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Emerging diseases, zoonoses and vaccines to control them

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ABSTRACT

Vaccination, when available, is undoubtedly the most cost-effective means of preventing and controlling, and even eradicating, infectious diseases. In recent years vaccination has also been used for other purposes in animal health, production and welfare, e.g. immunocastration.

Vaccination of animals serves many different purposes, such as controlling animal infections and infestations, thus improving animal health and welfare; controlling anthropozoonoses and food poisoning in humans, thereby protecting public health; solving problems associated with antibiotic and anthelmintic resistance; helping to leave food-producing animals free of chemical residues; protecting the environment and biodiversity and ensuring animal farming sustainability. The problem is nevertheless more complex when facing emerging or re-emerging infections particularly zoonotic ones.

1. Introduction

Vaccination, when available, is undoubtedly the most cost-effective means of preventing and controlling, and even eradicating, infectious diseases. Unfortunately the problem is more complex when facing emerging or re-emerging infections particularly zoonotic ones.

For instance canine parvovirosis was a real emergence in animal health [1,2]; the first step was to vaccinate dogs with a vaccine directed against feline panleukopaenia since the two causative viruses are antigenically nearly identical. This first step was rapidly followed by the development of vaccines, either inactivated or attenuated, specifically directed against canine parvovirosis. Some situations are more problematic when facing the outbreaks of diseases caused by viruses showing broad antigenic diversity such as *Foot-and-mouth disease virus* or *Bluetongue virus*; in this latter case it is even more difficult due to the fact that the infection is transmitted by a Culicoides vector from the family Ceratopogonidae (biting midges). It took two years in Northern Europe before inactivated vaccines against serotype 8 of *Bluetongue virus* were available [3]. In Northern America, the spectacular spread of *West Nile virus* infection, another vector transmitted disease, in humans and horses, was rapidly followed by the development of several vaccines, including a DNA-based vaccine for horses. One solution to be ready to vaccinate in face of an outbreak of a re-emerging infection is to stockpile vaccines as exemplified by *Foot-and-mouth virus* vaccines as concentrated antigens. Stockpiling is also envisaged for the possible pandemic of avian influenza H5N1 in humans [4] (pandemic preparedness) or to mitigate the risk of bio-agro-terrorisms. For time being it seems more appropriate to combat the H5N1 influenza infection at the animal source to reduce human exposure.

To prevent *Nipah virus* (*Henipavirus*) infection in pigs a vaccine has recently been developed but, unfortunately, in countries like Bangladesh, humans are directly infected by the reservoir, a fruit bat species. Animals may be vaccinated against certain infections not for their own sake, but to prevent human contamination. One of the best example being wildlife vaccination against terrestrial rabies by the oral route using baits [5]. Animal vaccination may also be used to prevent food poisoning in humans; a vaccine against *Escherichia coli* 0157:H7 has for example recently been conditionally approved for cattle in the United States.

The changes following globalisation, climatic change [6,7], and the opening of previously closed ecosystems, have considerably modified the pattern of endemic (or enzootic) infections/diseases, and contributed to the emergence of new agents that are pathogenic for humans and domestic animals.

Emerging infections is a collective name for infections that have been identified and taxonomically classified recently. In humans, in the final quarter of the twentieth century, more than 30 such conditions were recognised [8].

Zoonoses are defined as infectious diseases that can be transmitted naturally between humans and wild or domestic animals. These infections are particularly important in the context of emerging infectious diseases of humans as the majority of these are of zoonotic origin; a comprehensive review by Cleaveland et al. [9] identified 1415 species of infectious organisms known to be pathogenic to humans, including 217 viruses and prions, 538 bacteria and rickettsia, 307 fungi, 66 protozoa and 287 helminths. Out of these, 868 (61%) were classified as zoonotic and 175 pathogenic species were considered to be associated with emerging diseases.

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Of 175 emerging pathogens of this group, 132 (75%) were zoonotic [40], the vast majority of which coming from wildlife.

Wildlife obviously constitutes an important potential of new pathogenic agents for humans and domestic animals [10]. This paper will mainly focus on viruses, mammals and birds.

2. Biodiversity (viruses and vertebrates)

Nowadays, the total number of viruses identified reaches approximately 5000 species [11], but the likely number could exceed 130,000 according to the first estimates. Even this number is most probably an underestimate (e.g. a well-known mammal species like human beings harbours at least 8 different *Herpesviruses*, and 5 different *Herpesviruses* have been identified in cattle until now), but if one takes into account the estimated number of 130,000, only 4% of viruses have already been identified.

Moreover, it does not take into account their extreme variability, particularly RNA viruses, leading to populations of *quasi-species*.

If one considers that there are 5416 recognised mammal species and that, for instance, *Herpesviruses* have been isolated from all classes of vertebrates and even from oysters, one must admit that the world of viruses is huge. The use of viral metagenomics will help to identify more viruses [12].

For mammalians, 5416 different species have already been recognised, whereas the expected number of species is estimated to be around 5500; for mammalian species we are, therefore, nearly at the end of the inventory, since 99% of the species are already known.

The inventory of mammalian species was first established in 1982, when only 4170 species were recognised; the same inventory established in 1993 contained 4629 different species.

In 2005, as already mentioned, the complete list of mammal species consisted of 5416 species [13].

This increase in number seems to be paradoxical and even contradictory if one takes into account the extinction of some species during the same period of time. This increase in number can be accounted for when one considers that each phenotype of newly discovered species is listed separately and, more importantly, that the advent of modern molecular technology allows for the discrimination of species according to their genotypes and increasingly detailed comparisons of species limits and evolutionary relationships (taxonomic revision).

Among mammals, there are 2277 species of rodents pertaining to 481 genera. Since 1993, 128 new rodent species have been recognised. The rodents therefore compose 42% of recognised mammal species. This number is particularly important if one takes into account the fact that the order of rodents harbours, and is the reservoir of numerous zoonotic infections. Among the most spectacular are Hantaviroses [14]; some African *Sciuridae* species (*Funisciurus* spp., *Heliosciurus* spp.), are the reservoir of Monkeypox [15]. Recently, the introduction of one of these species into the United States nearly provoked an ecological disaster, due to the transmission of the virus to indigenous rodent species (prairie dogs) [16].

To date, the order of *Chiroptera* contains 1116 species, pertaining to 202 genera; 49 new species have been identified since 1993. Bats make up therefore 20.6% of the total number of mammal species. This is worrying, since bats have been the source of many emerging diseases, many of them being previously unknown. For instance, insectivorous and frugivorous bats are the reservoir of the *Archeolyssaviruses*, from which all *Lyssavirus* strains derive, even the strains responsible for terrestrial rabies. Frugivorous bats are the reservoir of newly discovered viruses such as *Nipah* and *Hendra* (*Henipavirus*), responsible for numerous human fatalities, of the *Coronavirus* responsible for the epidemics of the severe acute respiratory syndrome (SARS) and, most probably, of *Filoviridae* such as the virus responsible for *Ebola* disease in Africa.

There are approximately 10,000 species of birds. In 1990, 9672 species were recognised, pertaining to 2058 genera [17], 5712 of which are passerines (1162 genera) and 3960 are non-passerines (896 genera).

Birds, previously *Dinobirds*, descend from *Dinosaurs* and are therefore further removed from us than mammals but they are, nevertheless, reservoirs of zoonotic infections. The recent epidemics of *West Nile virus* infection in the Americas is a good example.

The problem arising from Highly Pathogenic Avian Influenza, particularly its strain H5N1, is equally worrying, since avian infection, which is already zoonotic, may be responsible for a new human pandemic, similar to the one following the First World War. The virus responsible for this pandemic, which caused more human fatalities than the war itself, was recently reconstituted [18–20] and is highly virulent when inoculated to non-human primates.

It is noteworthy that wildlife biodiversity hot-spots are mainly found in tropical and sub-tropical regions, such as sub-Saharan Africa, Indonesia and South America.

Through selection, man has created a number of different breeds of domestic animals, e.g. there are approximately 700 recognised breeds of cattle worldwide [21], but many of these are on the verge of extinction (less than 100 breeding cows). There is therefore currently a swift erosion of genetic variability in cattle that is really worrying.

There are more than 300 recognised dog breeds, showing a remarkable phenotypic and genotypic variability. For instance a survey of the adaptive humoral response of different dog breeds following vaccination against rabies within the British pet scheme showed that there was a significant variation in response between breeds after vaccination [22].

There obviously exists a large variation of responses between breeds after vaccination which could be used for the selection, marker assisted or not, of good or bad responders to vaccination. Poultry lines selected according to their humoral adaptive immune response have already been obtained [23]. As a matter of fact, the differences in the susceptibility of breeds to some infections or infestations has been well observed by breeders, for instance the “resistance” of the N’Dama cattle breed to trypanomosis.

3. Emergences of infections

The mechanisms allowing emergence or re-emergence of infections are numerous [24]. A key factor is the extreme variability of viruses (particularly RNA viruses) leading to generation of populations of *quasi-species*, which allows them to easily cross the species barrier. Viruses evolve far quicker than their hosts, by several mechanisms: point mutations, deletions, recombination, reassortment and acquisition of cellular genes. Moreover, viruses have co-evolved with their natural hosts, often leading to unapparent infections. In animal health, the spectacular emergence of canine parvovirosis in 1978, which resulted in a disastrous epizooty within the dog population worldwide, was the result of a mutation of another *Parvovirus* which is responsible for feline panleukopaenia [1,25], whereas dogs and cats were living peacefully before, without inter-specific transmission.

Another source of emergence is the opening of previously closed ecosystems, which leads to new contacts between unrelated species and shows that a species previously unknown to be susceptible to an infection (because of the lack of opportunity to be infected) is in fact fully susceptible. A recent illustration is given by the emergence of bluetongue serotype 8, in Northern Europe, transmitted by a culicoides vector *Culicoides dewulfi* previously unknown to be susceptible to the infection [26].

Invasive species or migratory species may also be responsible for emergence, as could be the deliberate or accidental release of foreign species in a new environment, as exemplified by the introduction of Monkeypox virus in the United States. Other possible sources of emergence include veterinary biologicals, climate change and globalisation with its 5 Ts (*Trade*, *Transport*, *Travel*, *Tourism* and *Terrorism*).

4. Vaccination in face of emergence or re-emergence

In animal health, in face of an emergency, there still exist two possibilities, either mass slaughtering of animals or vaccination. Unfortunately vaccines are not always available; for instance in face of an outbreak of African swine fever and in the absence of a vaccine, the only solution is to kill the infected animals as quickly as possible, and to destroy the carcasses, in order to avoid the transmission of infection to uninfected premises. Anyway, the pigs will die from a disease which provokes nearly 100% mortality. It is even more true when facing a really emerging disease that moreover is zoonotic such as *Nipah virus* infection [27] for which no vaccine was available yet, because the causative agent was previously unknown; the only solution is once again to kill and destroy the infected and in-contact animals. A vaccine has recently been developed to prevent *Nipah virus* infection in pigs [28]; unfortunately in countries like Bangladesh, man is mainly at risk due to direct contact with the reservoir, a fruit bat, or contact with its secretions.

In other cases, when re-emergence of a previously well-known infection and when a vaccine is already available one may have the choice; either slaughtering or vaccination [39].

Foot-and-mouth virus infection gives an excellent example. *Foot-and-mouth virus* is represented by seven serotypes, further divided into numerous sub-types. Preventive vaccines are available as highly purified concentrated antigens stockpiled in liquid nitrogen [29]; being highly purified, they allow the differentiation between vaccinated or infected animals (even if previously vaccinated) thanks to a companion diagnostic test based on the detection of antibodies directed against non-structural proteins. Unfortunately this technology only allows certification of freedom at the herd level. In the two recent outbreaks in United Kingdom, the choice was to slaughter the animals. Following the dramatic outbreak of foot-and-mouth disease in United Kingdom, and to a lesser extend in France and in The Netherlands, the European Union lightened its regulation and is nowadays more prone to consider emergency vaccination as an alternative to slaughtering.

If preventive vaccines are used in an emergency situation they could still be improved by conferring an early onset of protection.

Whenever viruses are represented by several serotypes, an infection can re-emerge in a previously vaccinated population against another serotype than the wild circulating one. For instance, an influenza pandemic can emerge in a human population with a herd immunity against seasonal flu.

In case of Highly Pathogenic Avian Influenza (particularly strain H5N1), one may choose to kill the birds or to vaccinate depending on the situation [30].

There are some instances where vaccination is the only reasonable option, particularly when facing arthropod-borne virus infections.

Among arthropod-borne infections, there are infections caused by viruses represented only by one serotype, such as *West Nile virus* or *Rift valley fever virus* and others caused by viruses presenting multiple serotypes such as *Bluetongue virus*.

The majority of animal infections involve only two partners: the pathogen and the host, which has at its disposal its genetic background (natural resistance to infection) [31] and its immune system. Besides these infections or infestations, some vectorial infections are arthropod-borne and mainly transmitted by biting arthropod. These infectious systems are therefore more complex, because the vectors must be competent and able to multiply the pathogenic agent.

In Northern America there was the spectacular spread of *West Nile virus* infection in humans and horses, rapidly followed by the development of several vaccines for horses, including a DNA-based one. Vaccination seems to be the only option since the reservoir is to find among birds and the infection is transmitted by mosquitoes. It is therefore nearly impossible to control the infection by other mean than vaccination without highly detrimental effect on the environment [32].

Rift valley fever is expanding its range in Africa [33]. Until it was introduced into Saudi Arabia and Yemen in 2000; Rift valley fever tended to be confined to sub-Saharan Africa. The disease has recently occurred in Madagascar. As of July 2008, at least 20 people reportedly died as a result of the infection, and the disease has claimed the lives of thousands of animals since the beginning of the year 2008. Since the disease is transmitted by mosquitoes, extreme weather events might create the necessary conditions for Rift valley fever to expand its geographical range northwards and cross the Mediterranean and Arabian seas, with an unexpected impact on the animal and human health of newly affected countries [34]. Once again, vaccination is the best way to prevent the disease; an attenuated vaccine exists for sheep but is still abortigenic and should be improved.

An arthropod-borne disease caused by a virus with multiple serotypes is typically bluetongue (24 serotypes) and perhaps a new one [35]. Until 2006, bluetongue was only observed in the Mediterranean regions of Europe and only serotypes 1, 2, 4, 9, and 16 were involved. The disease appeared unexpectedly in Northern Europe in 2006 and serotype 8 was involved, which is typically a sub-Saharan serotype. Cattle and sheep herds were fully susceptible to the infection; moreover, the strain involved was particularly virulent in cattle.

Bluetongue is transmitted by a biting midge, a member of the family Ceratopogonidae, the culicoides. In the Mediterranean region, the main species involved in the transmission is *Culicoides imicola*, which originated in Africa and Asia and extended its range towards the north of its previous distribution, probably due to climate change. However climatic change does not seem to be responsible for the extension of the infection in Northern Europe, since the main culicoides species involved is *Culicoides dewulfi*, a typically nordic species, whose transmission competence was unknown until bluetongue appeared in northern regions; in fact, this potential vector competence had not previously had the opportunity to be expressed due to the lack of *Bluetongue virus*. The biology of the larval stage of culicoides impedes the control of the vector without damaging the environment. The most sensible option is vaccination of domestic ruminants with an inactivated vaccine containing serotype 8.

5. Vaccination against other zoonoses

In developed countries, partly as a result of overproduction, public concern for food security has been replaced by a major concern about food safety [36]. This concern has increased following the BSE (bovine spongiform encephalopathy) crisis. People are concerned about food-borne infections, 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 [37].

Veterinary vaccines may help to solve some of these 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 human populations [5,38]. 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 protection 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. More recently a vaccine against *Escherichia coli* 0157:H7 has been conditionally approved for cattle in the United States.

A vaccine against sheep cysticercosis has 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 sector. Several antibacterial vaccines used in veterinary medicine disappeared after the Second World War, and were replaced by the use of antibiotics. The resistance to antibiotics in the animal health sector with possible implications 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 diseases 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.

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