gene (Sall) located on chicken chromosome 5 and it has been possible experimentally to breed lines of resistant chickens.The Sall gene is expressed functionally in macrophages and is correlated with the level of oxidative burst generated as a result of *Salmonella* infection. Full identification of the gene raises the possibility of breeding commercial birds equally resistant, without interfering with desirable traits such as weight gain. Such breeds should be resistant to invasive serotypes such as *S. gallinarum*. They may also be resistant to localisation of *Salmonella* in the ovary, which is one of the mechanisms resulting in infection of eggs. Unfortunately, the same gene does not confer resistance in the alimentary tract. Further experiments have, however, shown that inbred lines of chickens also vary in their susceptibility to intestinal colonisation. Hopefully, identification of the gene(s) responsible may lead to the production of chickens which will not be colonised, thus reducing reliance on antibiotics for the control of *Salmonella* in commercial flocks. It is also possible that similar genes may control colonisation in other species, and *Nramp1* has been described in cattle and pigs. Families of pigs with different susceptibilities to experimental *S. choleraesuis* infection have been identified in research at IAH Compton. Resistance was correlated with recovery of salmonellae from the tissues and faeces of infected animals and resistant animals gained weight more rapidly than those in susceptible groups.

In summary, recent advances in our knowledge of the pathogenesis of salmonellosis, and in particular mechanisms involved in colonisation and enteropathogenesis make the production of safe effective vaccines against systemic salmonellosis, enteritis and colonisation a possibility in the short term. In the longer term it should be possible to breed poultry and pigs which are resistant to salmonellosis and colonisation by salmonellas.

Animal Health and Welfare ; Environmental Protection

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

The value of animal models for veterinary vaccines is not to be ignored, particularly since researchers have access to target animal models which are often more relevant, 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 than cellular responses 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 the in vitro is 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 of avoiding animal suffering since they prevent disease. Furthermore, due to the short lifetime of

many 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.

Vaccination : an Old and outstanding Recipe to Face New Challenges : As a Conclusion

VACCINATION AND VACCINES ARE FACING NEW PROBLEMS NOT YET SOLVED:

1.adaptation to ever changing pathogens;

2.consumer's attitude towards vaccination;

3.globalisation (the five Ts and transboundary diseases);

4.harmonisation of international regulations;

5.vaccination and disease eradication;

6.vaccination and public health;

7.what is the most adapted and pragmatic way to prevent or combat new and emerging infections in the prevailing regulatory environment while mitigating risk?

8.what is the best attitude in the face of agro-and bio-terrorism?

9.what is the best way to adapt tight regulations in the presence of ever evolving pathogens?

10.what is the impact of consumers' attitudes towards the vaccination of food producing animals as experienced during the last outbreak of foot-and-mouth disease in the European Union?

11.how much do we need to change our attitude towards control policies, taking into consideration globalisation?

12.what will be the impact of harmonisation of regulations for trade and medicinal products towards our attitude to vaccination?

13.what are the diseases to be eradicated through vaccination campaigns?

14.how do we implement compulsory vaccination of livestock or wildlife to protect animal and human health?

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

References

Audonnet JC: New advances in veterinary vaccines. Proceedings ESVV Congress on Virus Persistence and Evolution, Saint Malo, France, August 2003.

Bazin H: A brief history of the prevention of infectious diseases by immunisation. Comp Immunol Microbiol Infect Dis 2003;26:293-308.

Brochier B, Kieny MP, Costy F, Coppens P, Bauduin B, Lecocq JP, Languet B, Chappuis G, Desmettre P, Afiademanyo K, Libois R, Pastoret PP: Large-scale eradication of rabies using recombinant vacciniarabies vaccine. Nature 1991;354:520-522.

EMEA/CVMP: Position paper on requirements for vaccines against food-and-mouth disease. Committee for Veterinary Medicinal Products. EMEA/CVMP/775/02 - post consultation.

Jones P: Salmonellosis in pigs and prospects for control. Magazyn Weterynaryjny, Supplement Swine, 2002, pp 61-64.

Pastoret PP: Veterinary Vaccinology - Vaccinologie vétérinaire. Comptes rendus de l'Académie des Sciences, Paris, Série III, Sciences de la vie - Life Sciences, Vol 322, n°l 1,909-1016, Novembre 1999, pp 967-972.

Pastoret PP: The place of immunological medicinal products. 9th International Congress of the European Association for Veterinary Pharmacology and Toxicology, Lisboa, Portugal. J Vet Pharmacol Therap 2003;26(supplement 1):11-17.

Pastoret PP, Brochier B:The development and use of a vaccinia-rabies recombinant oral vaccine for the control of wildlife rabies; a link between Jenner and Pasteur. Epidemiol Infect 1996;116:235-240.

Pastoret PP, Brochier B, Languet B, Thomas I, Paquot A, Bauduin B, Costy F, Antoine H, Kieny MP, Lecocq JP, Debruyn J, Desmettre Ph: First field trial of fox vaccination against rabies with a vacciniarabies recombinant virus. Vet Rec 1988 ;123 :481-483.

Pastoret PP, Brochier B, Blancou J, Artois M, Aubert M, Kieny MP, Lecocq JP, Languet B, Chappuis G, Desmettre P : Development and deliberate release of a vaccinia-rabies recombinant virus for the oral vaccination of foxes against rabies, in Mattheuw M, Binns G, Smith L (eds) : Recombinant Poxviruses. Baton Roca, USA, CRC Press, 1992, pp 163-206.

Pastoret PP, Mackay D: Regulatory considerations for emergency use of vaccines in the European Union, in Brown F, Roth JA (eds): Vaccines for OIE List A and Emerging Animal Diseases. Dev Biol. Basel, Karger, 2003, vol 114, pp 53-58.

Pastoret PP, Vanderplasschen A: Poxviruses as vaccine vectors. Comp Immunol Microbiol Infect Dis 2003;26:343-355.

Wallis T: Salmonella pathogenesis and immunity: we need effective multivalent vaccines. The Veterinary Journal 2001;161:104-106.

Yamanouchi K, Barrett T, Kai C: New approaches to the development of virus vaccines for veterinary use. Rev Sci Tech Off Int Epiz 1998;17(3):641-653.

Published in : Developments in Biologicals (2004), vol.119, pp.15-29
Status : Postprint (Author's version)

Further Readings

Pastoret PP, Blancou J, Vannier P, Verschueren C (eds): Veterinary Vaccinology. Amsterdam, Lausanne, New York, Oxford, Shannon, Tokyo, Elsevier, 1997.

Pastoret PP, Griebel P, Bazin H, Govaerts A (eds): Handbook of Vertebrate Immunology. San Diego, London, Boston, New York, Sydney, Tokyo, Toronto. Academic Press, 1998.

An update on zoonoses. Rev Sci Tech Off Int Epiz 2000;19(l).