Vaccination and control of infectious and parasitic diseases
M Éloit, Jj Benet, P Bourdeau

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Introduction

The design of vaccination strategies relies on a knowledge of the epidemiology of infections. Pathogens have developed different strategies for survival in animal populations. Epidemic processes are mainly dependent on interactions between hosts and pathogens. A presentation of these interactions and their consequences on epidemic processes will be made in the first part of this paper. The objectives of vaccination schemes will be analysed in connection with different kinds of diseases in the following section. Finally, analysis of the available vaccines and future trends for vaccine development will be presented.

Survival and propagation of pathogens

Interactions between host and pathogen

The mode and duration of shedding may be very different, depending on the host/pathogen relationship. The pathogen is shed by most hosts, as a general rule, in the days (weeks and even months, in the case of helminths) following infection or infestation of virgin hosts. Nevertheless, for diseases like rabies, for which there is a long incubation period, shedding may be delayed until the appearance of the symptoms. After the early phase of infection, the mechanism of the pathogen shedding depends of the kind of infection.

Acute infection

In the case of acute infection, the host develops an efficient immune response after the onset of primary infection, in such a way that the pathogen is eliminated or controlled within a few days or weeks. Nevertheless, the pathogen can remain present in some hosts for several weeks and even months. These long-lasting infections of a small proportion of hosts are called ‘chronic infections’. Because they only concern a small proportion of the infected host population and because they generally do not last their host’s entire lifetime, they must be differentiated from persistent infections. Most infections develop this way. Some examples are influenza, rinderpest, distemper disease, foot-and-mouth disease, self-limited coccidiosis (ie due to Eimeria) and babesiosis.

Shedding of the pathogen can occur before the appearance of any symptoms. For instance, the rabies virus can be excreted for up to 10 d before the symptoms are manifested, and the foot-and-mouth virus for 2–20 d. Generally speaking, the level of pathogen excretion is maximal during the period when the symptoms are manifested, for example, about $10^{12}$ Brucella sp are excreted during abortion. Chronic infection can last as long as 1 year (foot-and-mouth disease or babesiosis) in some individuals.

Persistent infection

Some pathogens remain in their infected hosts for much of their lifetime. These pathogens have developed various strategies that permit them to escape the immune response.

One of these strategies is to cross the placental barrier and to infect the foetus before the development of its immune system. In this way, the pathogen antigens are identified as self-antigens. In the case where there is no abortion or foetal death, the newborn animal will be persistently infected but will not mount any immune response against either the infecting strain or an eventual
superinfecting strain harbouring the same antigen. Examples of this kind of pathogen can be found in pestiviruses (BDV and HCV) and Brucella. In some rodent species, infection with arenaviruses (like LCMV) just after birth leads to the same situation.

Another strategy relies on the capacity of the pathogen to hide its antigens or to down-regulate the immune response. This can be done by infecting antigen-presenting cells or effector cells of the immune system (lentiviruses like FIV and visna virus, Theileria sp, Leshmania and Toxoplasma), by down-regulating the MHC antigens of infected cells (adenoviruses) or by repressing the synthesis of the structural proteins (retroviruses like BLV). This last strategy is very efficiently used by herpesviruses, which can totally repress the synthesis of almost all their gene products. In the infected cell, only the genome of the herpesvirus is present, so that these cells are not recognised by the immune system. These infections are called ‘latent infections’.

Another way of escaping the immune response is antigenic variation, a strategy used by lentiviruses and parasites (Trypanosoma sp), or antigenic mimicry (Schistosoma).

Shedding from persistently infected animals can be continuous (for example, most retroviruses). In other cases (latent infections of herpesviruses), shedding only occurs from time to time, after the latent genome has been re-activated by exogenous factors (like stress). Shedding is linked to the longevity of the adult in case of helminths.

Epidemic process

This section will present various modalities affecting the survival time of a pathogen in an animal population.

Survival of pathogens

Pathogens can follow different strategies in order to survive in animal populations, from single cycles to complex ones. In this presentation, cycles will be classified according to their number of compartments. A compartment is defined as a cluster where only one kind of transmission occurs.

One-compartment cycles

The simplest cycles occur in one compartment only. The modalities of surviving depend on the length of time of the excretion of the pathogen. Several examples are given in figure 1.

If the length of time is short, compensation must be made by having a high density of a susceptible animal population (fig 1A). For example, the rabies virus is excreted for a very short time (a few days before the onset of symptoms and during the symptoms, which are followed by the death of animal). In this situation, incidence and prevalence rates are similar and must be above a certain threshold value to allow the survival of the pathogen.

Other pathogens, like BLV, persist in the host for a very long time, often the animal’s entire lifetime, and are excreted throughout this period (fig 1B). This implies that the pathogen may persist even when there is a low density host population. Incidence rate is usually several orders of magnitude lower than prevalence rate, if no eradication program is conducted. Contrary to the previous example, prevalence rate may be very low without compromising the survival of the pathogen. Nevertheless, in certain conditions (high density area and pathogens that are shed at high titres), there may be evidence of a high prevalence of infected herds. Such examples can be also found in parasitology in the case of a direct life-cycle where only a single host is involved. The parasite may have a free living phase (with or without evolution) in its cycle (indirect transmission as in Trichostrongylosis in ruminants) or not (direct transmission as in infection by Oslerus in dogs).

A third class of pathogens includes the characteristics of the 2 previous classes (fig
For example, pestiviruses can persistently infect some animals if they are infected in utero, in such a way that infection may persist in herds which are free of susceptible animals (for instance, after vaccination). Such pathogens are also excreted for a short time at high titre after primoinfection, so that the virus can be efficiently spread horizontally in high density populations. This is also the case for herpesviruses, which can persistently infect animals and efficiently spread horizontally in non-immune animals.

**Two-compartment cycles**

Such pathogens show 2 kinds of survival modes (fig 2).

Arboviruses, such as African swine fever virus (fig 2A), are one example of this kind of pathogen. In southern Europe, the virus may survive in some pig herds through basic cycle of infection which develops between soft ticks and pigs. A population of ticks remains infected through both transovarian transmission and feeding on infected pigs. But this cycle is not indispensable for the survival of the virus. It can survive by horizontal transmission from acutely infected animals and also from chronically infected pigs. The infection thus appears as being enzootic, either at a low or high prevalence rate, depending on the main cycle involved.

Tellurian diseases, for example, anthrax or erysipelas, provide another example of this kind of pathogen (fig 2B). Anthrax is the prototype of such pathogens, because, after sporulation, it can survive for years in the environment. Contamination of susceptible animals (mostly ruminants) develops from the consumption of forage that is contaminated with spores of *Bacillus anthracis*. Dead animals contribute to the over-contamination of soils, and from time to time, are responsible for the contamination of new locations. This explains why the disease may persist for years in certain areas, with long periods of silence between outbreaks.

**Complex cycles: parasitic diseases**

Parasitic diseases with complex cycles are characterized by having an indirect life cycle involving several obligatory hosts: a final host in which the reproductive stage of the disease develops; and intermediate

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**Fig 1.** One-compartment cycles. The modalities of pathogen persistence in a population over time (represented by the arrow at the top of each rectangle). The bold circles represent animals that are shedding the pathogen. The length of the arrow attached to the circle represents the duration period of pathogen excretion. The empty circles symbolize pathogen-free animals. 1A: A short period of excretion and high density susceptible population (rabies, etc). 1B: A long period of excretion that permits the survival of the pathogens even in the case of a low density of susceptible animals (BLV, etc). 1C: Coexistence of animals with short and long duration pathogen excretion (pestiviruses).
Infection of hosts by pathogens may or may not lead to the development of the disease, depending on factors which determine the susceptibility of the animals. When the pathogen is necessary and sufficient to induce disease, this disease is called monofactorial disease. When the pathogen is necessary but not sufficient to provoke the disease by itself, it is called a multifactorial disease. Figure 3 summarizes this concept.

The notion of susceptibility of a host includes 2 concepts, which must be clearly differentiated in order to evaluate vaccine potency. Susceptibility can be defined as the ability of a host to permit the replication of a pathogen. For example, pigs and horses are respectively susceptible and non-susceptible to the foot-and-mouth disease virus. Susceptibility is also defined as the ability of a host to develop symptoms of the disease after infection. As an illustration of this second concept, rodents are not susceptible for the Venezuelan equine encephalitis virus; they remain asymptomatic after infection, but develop a viremia in such a way that they are considered to be a reservoir of this virus. Vaccinated animals can become completely non-susceptible for the target pathogen. The pathogen can no longer replicate within them and they do not develop symptoms of the disease. This is the case, for instance, for rabies vaccines. In other cases (i.e. herpesvirus vaccines, such as Aujesky’s disease, or infectious bovine rhinotracheitis vaccines), vaccination prevents the appearance of symptoms but the pathogen is still capable of replicating itself and being shed by a vaccinated animal.
It is important to bear in mind that the susceptibility of a host is dependent on the dose of the pathogen. A minimal dose is necessary to cause infection in an animal. For example, 10 TCID$_{50}$ of a virulent strain of Aujesky’s disease virus never leads to the development of symptoms in mice, 1 000 TCID$_{50}$ sometimes, and 100 000 TCID$_{50}$ always. This notion is also true for parasitic diseases, where the number of parasites a host acquires is invariably related to the severity of the disease. Generally speaking, higher doses of pathogens are necessary to infect vaccinated animals than non-vaccinated animals. This means that the best vaccines use doses that are improbable in field conditions. Nevertheless, infection of vaccinated animals remains possible in experimental conditions.

**Monofactorial diseases**

Major pathogens (rabies, foot-and-mouth viruses, Babesia) can cause the disease in any infected animal. Other pathogens are only pathogenic in some animals. Frequently, young animals are more susceptible than older ones (colibacillosis and toxoplasmosis). Some diseases are only apparent in immunocompromised animals (demodicosis in puppies with T lymphocytes deficiency). Others are frequently seen in stressed animals (erysipelas in pigs).

These differences in susceptibility must be differentiated from differences of exposure to the pathogen. For example, dogs and cats seem to be equally susceptible to *Mycobacterium tuberculosis*, but this disease is more often found in dogs, reflecting a greater exposure of dogs to the pathogen.

**Multifactorial diseases**

Many important diseases are now recognised as being multifactorial: one or several pathogens can be associated but they only act as pathogens in the presence of certain environmental conditions. Figure 3 summarizes this concept. Enteric diseases of the young, mastitis, enzootic bronchopneumonia, and coccidiosis in poultry belong to this category of diseases. Generally speaking, experimental reproduction of such diseases through inoculation of the pathogen or a combination of several pathogens is difficult. More often, these pathogens are prevalent in the population, and diseased herds represent only a small proportion of infected herds. Some environmental conditions, like the temperature of the shelters, humidity, association with other pathogens, concentration of animals seem to be necessary to bring about the onset of the disease. In the case of the last condition, a high concentration of animals often leads to a higher concentration of pathogens, which, in addition to stress, is an explanation for such a multifactorial relationship. As depicted in figure 3, the relative importance of the pathogen(s) compared with that of environmental conditions can be very different.

The distinction between monofactorial and multifactorial diseases is very important in designing adequate measures to combat disease, especially in relation to vaccination strategies.

**Vaccination strategies**

The different objectives for vaccination are depicted in figure 4 and referred as V1, V2 and V3. From the right to the left, it appears that 3 objectives are desirable: diminution of the disease consequences; diminution of its prevalence; and diminution of its incidence.

Diminution of the disease consequences (severity of the symptoms, duration of the disease, lag before full recovery) is the objective (V1) that is the easiest to reach. Generally speaking, it is the only objective which can be reached by vaccination against multifactorial diseases, as in, for instance, enzootic bronchopneumonia in cattle. Devel-
Diminution of incidence is an objective (V3) that is increasingly desired for veterinary vaccines against monofactorial diseases. Unfortunately, this implies that: i) the epizootic process occurs in a one-compartment cycle (see above); and ii) the immune response can control the multiplication of the pathogen, which will prevent shedding (or limit it to a very low titre). This latter point is generally the case for acute infections (see above). For example, the vaccination of fox against rabies and human against smallpox have been or are being successful in eradicating their respective diseases. The efficiency of these mass vaccination schemes only relies on the proportion of the animal population vaccinated. Nevertheless, it is clear from figure 4 that vaccination cannot protect against the risk factors of infection. Some isolated cases or outbreaks of the disease can still occur, although it does not propagate because the host animals are vaccinated, and they may even not be detected. This is why infection-free countries must restrain their trade exchanges with countries using vaccination strategies. On the other hand, when these 2 conditions are not reached, diminution of incidence through vaccination (and, indeed, eradication) is very difficult or impossible. These points will be developed with 2 examples.

The first example concerns diseases which develop through 2 compartments. It is clear that vaccination of domestic species against most arboviruses would have only marginal (if any) effect on the epidemic process. It is also the case for tellurian diseases like anthrax. The second example concerns persistent infection, even for a simplest case and one which develops through one-compartment cycles. A well-known example is Aujeszky's disease in pigs. Vaccination can neither stop shedding after infection, nor prevent latency of the infecting strain, thus, eradication of the disease through vaccination is very difficult, unless costly sanitary measures (like stamping out) are included.

Fig 4. Relationships between the epidemiology of disease (incidence, prevalence) and vaccination strategies. S1: sanitary measures; V1, V2, V3: vaccination strategies.
**Vaccines and future trends**

Different kinds of vaccines are either currently available or are being developed (Table I). It is clear that the choice of a development strategy of a vaccine is always made on a case-by-case basis, depending on the possibility of cultivating the pathogen, the existence of attenuated strains and the kind of immunity requiring stimulation (local/general, humoral/cellular). Never-

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Comments</th>
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<th>Licensed (L) or experimental (E)</th>
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<tr>
<td><strong>Live vaccines</strong></td>
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<td>Heterologous strains</td>
<td>Strain for another animal species</td>
<td>Shope virus (myxomatosis)</td>
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<td>Spontaneously attenuated strains</td>
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<td>Marek’s disease</td>
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<tr>
<td>Conventionally attenuated strain</td>
<td>Attenuation by chemical mutagenesis, cell culture passages at normal or low temperature, animal passage in another species, etc</td>
<td>SAD strain (rabies)</td>
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<td>Site-directed mutagenesis</td>
<td>Deletion of genes implicated in virulence</td>
<td>TK-gl-strains (Aujeszky’s disease)</td>
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<td>Vectored vaccines</td>
<td>Virus or bacteria expressing a foreign gene</td>
<td>Vaccinia-G (rabies)</td>
<td>E (November, 1994)</td>
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<td><strong>Inert vaccines</strong></td>
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<td>Inactivated whole pathogen</td>
<td>Inactivation by heat, formaldehyde, etc</td>
<td>Leptospira vaccines</td>
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<tr>
<td>Subunit vaccine</td>
<td>Use of immunogenic proteins of the pathogen</td>
<td>Detergent extracted glycoproteins (Aujeszky’s disease), anatoxin (tetanos)</td>
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<td>rDNA expressed proteins</td>
<td>Protein expressed in eukaryotic or prokaryotic cells</td>
<td>env protein (FeLV)</td>
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<td>Peptides</td>
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<td>Anti-idiotypic vaccines</td>
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<td>Genetic immunisation</td>
<td>Direct inoculation of a protein encoding gene</td>
<td>N protein (influenza)</td>
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Vaccines et vaccinations en santé animale
theless, some general requirements for both the present and future can be underlined.

Several points must be addressed about the efficiency of vaccines. Vaccines (or vaccination schemes) for the vaccination of young animals that still have maternal antibodies is an urgent need in several species, from pet to farm animals. Vaccines designed to induce a high level of mucosal immunity would also be very useful for many diseases. Until now, such immunity could only be stimulated for the most part through administration of live strains via local routes, a strategy which leads to a risk of dissemination of the vaccine strains. Vaccination against persistent infections is another main goal. For virus infections, this could be done through stimulation of a cytotoxic T-cell response against the conserved proteins of the pathogen. The definition of vaccines against parasitic infections is still difficult and relies on the identification of immunogenic proteins of the parasite.

The ease of administration of the vaccines also affects the possibility and often the cost of vaccination schemes. For this reason, and also for reasons related to the stimulation of a local immunity, the oronasal route seems to be a preferable local route for vaccination. This is particularly true for the vaccination of wild animals (rabies in foxes and hog cholera in wild boars), but also for animals in intensive livestock production units (pigs and chickens).

**Bibliography**


**Veterinary vaccines. Specificities and the weight of regulations.** P Vannier (CNEVA, BP 53, 22440 Ploufragan, France)

The specificities of veterinary vaccines or immunological veterinary medicinal products (IVMPs) need to be considered in the light of the present market and its worldwide distribution and the restrictions induced by the economy and regulations. Most of the data presented here are extracted from the inquiry carried out by FEDESA (Fédération Européenne de la Santé Animale) which was ordered by the Commission of the European Communities (Anon, 1994).

**The world market for IVMPs**

The market share for IVMPs is 1% of total world pharmaceuticals market. It also forms approximately 18% of the animal health product market which has a value of 1 323 millions ECU (Anon, 1994). The distribution of the IVMP market in the world is the following: Latin America 14%; North America 27%; East Asia 17%, Western Europe 26%; and others 16%. In the European Union, the distribution of the market is the following: Belgium 4%; Germany 20%; Denmark 4%; Spain 10%; France 24%; Greece 1%; Ireland 2%; Italy 10%; the Netherlands 6%; Portugal 2%; and the United Kingdom 18%. There is no relationship between the market value and the number of products it represents. For example, France, the largest market, has fewer products for most species than the second largest market Germany (table I; Anon, 1994). Slight differences exist in the US, Japanese and European markets. In US, the vaccines for ruminants, pets, swine and poultry represent respectively 33, 30, 13 and 10% of the market. In Japan, the vaccines for poultry predominate the market with 45% of the total sales. They are followed by pigs (25%) and pets (20%).