THIS MANUSCRIPT HAS BEEN PUBLISHED IN THE IVIS WEBSITE WITH THE PERMISSION OF THE CONGRESS ORGANIZERS.
To return to the Table of Content **click here** or go to **http://www.ivis.org**

CATTLE EPIZOOTICS, OLD AND NEW

Paul-Pierre Pastoret

Biotechnology and Biological Sciences Research Council (BBSRC), UK
paul-pierre.pastoret@skynet.be paul-pierre.pastoret@scarlet.be

1. INTRODUCTION

Rinderpest is certainly one of the epizootic diseases for which the most historical information exists (Barrett *et al.* 2006), this is no doubt due to the spectacularly high mortality that it causes and the speed with which it spreads, giving it all the hallmarks of an economic and social disaster. It explains why many of the people in Europe, Asia and Africa held painful memories of the incursion of this disease and faithfully recorded the events.

Originating in Asia it frequently spread into Europe and at the end of nineteenth century, Africa was stricken with Rinderpest. Early in the twentieth century Australia and the Americas faced accidental incursions: Brazil in 1920 and Australia in 1923, which each outbreak originating with importation of cattle from Asia. The outbreaks in Australia and Brazil were quickly contained.

In Western Europe the disease was eliminated through mere prophylactic hygienic measures, before even knowing the real origin of the infection. The viral origin of the infection was demonstrated as early as 1902 by Nicolle and Adil-Bey in Turkey. It is presently foreseen that Rinderpest will be eradicated from earth around 2010 thanks to vaccination.

Vaccination is without doubt the most useful single measure available to prevent animal infectious diseases. 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 (Pastoret & Jones, 2005). Mass slaughtering of animals raises ethical concern in developed countries, is unacceptable in developing ones, and is not in line with agricultural sustainability. Available technologies allow us to design "Marker" (DIVA) 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 with foot-and-mouth disease, Bluetongue, or infectious bovine rhinotracheitis where carrier state or latency remain an issue after vaccination.

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.

Nowadays vaccines should be designed to prevent infection rather than to prevent clinical signs of disease and should, wherever possible, produce sterile immunity.

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 or from treatment for a cure, which may result in antibiotic resistance and pharmaceutical residues in food.

2. RINDERPEST

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.

Eradication means the complete elimination of the infection (causal agent)/disease worldwide; as already mentioned, only one disease has been eradicated so far, smallpox. A similar simian infection with a rodent reservoir still prevails.

According to Frank Fenner, the characteristics of the disease which permitted the eradication of smallpox were:

- that it was an important and “serious” disease,
- the absence of sub-clinical infection or silent excretion,
- the animals were not contagious during the incubation or prodromic periods,
- the absence of asymptomatic carriers or recurrent access of excretion or disease,
- one virus serotype,
- the availability of an efficacious and stable vaccine,
- seasonal incidence,
- no alternative reservoir.

The only animal disease which may be eradicated in the same way, because it possesses the same characteristics necessary for eradication, is presently Rinderpest.

Morbilliviruses have infected animals and man since the time of early civilisations, 5000 to 6000 years ago. These civilisations presented, for the first time, large populations of susceptible animals and people, a fact which guaranteed the presence of young naïve individuals in sufficient numbers for transmission and maintenance of the infection; 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 expansion of Rinderpest was always encouraged by wars, civil disturbances 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, as already mentioned, Rinderpest was the major plague of cattle up to the end of the 19th 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. Prophylactic measures (slaughtering, sequestration, disinfection) were applied and the disease was eliminated after approximately five months. The reintroduction of Rinderpest into continental

Europe highlighted the need for international collaboration to fight against the major contagious diseases of domestic and wild animals. This resulted in setting up the Office International des Epizooties (OIE), the World Animal Health Organisation. 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 the infection; 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 (lineage 2) in East Africa (Somalian ecosystem), and the coexistence of a similar disease in small ruminants (Peste des petits Ruminants); once the problem of Rinderpest will be solved, the same strategy could be applied to the eradication of this infection.

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 constitutes a dead end. The struggle to eradicate Rinderpest is therefore limited to domestic cattle, and the best tool for eradication is vaccination.

3. "MARKER" (DIVA) 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 or 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 no more be accepted 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) Pestivirus (Mignon *et al.* 1992).

Other diagnostic methods are indirect since they are based upon the detection of specific antibodies against the suspected infectious agent. These methods, even often more reliable mainly because of the temporary presence of the infectious agent within the animal, do not give immediate results since they depend upon the synthesis of specific antibodies by the animal after infection or vaccination.

Many diagnostic problems can be overcome by the use of "Marker" (DIVA) vaccines and companion diagnostic tests.

There are two types of system used; these are either based upon the detection of a serological response against a protein, the gene coding for being deleted in the vaccine strain (attenuated or inactivated; 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 single 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) the choice of the marker may vary and be linked to several other proteins. To standardise diagnostic tests a choice must be made.

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, not usually immunologically recognised by the animal, 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 allow detection of 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 previously mainly designed to prevent clinical signs without necessarily acting upon the epidemiology of the infection; excretion and transmission of wild virus following infection, dissemination and circulation. Nevertheless, with marker vaccines, there can be a problem if wild virus multiplication is inhibited to such an extend as to prevent synthesis by the animal of specific antibodies against the vaccine-deleted protein, or non-structural proteins produced during wild virus infection.

The attitude of Society at large towards mass slaughtering of infected or in-contact animals is evolving. A better alternative to mass slaughtering is “vaccination for life” (i.e. vaccination strategy 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 some of the available companion diagnostic tests can only be used for herd certification instead of individual certification; diagnostic tests should be validated and certified for use.

4. THE EXAMPLE OF INFECTIOUS BOVINE RHINOTRACHEITIS

Original vaccines against Infectious Bovine Rhinotracheitis (IBR) were mainly designed to prevent clinical signs of the disease after infection of the animal with a wild virus. In the European Union several countries have implemented a programme of Infectious Bovine Rhinotracheitis elimination. The Herpesvirus responsible for the infection remains latent after infection, regardless of whether the animal is vaccinated or not. Wild virus can become latent whether an inactivated or an attenuated vaccine was 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 (undeleted) 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 IBR 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 vaccines, all the seropositive ones must be eliminated from the herd.

In fact in these circumstances, an animal can either be:

- vaccinated,
- infected,
- vaccinated and infected afterwards,
- infected and vaccinated afterwards.

A solution may come from the use of a marked/deleted vaccine. The deleted gene in the vaccine strain must code for a protein showing the listed characteristics:

- be a structural protein (inactivated vaccines),
- not be essential in order to produce the vaccine,
- not be an essential protective immunogen in order to still have an effective vaccine,

- induce a significant and long-lasting humoral immune response when present,
- be present in all wild virus strains,
- induce a humoral immune response in vaccinated animals when infected by a wild virus.

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

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

The main issue with marker vaccines against Infectious Bovine Rhinotracheitis is their limited epidemiological impact. Vaccines able to induce a sterile immunity are not currently available.

Vaccination schedules must be more stringent than those used at present, designed for protection against clinical signs; vaccination must be repeated and associated with strict health measures. For an elimination campaign, epidemiological protection must only include prevention of excretion of wild virus by naïve animals, but also prevent re-excretion by latently infected ones. Attenuated vaccines produced with identical strains, deleted or not, are more efficacious than their inactivated counterparts.

5. VACCINATION AGAINST FOOT-AND-MOUTH DISEASE AND PURIFIED VACCINES

Foot-and-Mouth Disease was first scientifically described during the Renaissance period. Since the 17^{th} 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 in place against Rinderpest, were inefficient 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 with inactivated vaccines has been prohibited in the European Union since 1991, with some amendments nowadays. This prohibition ended a 30-years period of preventive vaccination and consequently produced the progressive appearance of completely naïve cattle populations.

This is particularly detrimental in case of accidental re-introduction as seen the last European outbreaks. To overcome the risks linked to the complete susceptibility of European livestock, vaccine banks of concentrated inactivated antigens have been established and there is now the prospect of using marker vaccines in case of an emergency.

In fact, when a highly purified vaccine is used, whenever an animal is seropositive against non-structural proteins coded by the virus (NPS) it is clear that it has been infected by a wild virus.

During Foot-and-Mouth Disease virus multiplication the NPS are synthetised at the same level as structural proteins (cleaved polyprotein). The NPS are only produced when virus multiplication occurs and are not contained in extracellular virions used to produce purified inactivated vaccines. To remove contaminating NPS during vaccine production, it must be submitted to a purification procedure to ascertain that it only contains structural proteins before formulation. Unfortunately the companion diagnostic test currently available only allows the certification of the absence of contamination at a herd level instead of an individual one.

In case a policy vaccination for life is in place to control Foot-and-Mouth Disease outbreaks, it will be necessary to distinguish between preventive and emergency vaccines. With emergency vaccines, early onset of protection is essential, whereas with preventive ones, the duration of protection is the main goal.

6. ELIMINATION OF TERRESTRIAL RABIES IN EUROPE WITH A VECTORED VACCINE

Elimination of terrestrial rabies is predicted in the European Union thanks mainly through the use of a recombinant vaccinia-rabies vaccine (Brochier *et al.* 1991).
Cattle was previously the main source of contamination for man. Through the systematic vaccination of the European wildlife reservoir, the red fox (*Vulpes vulpes*) rabies was eliminated from Belgium and other European countries.

The fact that bats are the “Archeoreservoir” of Lyssaviruses and a potential 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.

7. CONCLUSION

Thanks to the use of old prophylactic methods and veterinary policy main epizootic diseases could be eliminated or even eradicated.

Nevertheless the epidemiological situation is continuously evolving and new diseases appearing or emerging; a new haemorrhagic form of Bovine pestivirus infection appeared in North America, Bovine Spongiform Encephalopathy did spread worldwide, and Bluetongue is extending its range in the Mediterranean region. Viruses, especially RNA viruses are evolving rapidly and we can still expect further development in the epidemiology of cattle diseases.

Fortunately new technologies and better surveillance allow more predictive epidemiology.

Infections caused by multiple serotypes pose specific problems since vaccines must fit with the prevailing strains in the field, and one may ask what is the best way to adapt tight regulations in the presence of ever changing pathogens.

8. SUMMARY

Several epizootic diseases can be eliminated through hygienic measures or thanks to the use of efficacious vaccines. The eradication of Rinderpest, the old plague, is foreseen by the year 2010. New technologies allow us to develop “marker vaccines” (DIVA) with their companion diagnostic tests in order to differentiate vaccination from infection. New technologies and better surveillance also allow us to better predict epidemiological trends of infections. Nevertheless pathogens are evolving rapidly, some of them have multiple serotypes, and we are still facing emerging new infections. Even if tightly regulated vaccines must fit with the prevailing pathogens in the field.

9. KEY WORDS

Epizootic diseases, rinderpest, marker vaccines.

10. RÉSUMÉ

Plusieurs maladies épizootiques ont été éliminées grâce à la stricte application de mesures de prophylaxie hygiénique ou grâce à l’emploi de vaccins efficaces. L’éradication de la Peste bovine,

ce vieux fléau, est prévue pour l'année 2010. Les nouvelles technologies nous permettent actuellement de développer des vaccins marqués (DIVA) assortis de leurs tests de diagnostic compagnons qui autorisent la distinction entre une vaccination et une infection. Les nouvelles technologies et l'amélioration de la surveillance nous permettent également de mieux prédire les tendances épidémiologiques des infections. Néanmoins les agents pathogènes évoluent rapidement, certains d'entre eux se présentent sous de multiples sérotypes, et nous faisons régulièrement face à de nouvelles infections émergentes. Même si les vaccins sont l'objet d'une réglementation rigoureuse, ils doivent être adaptés aux agents pathogènes présents sur le terrain.

11. MOTS CLÉS

Maladies épizootiques, peste bovine, vaccins marqués.

12. REFERENCES

Barrett T, Pastoret PP, Taylor WP. Rinderpest and Peste des Petits Ruminants. Virus Plagues of Large and Small Ruminants. Biology of Animal Infections. Academic Press (Elsevier), 2006.

Nicolle M, Adil-Bey M. Etudes sur la peste bovine (3ème mémoire) Ann Inst Pasteur, 1902; 16:50-67.

Pastoret PP, Jones P. Veterinary Vaccines for Animal and Public Health. In: Control of Infectious Animal Diseases by Vaccination. A. Schudel, M. Lombard, Ed. Dev Biol, 2005; 119:15-29.

Mignon B, Waxweiler S, Thiry E, Boulanger D, Dubuisson J, Pastoret PP. Epidemiological evaluation of a monoclonal ELISA detecting Bovine Viral Diarrhea Pestivirus in field blood samples of persistently infected cattle. J Virol Methods, 1992; 40:85-94.

Brochier B, Kieny MP, Costy F *et al.* Large-scale eradication of rabies using recombinant vaccinia-rabies vaccine. Nature, 1991; 354:520-522.

Pastoret PP, Blancou J, Vannier P, Verschueren C. Veterinary Vaccinology. Elsevier, 1997.

An update on zoonosis. Rev Sci Tech OIE, 2000; 19:1.