Vaccination in conservation medicine

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Summary
Unprecedented human population growth and anthropogenic environmental changes have resulted in increased numbers of people living in closer contact with more animals (wild, domestic, and peridomestic) than at any other time in history. Intimate linkage of human and animal health is not a new phenomenon. However, the global scope of contemporary zoonoses has no historical precedent. Indeed, most human infectious diseases classed as emerging are zoonotic, and many of these have spilled over from natural wildlife reservoirs into humans either directly or via domestic or peridomestic animals. Conservation medicine has recently emerged as a meaningful discipline to address the intersection of animal, human, and ecosystem health. Interest in the development of novel vaccines for wildlife encounters important challenges that may prevent progress beyond the conceptual phase. Although notable examples of successful wildlife immunisation programmes exist, depending upon key considerations, vaccination may or may not prove to be effective in the field. When implemented, wildlife vaccination requires a combination of novel zoonosis pathogen management strategies and public education to balance conservation, economic, and public health issues.

Keywords
Brucellosis – Conservation medicine – Emerging disease – Endangered species – Public health – Rabies – Vaccination – Vaccine delivery – Wildlife – Zoonosis.

Introduction

Zoonotic infections (i.e. those that can be transmitted from animals to people and vice versa) can have major impacts on wild and domestic animal and human health and can result in serious damage to the economies of developing and developed countries (79, 81). Yet, for ethical, ecological and economic reasons, it is no longer optimal to control and eliminate zoonoses mainly by mass slaughter of animals. Vaccination is without doubt one of the most useful measures to prevent animal diseases (50). Since its inception, veterinary science has been strongly linked with the development of vaccinology (82). Veterinary public health (VPH) has been defined as 'the contributions to the physical, mental, and social well-being of humans through an understanding, and application of veterinary science' (29). Despite the laudable contributions of VPH to the human condition, good intentions combined with ecological ignorance, are a blueprint for iatrogenic disaster (66). In response to these realities, conservation medicine has arisen as a relatively new field situated at the crossroads of VPH, wildlife diseases, and ecological health. The persistence of zoonotic diseases in domestic livestock, companion animals, or wildlife continues to pose significant risks to human health. For many of these diseases, veterinary vaccines or regulatory programmes have been developed to prevent transmission to humans,

protect companion animal health, and prevent economic losses. In addition to the zoonotic diseases for which control measures have been implemented, new zoonotic diseases continue to emerge worldwide. In a global society, known or unknown zoonotic diseases can be rapidly transported to naïve populations on other continents by animal reservoirs or infected humans. Development of efficacious vaccines and rapid diagnostics continues to be needed to protect human health, control zoonotic diseases identified in animal reservoirs, and prevent both domestic and international transmission of zoonotic diseases. Our ability to meet the VPH and conservation medicine challenges of the 21st Century will be greatly influenced by our ability to expand relevant, cost-effective, problem-oriented basic and applied zoonotic vaccinology research, while coordinating international research efforts and communicating research output to end-users. This paper reviews key issues, challenges, and opportunities in vaccinology for conservation medicine.

Emerging zoonoses, conservation medicine and vaccination

Animal-borne pathogens are important, not only because of the disease they can cause, but because new human diseases can arise from unsuspected animal reservoirs (79). Indeed, nearly 75% of all human infectious diseases classed as emerging are zoonotic, and many of these have spilled over from natural wildlife reservoirs into humans either directly or via domestic or peridomestic animals (80). Unprecedented human population growth and anthropogenic environmental changes have resulted in greater numbers of humans living in closer contact with more animals (wild, domestic, and peridomestic) than at any other time in history. Intimate linkage of human and animal health is not a new phenomenon. However, the scope, scale, and worldwide impacts of contemporary zoonoses have no historical precedent (81).

Historically, zoonotic diseases have been suggested or described for millennia, e.g. the Eshnunna Code (2300 BC), an ancient legal text from Mesopotamia, lists the penalties to be paid by animal owners should a man die from the bite of a 'mad' dog; vedic medical texts from India (1800-1200 BC) describe anthrax in cattle; and the Roman writer *Columella* (~AD 100), who wrote mainly on agricultural topics, recommends methods to decrease the disease now recognised as rabies in goats, swine, and dogs. More recent events such as Jenner's work with cowpox and Pasteur's research on anthrax and rabies established the concept of vaccination with live organisms as a mechanism to prevent zoonotic diseases (65).

Pathogen emergence continues, with more than 35 new infectious diseases in humans recognised since 1980 (34). Causes for pathogen emergence are many, but most likely include changes in human demography and behaviour, loss of wildlife habitats, wildlife consumption, the global wildlife trade, and transmission of pathogens to naïve reservoirs via close association of species that do not normally interact (19, 20, 46, 78). As the world population increases and interactions between human and wildlife increase, it is unlikely that the emergence of new zoonotic agents will decline. Recent disease events have focused global attention on how the interrelated factors of land-use changes, natural resource management, and the demands of human population growth alter the inherent ecological balance between zoonotic pathogens and their human and animal hosts. Zoonotic pathogens, such as avian influenza, are the most significant cause of emerging infectious diseases in people, especially from the standpoint of conditions that appear in a population for the first time or are increasing in prevalence or geographic distribution (68). Accordingly, wildlife and domestic animals are an important part of the public health picture, as they provide a 'zoonotic pool' from which diseases may emerge (19).

Notably, in the autumn of 2002, an influenza-like illness was described in Guangdong province, the People's Republic of China, which was eventually designated as severe acute respiratory syndrome (SARS) (40). Data suggest that the causative agent of SARS, a coronavirus, was maintained in Himalayan palm civets (*Paguma larvata*) or raccoon dog (*Nyctereutes procyonoides*) reservoirs in markets (31). However, the primary host species for SARS may reside in Chiroptera, such as horseshoe bats (*Rhinolophus* sp.) (40). Transmission of SARS to humans may have been via exposure to live animals, or association with restaurants in which palm civet meat was prepared and consumed. The 2003 outbreak was associated with a 10% mortality rate in humans (54). Although vaccine candidates are in the process of evaluation (6, 61), outbreaks in the near future would most likely be controlled by quarantine and isolation procedures for humans, and limited culling of wildlife reservoirs, as utilised in 2003.

Bats (*Pteropus* sp.) have also been implicated as reservoirs in the emergence of the Hendra and Nipah paramyxoviruses, highly pathogenic viruses associated with disease outbreaks in humans and livestock (25). Hendra virus was the cause of human and horse mortalities in Australia in 1994, 1999, and 2004 and Nipah virus caused encephalitis in humans in Malaysia in 1998 and 1999, and Bangladesh beginning in 2001. Both viruses are highly pathogenic in humans with fatality rates of 40% to 70% (26). In regards to the emergence of Nipah virus in Malaysia, climate changes, habitat loss caused by deforestation, and movement of the reservoir host into areas where domestic swine were raised have allowed

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transmission to domestic livestock and humans (14). Although human vaccines are under development, and an efficacious Nipah virus vaccine for pigs has been reported (73), effective vaccines to prevent zoonotic infections or address the reservoir of this disease are lacking.

The recent emergence of H5N1 influenza virus in domestic and wild birds has caused economic losses and anxiety across the globe. An intermediate host, such as swine, has been proposed as a likely remixing vessel in which co-infection with avian and human influenza viruses leads to emergence of antigenically different strains (2). The emergence of antigenically different strains of influenza has led to human pandemics in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 1977 (H1N1) (2). The rapid dissemination of H5N1 via the domestic fowl trade and migrating wild birds and the transmission to humans through contact with domestic poultry have led to human mortalities and significant economic costs in a number of countries.

As a logical outgrowth of these historic and recent experiences, conservation medicine has emerged as a meaningful discipline to address the intersection of animal health, human health, and ecosystem health (67). This intersection occurs between physicians, veterinarians, wildlife biologists, ecologists, epidemiologists, anthropologists, sociologists, and economists and builds upon integrating reliable knowledge derived from conservation biology (ecology of fragmented habitats, global change, invasive species); studies on the evolution of host–parasite relations (invasion, competition, and virulence); and the principles and practices of public health (20). The principal goals of conservation medicine are to develop scientific understanding of the connections between environmental crises and human and non-human health and to develop solutions to problems at this interface between environmental and health sciences (49).

Although primarily designed to address the disease in the animal host, veterinary programmes have a positive contribution to make in preventing human infection and clinical illness. The most common tool for disease control in veterinary medicine has been vaccination, with success influenced by vaccine efficacy and the proportion of the population inoculated (16, 32, 59). Veterinary vaccines have historically been produced from attenuated strains, although molecular techniques are facilitating development of safer and more efficacious vaccines which facilitate diagnostic investigation and enhanced surveillance. Wildlife disease reservoirs offer unique challenges for control programmes and vaccine development. In wildlife populations, capture of all animals is usually not practical, and remote vaccine delivery will then be required. Species differences in immunologic responses have been noted in addition to

differences in responses to vaccines delivered via routes other than injection (48, 55). In a global society, veterinary medicine can be the front line for detection of many zoonoses, and thus veterinary vaccination must continue to be considered within the realm of conservation medicine.

There are many reasons to consider vaccination programmes aimed at free-ranging wildlife, not the least of which is protection of public health. Just as wildlife vaccination programmes may be designed to protect public health, they may also be aimed at protecting economic interests when the disease is transmissible between wildlife and domestic animals. Wildlife vaccination programmes may also be aimed at reducing the impacts of disease on susceptible wildlife. Conservation of endangered species threatened by infectious disease can also be a goal of wildlife vaccination. Vaccination programmes may be employed to reduce the signs of disease that negatively affect wildlife viewing and therefore reduce the potential for tourism. Protection of livestock health and productivity is also a major concern and can result in dramatic conflicts between those working in wildlife conservation, agriculture, and land-use planning.

Novel vaccine development for wildlife: the example of brucellosis

At Yellowstone National Park (8,987 km^2), the only free-ranging North American plains bison (*Bison bison*) population that survived the 19th Century *in situ* was infected with brucellosis (*Brucella abortus*) from transmission by livestock early in the 20th Century (45). Following this, Rocky Mountain elk (*Cervus elaphus*) living in the 90,000 km^2 greater Yellowstone area (GYA) surrounding the park also acquired *B. abortus*. The potential for 'spillback' transmission of brucellosis from wildlife to livestock across the GYA has led to intensive local, regional, and national concerns including extremely divisive legal and policy conflicts. Remote brucellosis vaccination of the Yellowstone bison population is increasingly being viewed as a component of adaptive risk management strategies which aim to eventually eliminate the disease (52). However, novel vaccines will need to be developed because the extant bovine brucellosis vaccines S19 and RB51 have not proved very effective in limiting bison or elk maternal and foetal infection or reducing shedding of *B. abortus* into the environment (70).

Development of novel vaccines or improvement of existing vaccine platforms is impaired by a number of issues, including, but not limited to: funding, differences in

wildlife species immunology, remote delivery, and economic issues. Some zoonotic agents such as tuberculosis or brucellosis require higher levels of biosafety containment facilities for vaccine research, which are expensive and not always readily available. Biosafety facilities that are available may not be suitable for housing or handling certain wildlife species due to their size, behaviour or social activity, or because of other factors. Immunologic characterisation of responses to vaccination may be limited by lack of reagents for individual wildlife species. Species differences in immunologic responses may influence the sensitivity and specificity of diagnostic tests and the protective immunity induced by vaccination. Therefore, vaccine development may need to target each reservoir separately and may require development of species-specific vaccines. Public concerns regarding environmental issues or infection of non-target species may also limit the ability to deliver live vaccines to free-ranging wildlife. This creates problems for developing vaccines for some zoonotic agents, such as brucellosis, in which efficacious vaccines are currently limited to live attenuated strains.

Moreover, development of a novel vaccine for wildlife will require basic research to be simultaneously initiated along with applied research to explore novel approaches, establish basic science practices which yield incremental discoveries, and develop information which will facilitate advances in diagnostics and vaccine development (70). In the event that all vaccines evaluated under an empirical approach prove unacceptable, knowledge gained through a basic research approach should then offer alternative vaccines that might be successful. Novel vaccine development will necessarily be underpinned by new reliable knowledge in the areas of reproducible disease models, correlates of protective immunity, host-specific immunologic responses, antigen discovery, adjuvant/formulation/delivery optimisation, genetically-engineered vaccines, and durability of immunogenicity (70). For example, T-cell epitope mapping has emerged as a potentially powerful discovery tool with a range of biomedical applications extending from reengineering protein therapeutics (such as toxins for medical use) to vaccine discovery and design (22). Application of this technology to wildlife vaccines has potential for pathogens for which traditional 'shake and bake' vaccine development approaches have failed.

Illustrative of these novel vaccine development issues are the reviews of brucellosis in bison and elk in the GYA, which have identified a need for sustainable, innovative, basic and applied vaccine research and discovery programmes (30, 45, 70). The three main areas of emphasis for addressing vaccine research needs are:

– consideration of interrelated issues which will influence research progress, implementation, and efficiency

– empirical approaches to rapidly screen new vaccine candidates for efficacy in bison and elk

– discovery or basic research approaches to expand knowledge on pathogenesis, protective antigens, and immunologic responses to *B. abortus* in bison and elk to facilitate development of new second and third generation vaccines.

Several interrelated issues at local, state, national, international, and/or regulatory levels will influence efforts to facilitate brucellosis vaccine development for bison and elk, they include:

– maximising and prioritising productivity and efficiency

– coordinating the work of multidisciplinary teams

– securing funding

– amending regulatory policies which hinder *Brucella vaccine* research

– ensuring that there are sufficient biosafety facilities to conduct the identified research.

To address these issues, it has been suggested that an oversight consortium of industry, academic, and government representatives be formed to oversee efforts in the area of bison and elk brucellosis vaccine research (70). This consortium would identify funding; prioritise research needs; coordinate multidisciplinary or consortium research teams that would integrate vaccine, diagnostic, and delivery expertise; and disseminate progress from empirical and discovery approaches to ensure integrated and coordinated technology transfer towards applied solutions.

As free-ranging bison and elk cannot be readily caught or restrained like domestic livestock or companion animals, development of novel approaches for remote delivery of vaccines will also be necessary, potentially including oral delivery (baits, spiking natural or artificial water sources, incorporating vaccines into salt attractants, engineered recombinant forage, innovative encapsulation technologies), injection (dart delivery, biocompatible bullets, application to antlers/horns taking advantage of evolved fighting behaviours), transdermal delivery (ballistic and contact), delivery via biological vectors (biting arthropods, phages, nematodes, other virus or bacteria parasites), and mucosal delivery (aerosol, bioengineered venereal disease, ocular delivery) (70). It may also be that with vaccines, immunologic responses and protective immunity may differ between parenteral inoculation and other routes of delivery (10, 48, 60).

The difficulties involved in combating wildlife brucellosis in the GYA are considerable and they include several challenges which will increase the cost and time required

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to develop novel vaccines to address zoonotic agents in wildlife reservoirs. Yet, the success of the oral rabies baits in free-ranging wildlife described below suggests that challenges are not insurmountable (43).

Vaccine delivery to wildlife: the example of rabies

Vaccination to prevent infectious disease is a cornerstone of modern human and veterinary medicine. Regardless of the patient, strategies for delivery (whether direct or remote) of any biologic have two major barriers to overcome: the skin or mucosal surfaces. Still, both of these basic portals are not mutually exclusive for vaccine delivery consideration. Vaccination remains a prime procedure in zoological medicine because some animals brought into captivity for exhibition, applied research or conservation purposes are incubating disease, or may be surrounded by others in an infectious state. However, delivery beyond restrained animals offers many unique challenges. Wildlife poses substantial hurdles to disease control, not only because of basic species diversity and the limited knowledge of how these different species will react to vaccination, but also due to their motility and distribution; such animals are rarely an obvious or captive audience. As stated clearly by Wandeler (72), wildlife '...does not follow an invitation to visit a veterinarian, and there is no owner to bring it there. It has to be lured by some trick into vaccinating itself'. In this regard, specific vaccine formulations, and applied immunological, administrative, environmental, and regulatory issues will vary greatly dependent upon the choice of vaccine and the favoured method of delivery.

Rabies, a progressive encephalitis, is an ancient zoonosis, but it is one of the best modern paradigms for wildlife vaccination (59). A brief review of the history of rabies vaccination offers a wealth of insight for potential application to other wildlife diseases (74). The disease is global in distribution, with the exception of Antarctica, and the etiological agents are RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus* (38, 47). All mammals are believed to be susceptible, but members of the *Carnivora*, especially domestic dogs, are the most affected species (36). After initial developments in the laboratory, early canine rabies prevention offered insights that helped related efforts in the control of other diseases, which continues to be the case today (16). During the 1920s, Japan became one of the first countries to successfully apply the idea of mass vaccination to domestic dogs in a practical fashion. Routine veterinary use of rabies vaccination advanced gradually in other countries, especially after World War II. Thereafter, the extension of vaccination to non-traditional species occurred as a result of the combination of several, critical, inter-related factors:

– the basic overarching realisation that dog rabies could be eliminated by achieving herd immunity

– the appreciation of the fundamental role of wildlife reservoirs in disease dissemination

– the demonstration that population reduction was not the ultimate solution to disease control

– experimental recognition that oral vaccine administration was effective as an alternative means of delivery to the parenteral route

– eventual progress in development of remote delivery methods (4).

Parenteral administration of biologicals via needle and syringe is a straightforward method for individual animals. As with domestic species, even more exotic wildlife such as the Egyptian fruit bat (*Rousettus aegyptiacus*) can respond to potent inactivated vaccines by parenteral administration (51). While no vaccines are licensed specifically for parenteral use in wildlife, commercial biologicals can be administered off-label (i.e. prescribed for purposes not listed on the product label) not only for pre-exposure use, but also for post-exposure management during outbreaks in or near captive or managed groups. Such use may work when the products are administered in accordance with the guidelines in use for domestic species (13). Although direct intramuscular or subcutaneous vaccination may be very safe in captivity and quite effective under certain circumstances, it is generally believed to be largely impractical for most free-ranging animals that are spread out over large and inaccessible areas. Still, while less than 30% of Swiss foxes were estimated as reachable by trapping and hand vaccination, this technique was successfully applied to control rabies in urban Toronto (55, 72). Historically, automatic devices have been developed, such as vaccine-loaded syringes designed to spring out of the ground, or revamped 'coyote-getters' armed with explosive charges to deliver product in the mouth, but they were never widely deployed (77).

Ultimately, progress in the use of oral rabies vaccination (ORV) depended upon the development of attractive baits (5, 8, 21, 41, 76). Early prototypes were based on eggs or meat and were placed around a sterile vaccine container, usually made by hand. For example, the original Swiss campaigns against fox rabies utilised chicken head baits (72). These 'cottage industry' beginnings eventually gave rise to mass-produced, factory compiled baits of fishmeal, pet food meal, or other derivates. Throughout the late 1970s and up to the present day, field applications of rabies vaccine-laden baits over substantial regions of Europe and North America led to the widespread control, and in some cases the elimination, of the disease among wild mammalian carnivores (9, 17, 42, 43, 64). To date, only self-replicating modified-live or recombinant viruses have

been employed in ORV; inactivated vaccines do not work by the oral route. The use of vaccine-laden bait could be extended to other terrestrial mammals and diseases.

The use of rabies vaccination in wildlife has proved to be a successful additional use of a veterinary control technique that was traditionally only implemented among domestic animals. However, long-term disease elimination may be hampered by the existence of other relevant major reservoirs. Obviously, alternative techniques will be needed for field applications for a wider variety of scenarios related to different taxa, diseases, and circumstances (18). Some tactics may exploit the behavioural ecology of a given species. In large aggregations, colonies, herds, flocks or packs, the aerosol route of delivery may be useful, especially after critical new insights into agent acquisition via this under-exploited route are further explored (33). Besides mists, fine liquid sprays could be envisioned for joint respiratory or mucosal use, and depending upon the vaccine, application to one individual could result in the spread of vaccine to others in a group setting via social grooming (3). For remote delivery, in addition to the use of solid bait, stable liquid products could be added to critical water sources such as troughs; this is already done for livestock on remote ranges and the practice could also be used on a small scale in birds at backyard sites, or development of special crops expressing vaccine antigen for consumption (69). Considering future vaccine candidates, given the revolution in genetics, various viruses could be used as expression vectors, for incorporation of foreign genes. Some agents could be constructed by the creation of transgenic vectors, expressing the immunogen of interest in an appropriate context (56). Extrapolating from the concepts of remote delivery and natural hypodermics, ectoparasites may be designed to harbour and administer vaccine vectors of interest. For potential focus, one could imagine reverse-engineered viruses (as many are shared between invertebrates and vertebrates) opening new arenas for discovery, as is underway for lyssaviruses and other rhabdoviruses (24, 39).

With this background in mind, a 'Programmatic Environmental Assessment' was developed to evaluate animal rabies management alternatives in the United States of America (USA) (71). Impacts on the biological, physical, economic and social environments, as well as risks and mitigation associated with each alternative, were assessed in relation to selecting the preferred alternative of coordinated ORV. Among the salient issues considered were potential impacts on humans, such as vaccine exposure and infection (57), and programme impacts on non-target species, including those species classified at state or national level as threatened and endangered. At the completion of the ORV programmes each year, an annual evaluation is performed. This includes a review of the effectiveness of the projects and the proposal of any

necessary mitigation, including recommendations for improvement in subsequent actions. This process is designed to ensure sound multidisciplinary programme planning and implementation and critical public involvement (71). Such a model should be considered and developed well in advance of any intended vaccination of wildlife to minimise unintended consequences and provide a mechanism for ongoing stakeholder engagements. Development of integrated frameworks involving public health, veterinary, wildlife conservation and animal welfare agencies and regulatory authorities is crucial to the control of wildlife diseases by vaccination.

To vaccinate or not to vaccinate?

Although primarily designed to address the disease in the animal host, veterinary control programmes have a positive contribution in preventing human infection and clinical illness. The most common tool for disease control in veterinary medicine has been vaccination, with success influenced by vaccine efficacy and the proportion of the population inoculated (32). Veterinary vaccines have historically been produced from attenuated strains, although molecular techniques are facilitating development of safer and more efficacious vaccines which make diagnosis easier. Vaccination of a particular host protects not only key target populations, but can also serve as a barrier to protect human and veterinary health. Clearly, lessons learned from rabies vaccination of carnivores (43, 58) provide key insights and models for the prevention of other emerging diseases in a variety of species, especially when combined with additional applied advances in veterinary vaccinology, regardless of whether the target sprints, crawls, swims, or flies (1, 11, 28, 35, 44, 62).

The heightened public attention on zoonotic diseases has fanned the flames of debate on how best to manage diseases in free-ranging wildlife. When the wildlife host is also the focus of conservation efforts, such as endangered species recovery, the management issues take on a whole new level of complexity. Should the wildlife species, which serve as a reservoir for the pathogen, be strongly reduced or eliminated to protect people and domestic animals or should the pathogen be eliminated from the wildlife? If pathogen elimination is possible through vaccination, are there negative consequences of eliminating pathogens from ecosystems?

When considering development of a vaccination programme in wildlife, it is important to carefully define the goals. Disease eradication requires an efficacious vaccine that can be delivered safely to the target species.

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For pathogen elimination across larger landscapes, restricted host susceptibility is also likely to be required, as identification and vaccination of wildlife disease has proven to be near impossible in systems with multiple alternative hosts (15, 45, 70). The only success in worldwide disease eradication is presently smallpox, for which an effective and deliverable vaccine has been employed and the host susceptibility is limited to humans (27), but the eradication of rinderpest is also foreseen in the near future (7).

The many different challenges that can present themselves when designing a vaccine programme with conservation implications become apparent when considering the programme's goals. Is the primary goal to eliminate disease in an endangered species; to limit the transmission of disease from wildlife to domestic animals; or to protect people from exposure to wildlife diseases? Each of these goals presents difficulties related to scale. For example, a programme to protect an endangered species will be on a small scale, as there is probably a small population to be vaccinated; unfortunately, vaccines have not been developed for most wildlife species, and it is problematic to secure the necessary investment of resources to develop vaccines with such a finite market. Therefore, vaccines developed for domestic animals are the next best logical choice, but questions of safety and efficacy then become paramount. For example, wildlife managers tasked with recovery of the endangered North American black-footed ferret (*Mustela nigripes*) were severely hampered by the inadequate attenuation of canine distemper virus in the commercially available modified live virus vaccine, when the vaccine caused mortality in this sensitive species (12). Nearly three decades later, safety concerns were alleviated by the development of a canine distemper virus recombinant vaccine for domestic animals and wildlife; however, the question of efficacy for the black-footed ferret and the many other wildlife species susceptible to canine distemper virus remains (75).

Scale continues to be a fundamental programme design challenge when the vaccine must be aimed at a wildlife reservoir that jeopardises threatened species, domestic animals, or people. Consider for example, attempting to design a vaccine programme aimed at migrating wild fowl for the prevention of human exposure to highly pathogenic avian influenza. Even if one focused on a finite area like California's Central Valley (USA), the scale of the programme would be immense. California's Central Valley is a major stop for migrating waterfowl, receiving 60% to 70% of ducks and geese traversing the Pacific Americas Flyway. Therefore, the vaccine programme would be aimed at immunising approximately six million waterfowl to protect the five million people who reside in the same area. In the end, this programme would most likely be ineffective, as a waterfowl vaccination programme would probably only be able to target a small range of potential

reservoirs; delivery would be an enormous problem; and vaccine efficacy would be difficult to evaluate.

Vaccination of domestic animal reservoirs has also been attempted to protect endangered species. The Ethiopian wolf, the world's rarest canid, occupies a small range in the Ethiopian Highlands and has suffered severe impacts from rabies virus, presumably introduced from the local domestic dog population in which rabies is prevalent (63). Despite the substantial investment of resources and the successful vaccination of approximately 70% of domestic dogs surrounding the Ethiopian wolf populations in the Bale Mountains, the endangered wolf was not protected, and a subsequent rabies outbreak resulted in significant mortality (53). Fortunately, the outbreak was halted by emergency intervention through direct vaccination of the Ethiopian wolves at the front wave of the emerging epidemic. Why did this vaccine programme targeting the reservoir fail? It is likely that coverage of 70% of the domestic dog population was not enough; migrant populations of people and domestic dogs could not be reached by the community-based vaccine programme; or rabies was introduced by one of the many other possible rabies reservoirs occupying the same habitat – in short: scale.

If programmes targeting density-dependent wildlife diseases are successful, unintended consequences in ecological communities may occur. For example, predation by red foxes (*Vulpes vulpes*) was identified as one major factor limiting the annual numbers of coastal water bird breeding pairs on two islands in the Wismar Bay of the western German Baltic Sea coast (37). Increased predation upon birds after the 1990s was attributed to an increase in overall fox density after the regional introduction of ORV led to a fall in the number of rabies mortalities among foxes (37). The decrease in the bird population was believed to be exacerbated by other concomitant effects, such as seasonal food shortages for waterfowl. Similarly, improved survivorship of certain taxa (e.g. carnivores) could be associated with an enhanced parasite burden (for example, *Echinococcus*) at the local population level, with consequent public health, veterinary, or environmental repercussions (23).

Vaccination of free-ranging animals is also likely to involve considerable regulatory oversight, particularly with any modified-live or recombinant organisms that are delivered to the environment. For example, in the USA, compliance with the National Environmental Policy Act of 1969 (NEPA) is a legal requirement for 'federal actions' (i.e. actions involving federal funding or personnel) such as ORV within the USA and its territories and possessions. The legal authorisation to conduct ORV can also require compliance with additional state or federal environmental statutes (e.g. the United States Endangered Species Act of 1973). After projects have been initiated, NEPA requires

annual monitoring to determine the current status of programme impacts on the environment and the effectiveness of mitigation measures to reduce adverse impacts.

There are specific circumstances in which vaccine usage in wildlife could be practical and effective, e.g. small populations can be protected from extinction risk due to infectious disease when a safe and efficacious vaccine is available. The use of such a vaccine is most successful in animals in captivity, such as those in zoological institutions and captive breeding facilities. In addition, endangered species recovery programmes in the wild may employ vaccines to attempt to protect all individuals, a critical mass of a population, or a portion of a population residing in a high-risk area (32). Even in these situations, careful consideration should be given to the attempted elimination of an organism from an ecosystem. Is the pathogen playing a role that will prove critical to the functioning of the ecosystem? Usually the desire to recover an endangered vertebrate population outweighs concerns for biodiversity at the microorganismal level, but should it? In most cases the point is moot since total pathogen elimination is unlikely given imperfect vaccines and delivery systems, but what will happen to the wildlife population once a vaccination programme is terminated? The goal of endangered species recovery programmes is the return of populations to viable levels. This return to viability usually coincides with reduction in intervention and intensive management. If a vaccine programme has aided recovery but also helped to develop a wildlife population naïve to the pathogen that put it at risk, the population may ultimately decline again if management by vaccination is ceased.

Since citizens and policy-makers demand action on public health and economic issues, vaccination programmes should be considered as a potential line of defence for infectious diseases. In these situations it is important to carefully consider the scale of the vaccine programme to be developed, feasibility, costs, and likely outcomes and benefits (17). While vaccination programmes may be successful if carefully planned, especially in restricted areas and small populations of wildlife, a more common outcome may be the improvement of the public's perception of the handling of the problem. Many times, the most scientifically justifiable and cost-effective vaccine programmes will be aimed at the people or domestic animals which are in need of protection, but social concerns may make these targets unpalatable. In these situations, a combination of pathogen management strategies and public education will be necessary to balance conservation, economic, and public health issues.

Acknowledgements

La vaccination et la médecine environnementale

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Résumé
Du fait de la croissance démographique et de changements environnementaux d'origine anthropique sans précédent, un nombre toujours plus grand d'individus vit aujourd'hui en contact étroit avec des animaux (sauvages, domestiques ou péri-domestiques) que par le passé. L'étroite interconnexion entre la santé humaine et la santé animale n'est pas un phénomène nouveau. En revanche, la dimension mondiale des zoonoses contemporaines n'a pas de précédent dans l'histoire. De fait, la plupart des maladies infectieuses classées comme émergentes sont des zoonoses et un grand nombre d'entre elles se sont propagées à l'homme à partir d'un réservoir naturel sauvage, soit directement, soit par l'intermédiaire d'animaux domestiques ou péri-domestiques. La médecine environnementale (*conservation medicine*) a récemment vu le jour en

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tant que véritable discipline à l'interface de la santé animale, de la santé publique et de la santé de l'écosystème. L'innovation en matière de vaccins destinés à la faune sauvage se heurte à des enjeux importants susceptibles de freiner le développement de ces vaccins au-delà de la phase de conception. Malgré des exemples remarquables de programmes d'immunisation appliqués avec succès à la faune sauvage, sur le terrain la vaccination s'avère plus ou moins efficace suivant les situations. Une fois mise en route, la vaccination des animaux sauvages doit s'accompagner de stratégies nouvelles de gestion des agents de zoonoses et de mesures pédagogiques destinées au public, afin de trouver un équilibre entre les exigences de la protection de la nature, celles de l'économie et celles de la santé publique.

Mots-clés

Brucellose – Distribution de vaccin – Espèce menacée d'extinction – Faune sauvage – Maladie émergente – Médecine environnementale – Rage – Santé publique – Vaccination – Zoonose.

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La vacunación en medicina de la conservación

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Resumen

El crecimiento sin precedentes de la población humana, aunado a los cambios ambientales de origen antrópico, ha hecho que un mayor número de personas vivan en más estrecho contacto con más animales (salvajes, domésticos o peridomésticos) que en ningún otro periodo de la historia. La íntima relación entre la salud humana y la animal dista de ser un nuevo fenómeno. Sin embargo, lo que no tiene precedente histórico es el alcance planetario de las zoonosis contemporáneas. La mayoría de las enfermedades infecciosas del hombre catalogadas como emergentes son en efecto zoonóticas, y muchas de ellas han saltado al ser humano desde un reservorio salvaje natural, ya sea directamente o a través de animales domésticos o peridomésticos. En este sentido, la medicina de la conservación, aparecida en fechas recientes, constituye una disciplina muy apropiada para trabajar en la intersección entre la salud humana, la animal y la ecosistémica. El interés por obtener nuevas vacunas para la fauna salvaje tropieza con una serie de notables dificultades que quizá impidan pasar de la fase meramente teórica. Aunque no faltan ejemplos de programas de inmunización de animales salvajes que han dado buenos resultados, hay una serie de consideraciones básicas de las que depende la eficacia de una vacunación sobre el terreno. Para llevar a cabo una campaña de vacunación de animales salvajes es indispensable combinar estrategias de control del agente etiológico de una nueva zoonosis con una labor de pedagogía pública, a fin de alcanzar un correcto equilibrio entre las cuestiones de conservación, las económicas y las de salud pública.

Palabras clave

Administración de vacunas – Brucelosis – Enfermedad emergente – Especie amenazada – Fauna salvaje – Medicina de la conservación – Rabia – Salud pública – Vacunación – Zoonosis.

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References

1. Adams A. & Thompson K.D. (2006). – Biotechnology offers revolution to fish health management. *Trends Biotechnol.*, **24**, 201-205.

2. Alexander D.J. & Brown I.H. (2000). – Recent zoonoses caused by influenza A viruses. *In* An update on zoonoses (P.-P. Pastoret, ed.). *Rev. sci. tech. Off. int. Epiz.*, **19** (1), 197-225.

3. Almeida M.F., Martorelli L.F., Aires C.C., Sallum P.C. & Massad E. (2005). – Indirect oral immunisation of captive vampires, *Desmodus rotundus. Virus Res.*, **111**, 77-82.

4. Baer G.M. (1988). – Oral rabies vaccination: an overview. *Rev. infect. Dis.*, **10**, Suppl 4, S644-S648.

5. Baer G.M., Abelseth M.K. & Debbie J.G. (1971). – Oral vaccination of foxes against rabies. *Am. J. Epidemiol.*, **93**, 487-490.

6. Baric R.S., Sheahan T., Deming D., Donaldson E., Yount B., Sims A.C., Roberts R.S., Frieman M. & Rockx B. (2006). – SARS coronavirus vaccine development. *Adv. exp. Med. Biol.*, **581**, 553-560.

7. Barrett T., Pastoret P.-P. & Taylor P. (eds) (2006). – Rinderpest and peste des petits ruminants: virus plagues of large and small ruminants. Monograph Series: Biology of Animal Infections. Academic Press, Elsevier, Amsterdam-London.

8. Black J.G. & Lawson K.F. (1973). – Further studies of sylvatic rabies in the fox (*Vulpes vulpes*). Vaccination by the oral route. *Can. vet. J.*, **14**, 206-211.

9. Brochier B., Kieny M.P., Costy F., Coppens P., Bauduin B., Lecocq J.P., Languet B., Chappuis G., Desmettre P., Afiademanyo K., Libois R. & Pastoret P.-P. (1991). – Large-scale eradication of rabies using recombinant vaccinia-rabies vaccine. *Nature*, **354**, 520-522.

10. Buddle B.M., Aldwell F.E., Skinner M.A., de Lisle G.W., Denis M., Vordermeier H.M., Hewinson R.G. & Wedlock D.N. (2005). – Effect of oral vaccination of cattle with lipid-formulated BCG on immune responses and protection against bovine tuberculosis. *Vaccine*, **23**, 3581-3589.

11. Capua I. & Alexander D.J. (2006). – The challenge of avian influenza to the veterinary community. *Avian Pathol.*, **35**, 189-205.

12. Carpenter J.W., Appel M.J.G., Erickson R.C. & Novilla M.N. (1976). – Fatal vaccine-induced canine distemper virus infection in black-footed ferrets. *JAVMA*, **169**, 961-963.

13. Centers for Disease Control and Prevention (2006). – Compendium of animal rabies prevention and control. *Morb. Mort. weekly Rep.*, **55** (RR-1), 1-8.

14. Chua K.B. (2003). – Nipah virus outbreak in Malaysia. *J. clin. Virol.*, **26**, 265-275.

15. Cleaveland S., Hess G.R., Dobson A.P., Laurneson M.K., McCallum H.I., Roberts M.G. & Woodroffe R. (2002). – The role of pathogens in biological conservation. *In* The ecology of wildlife diseases (P.J. Hudson, A. Rizzoli, B.T. Grenfell, H. Heesterbeek & A.P. Dobson, eds). Oxford University Press, United Kingdom, 139-150.

16. Cleaveland S., Kaare M., Knobel D. & Laurenson M.K. (2006). – Canine vaccination, providing broader benefits for disease control. *Vet. Microbiol.*, **117**, 43-50.

17. Cliquet F. & Aubert M. (2004). – Elimination of terrestrial rabies in Western European countries. *Dev. Biol. (Basel)*, **119**, 185-204.

18. Constantine D.G. (2003). – Geographic translocation of bats: known and potential problems. *Emerg. infect. Dis.*, **9**, 17-21.

19. Daszak P., Cunningham A.A. & Hyatt A.D. (2001). – Anthropogenic environmental change and the emergence of infectious diseases in wildlife. *Acta trop.*, **78**, 103-116.

20. Daszak P. & Cunningham A.A. (2002). – Emerging infectious diseases: a key role for conservation medicine. *In* Conservation medicine: ecological health in practice (A.A. Aguirre, R.S. Ostfeld, G.M. Tabor, C. House & M.C. Pearl, eds). Oxford University Press, New York.

21. Debbie J.G. (1974). – Use of inoculated eggs as a vehicle for the oral rabies vaccination of red foxes (*Vulpes fulva*). *Infect. Immun.*, **9**, 681-683.

22. De Groot A.S., Vishvanath N., Nagendra R.H., Srikumaran S., Rayner J. & Martin W. (2003). – T cell epitope identification for bovine vaccines: an epitope mapping method for BoLA A-11. *In* Vaccines in the 21st Century: Expanding the boundaries of human and veterinary medicine (D. Brake, ed.). *Int. J. Parasitol.*, **33** (5-6), 641-653.

23. Deplazes P. (2006). – Ecology and epidemiology of *Echinococcus multilocularis* in Europe. *Parassitologia*, **48**, 37-39.

24. Dietzschold B., Faber M. & Schnell M.J. (2003). – New approaches to the prevention and eradication of rabies. *Expert Rev. Vaccines*, **2**, 399-406.

25. Eaton B.T., Broder C.C., Middleton D. & Wang L.F. (2005). – Hendra and Nipah viruses: different and dangerous. *Nat. Rev. Microbiol.*, **4**, 23-35.

26. Eaton B.T., Broder C.C. & Wang L.F. (2005). – Hendra and Nipah viruses: pathogenesis and therapeutics. *Curr. molec. Med.*, **5**, 805-816.

27. Fenner F., Henderson D.A., Arita I., Jeszek Z. & Ladnyi I.D. (1988). – Smallpox and its eradication. History of International Public Health, No. 6. World Health Organization, Geneva. Available at: http://whqlibdoc.who.int/smallpox/9241561106.pdf (accessed on 5 November 2006).

Rev. sci. tech. Off. int. Epiz., **26** (1)

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28. Field H., MacKenzie J. & Daszak P. (2004). – Novel viral encephalitides associated with bats (Chiroptera)-host management strategies. *Arch. Virol. Suppl.*, **18**, 113-121.

29. Food and Agriculture Organization (FAO) (2002). – Definition of Veterinary Public Health. Animal Production and Health Division Website. Available at: http://www.fao.org/ag/againfo/programmes/en/vph/about.html (accessed on 1 May 2005).

30. Greater Yellowstone Interagency Brucellosis Committee (2002). – Brucellosis in elk and bison in the Greater Yellowstone Area. Proc. of a national symposium, 17-18 September, Jackson, Wyoming. Wyoming Game and Fish Department, Cheyenne, Wyoming, USA.

31. Guan Y., Zheng B.J., He Y.Q., Liu X.L., Zhuang Z.X., Cheung C.L., Lao S.W., Li P.H., Zhang J., Guan Y.J., Butt K.M., Wong K.L., Chan K.W., Lin W., Shortridge K.F., Yuen K.Y., Peiris J.S. & Poon L.L. (2003). – Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*, **302**, 276-278.

32. Haydon D.T., Randall D.A., Matthews L., Knobel D.L., Tallents L.A., Gravenor M.B., Williams S.D., Pollinger J.P., Cleaveland S., Woolhouse M.E.J., Sillero-Zubiri C., Marino J., Macdonald D.W. & Laurenson M.K. (2006). – Low-coverage vaccination strategies for the conservation of endangered species. *Nature*, **443** (7112), 692-695.

33. Johnson N., Phillpotts R. & Fooks A.R. (2006). – Airborne transmission of lyssaviruses. *J. med. Microbiol.*, **55** (Pt 6), 785-790.

34. Karesh W.B., Cook R.A., Bennett E.L. & Newcomb J. (2005). – Wildlife trade and global disease emergence. *Emerg. infect. Dis.*, **11**, 1000-1002.

35. Knobel D.L., du Toit J.T. & Bingham J. (2002). – Development of a bait and baiting system for delivery of oral rabies vaccine to free-ranging African wild dogs (*Lycaon pictus*). *J. Wildl. Dis.*, **38**, 352-362.

36. Knobel D.L., Cleaveland S., Coleman P.G., Fevre E.M., Meltzer M.I. & Miranda M.E. (2005). – Re-evaluating the burden of rabies in Africa and Asia. *Bull. WHO*, **83**, 360-368.

37. Kube J., Brenning U., Kruch W. & Nehls H.W. (2005). – Population trends of ground-breeding seabirds on islands in Wismar Bay (southwestern Baltic Sea): lessons learned from 50 years of predator management. *Vogelwelt*, **126**, 299-320.

38. Kuzmin I.V., Hughes G.J., Botvinkin A.D., Orciari L.A. & Rupprecht C.E. (2005). – Phylogenetic relationships of Irkut and West Caucasian bat viruses within the *Lyssavirus* genus and suggested quantitative criteria based on the N gene sequence for lyssavirus genotype definition. *Virus Res.*, **111**, 28-43.

39. Kuzmin I.V., Hughes G.J. & Rupprecht C.E. (2006). – Phylogenetic relationships of seven previously unclassified viruses within the family *Rhabdoviridae* using partial nucleoprotein gene sequences. *J. gen. Virol.*, **87**, 2323-2331.

40. Li W., Wong S.K., Li F., Kuhn J.H., Huang I.C., Choe H. & Farzan M. (2006). – Animal origins of the severe acute respiratory syndrome coronavirus: insight from ACE2-S-protein interactions. *J. Virol.*, **80**, 4211-4219.

41. Linhart S.B., Wlodkowski J.C., Kavanaugh D.M., Motes-Kreimeyer L., Montoney A.J., Chipman R.B., Slate D., Bigler L.L. & Fearneyhough M.G. (2002). – A new flavor-coated sachet bait for delivering oral rabies vaccine to raccoons and coyotes. *J. Wildl. Dis.*, **38**, 363-377.

42. MacInnes C.D., Smith S.M., Tinline R.R., Ayers N.R., Bachmann P. & Ball D.G. (2001). – Elimination of rabies from red foxes in eastern Ontario. *J. Wildl. Dis.*, **37**, 119-132.

43. Matouch O., Vitasek J., Semerad Z. & Malena M. (2006). – Elimination of rabies in the Czech Republic. *Dev. Biol. (Basel)*, **124**, 141-143.

44. Mohan K., Foggin C.M., Dziva F. & Muvavarirwa P. (2001). – Vaccination to control an outbreak of *Mycoplasma crocodyli* infection. *Onderstepoort J. vet. Res.*, **68**, 149-150.

45. National Research Council (1998). – Brucellosis in the Greater Yellowstone Area. National Academy Press, Washington, DC, 186 pp.

46. National Research Council (2005). – Animal health at the crossroads: preventing, detecting, and diagnosing animal diseases. National Academy Press, Washington, DC, 266 pp.

47. Nel L.H. (2005). – Vaccines for lyssaviruses other than rabies. *Expert Rev. Vaccines*, **4**, 533-540.

48. Olsen S.C., Kreeger T.J. & Schultz W. (2002). – Immune responses of bison to ballistic or hand vaccination with *Brucella abortus* strain RB51. *J. Wildl. Dis.*, **38**, 738-745.

49. Ostfeld R.S., Meffe G.K. & Pearl M.C. (2002). – Conservation medicine: the birth of another crisis discipline. *In* Conservation medicine: ecological health in practice (A.A. Aguirre, R.S. Ostfeld, G.M. Tabor, C. House & M.C. Pearl, eds). Oxford University Press, New York.

50. Pastoret P.-P. & Jones P. (2004). – Veterinary vaccines for animal and public health. *Dev. Biol. (Basel)*, **119**, 15-29.

51. Peters C.J., Isaza R., Heard D.J., Davis R.D., Moore S.M. & Briggs D.J. (2004). – Vaccination of Egyptian fruit bats (*Rousettus aegyptiacus*) with monovalent inactivated rabies vaccine. *J. Zoo Wildl. Med.*, **35**, 55-59.

52. Plumb G. & Aune K. (2002). – The Interagency Bison Management Plan for Yellowstone National Park and Montana. *In* Brucellosis in elk and bison in the Greater Yellowstone Area, 17-18 September, Jackson, Wyoming (T.J. Kreeger, ed.). Wyoming Game and Fish Department, Cheyenne, Wyoming, USA.

53. Randall D.A., Williams S.D., Kuzmin I.V., Rupprecht C.E., Tallents L.A., Tefera Z., Argaw K., Shiferaw F., Knobel D.L., Sillero-Zubiri C. & Laurenson M.K. (2004). – Rabies in endangered Ethiopian wolves. *Emerg. infect. Dis.*, **10**, 2214-2217.

54. Roberts A., Wood J., Subbarao K., Ferguson M., Wood D. & Cherian T. (2006). – Animal models and antibody assays for evaluating candidate SARS vaccines: summary of a technical meeting 25-26 August 2005, London. *Vaccine,* **24**, 7056-7065.

55. Rosatte R.C., Power M.J., MacInnes C.D. & Campbell J.B. (1992). – Trap-vaccinate-release and oral vaccination for rabies control in urban skunks, raccoons and foxes. *J. Wildl. Dis.*, **28**, 562-571.

56. Rupprecht C.E., Shankar V., Hanlon C.A., Hamir A. & Koprowski H. (1994). – Beyond Pasteur to 2001: future trends in lyssavirus research? *Curr. Top. dev. Biol.*, **187**, 325-340.

57. Rupprecht C.E., Blass L., Smith K., Orciari L.A., Niezgoda M., Whitfield S.G., Gibbons R.V., Guerra M. & Hanlon C.A. (2001). – Human infection due to recombinant vaccinia-rabies glycoprotein virus. *N. Engl. J. Med.*, **345**, 582-586.

58. Rupprecht C.E., Hanlon C.A. & Hemachudha T. (2002). – Rabies re-examined. *Lancet infect. Dis.*, **2**, 327-343.

59. Rupprecht C.E., Hanlon C.A. & Slate D. (2006). – Control and prevention of rabies in animals: paradigm shifts. *Dev. Biol. (Basel)*, **125**, 103-111.

60. Sedgemen B.J., Meeusen E.N., & Lofthouse S.A. (2004). – Alternative routes of mucosal immunization in large animals. *Immunol. Cell Biol.*, **82**, 10-16.

61. See R.H., Zakhartchouk A.N., Petric M., Lawrence D.J., Mok C.P., Hogan R.J., Rowe T., Zitzow L.A., Karunakaran K.P., Hitt M.M., Graham F.L., Prevec L., Mahony J.B., Sharon C., Auperin T.C., Rini J.M., Tingle A.J., Scheifele D.W., Skowronski D.M., Patrick D.M., Voss T.G., Babiuk L.A., Gauldie J., Roper R.L., Brunham R.C. & Finlay B.B. (2006). – Comparative evaluation of two severe acute respiratory syndrome (SARS) vaccine candidates in mice challenged with SARS coronavirus. *J. gen. Virol.*, **87**, 641-650.

62. Shams H. (2005). – Recent developments in veterinary vaccinology. *Vet J.*, **170**, 289-299.

63. Sillero-Zubiri C., King A.A. & Macdonald D.W. (1996). – Rabies and mortality in Ethiopian wolves (*Canis simensis*). *J. Wildl. Dis.*, **32**, 80-86.

64. Slate D., Rupprecht C.E., Rooney J.A., Donovan D., Lein D.H. & Chipman R.B. (2005). – Status of oral rabies vaccination in wild carnivores in the United States. *Virus Res.*, **111**, 68-76.

65. Smithcors J.F. (1957). – Evolution of the veterinary art: a narrative account to 1850. Veterinary Medicine Publishing Co., Kansas City, Missouri, 408 pp.

66. Soule M. (2002). – Foreword: giant moths and doing no harm. *In* Conservation medicine: ecological health in practice (A.A. Aguirre, R.S. Ostfeld, G.M. Tabor, C. House & M.C. Pearl, eds). Oxford University Press, New York, 407 pp.

67. Tabor G.M. (2002). – Defining conservation medicine. *In* Conservation medicine: ecological health in practice (A.A. Aguirre, R.S. Ostfeld, G.M. Tabor, C. House & M.C. Pearl, eds). Oxford University Press, New York, 8-16.

68. Taylor L.H., Latham S.M. & Woolhouse M.E.J. (2001). – Risk factors for human disease emergence. *Philos. Trans. roy. Soc. Lond., B, biol. Sci.*, **356**, 983-989.

69. Thanavala Y., Huang Z. & Mason H.S. (2006). – Plant-derived vaccines: a look back at the highlights and a view to the challenges on the road ahead. *Expert Rev. Vaccines*, **5**, 249-260.

70. United States Animal Health Association (2006). – Enhancing brucellosis vaccines, vaccine delivery, and surveillance diagnostics for elk and bison in the Greater Yellowstone Area (T. Kreeger & G.E. Plumb, eds). A technical report from a working symposium held 16-18 August 2005 at the University of Wyoming, Laramie, Wyoming, USA. Available at: www.usaha.org/pubs/2006Aug_TechnicalReport_GYA-Elk-Bison-Brucellosis.pdf (accessed on 15 November 2006).

71. United States Department of Agriculture (USDA) (2005). – Monitoring report-Calendar Year 2004-for environmental assessments concerning the management of rabies in the United States. Wildlife Services, Animal and Plant Health Inspection Service, USDA, Raleigh, North Carolina.

72. Wandeler A.I. (1991). – Oral immunization of wildlife. *In* The natural history of rabies, 2nd Ed. (G.M. Baer, ed.). CRC Press, Boca Raton, Florida, 485-503.

73. Weingartl H.M., Berhane Y., Caswell J.L., Loosmore S., Audonnet J.C., Roth J.A. & Czub M. (2006). – Recombinant nipah virus vaccines protect pigs against challenge. *J. Virol.*, **80**, 7929-7938.

74. Wilkinson L. (2002). – History. *In* Rabies (A.C. Jackson & W.H. Wunner, eds). Academic Press, New York, 1-22.

75. Wimsatt J., Biggins D., Innes K., Taylor B. & Garell D. (2003). – Evaluation of oral and subcutaneous delivery of an experimental canarypox recombinant canine distemper vaccine in the Siberian polecat (*Mustela eversmanni*). *J. Zoo Wildl. Med.*, **34**, 25-35.

76. Winkler W.G., McLean R.G. & Cowart J.C. (1975). – Vaccination of foxes against rabies using ingested baits. *J. Wildl. Dis.*, **11**, 382-388.

77. Winkler W.G. & Bögel K. (1992). – Control of rabies in wildlife. *Sci. Am.,* **266** (6), 86-92.

78. Woo P.C., Lau S.K. & Yuen K.Y. (2006). – Infectious diseases emerging from Chinese wet-markets: zoonotic origins of severe respiratory viral infections. *Curr. Opin. infect. Dis.*, **19**, 401-407.

79. World Health Organization (WHO) (2002). – Future trends in veterinary public health. WHO Technical Report Series, no. 907. WHO, Geneva, 85 pp.

Rev. sci. tech. Off. int. Epiz., **26** (1)

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80. World Health Organization (WHO) (2004). – Report of the WHO/FAO/OIE joint consultation on emerging zoonotic diseases, 3-5 May, 65 pp. Available at http://whqlibdoc. who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.9.pdf.

81. World Organisation for Animal Health (OIE) (2004). – Emerging and re-emerging zoonoses. Editorial from the OIE Director General, B. Vallat. Available at: http://www.oie.int /eng/Edito/en_edito_nov04.htm (accessed on 1 May 2005).

82. World Organisation for Animal Health (OIE) (2004). – Conclusions and recommendations. OIE international conference on the Control of infectious animal diseases by vaccination, 13-16 April, 2004, Buenos Aires, Argentina. Available at: http://www.oie.int/eng/press/rec_concl_ argentine_04.pdf (accessed on 1 May 2005).