

Vaccines for emerging infections

N. Marano, C. Rupprecht & R. Regnery

Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Summary

Emerging infectious diseases represent a grave threat to animal and human populations in terms of their impact on global health, agriculture and the economy. Vaccines developed for emerging infections in animals can protect animal health and prevent transmission of zoonotic diseases to humans. Examples in this paper illustrate how industry and public health can collaborate to develop a vaccine to prevent an emerging disease in horses (West Nile virus vaccine), how poultry vaccination can protect animals and prevent transmission to people (avian influenza vaccine), how regulatory changes can pave the way for vaccines that will control the carrier state in animals and thus prevent infection in humans (*Bartonella henselae* vaccine in cats) and how novel technologies could be applied to vaccinate wildlife reservoir species for rabies. Stemming from the realisation that zoonotic diseases are the predominant source of human emerging infectious diseases, it behoves academic, public health, and animal health agencies to consider creative constructive approaches to combat serious public health challenges. Vaccination of vector/reservoir species, when efficacious vaccines are available, offers significant advantages to combating zoonotic human disease.

Keywords

Animal vaccination – Avian influenza vaccine – Emerging infection – Public health – Rabies vaccine in wildlife – West Nile virus vaccine – Zoonotic disease.

Introduction

In its 1992 report 'Emerging infections: microbial threats to health in the United States', the Institute of Medicine (IOM) in the United States of America (USA) defined the causes of emergence as follows: 'emergence may be due to the introduction of a new agent, or the reappearance of a known disease after a decline in incidence, recognition of an existing disease that has gone undetected, or to a change in the environment that provides an epidemiologic "bridge"'(31). In its follow-on report in 2003, the IOM's Convergence Model described factors leading to the emergence of an infectious disease as 'the combination of biological, environmental and host-related risk factors that create the opportunity for microbial pathogens to wreak havoc on their human and animal hosts' and as a 'microbial perfect storm' that is, 'a tempest that may

happen only once in a century, created by so rare a combination of factors that it could not possibly have been worse' (32).

Many factors contribute to the emergence of infectious diseases. Increasing human populations have multiplied the global demand for animal protein as a food source. As larger numbers of animals are reared in situations of high confinement, as is often done in modern methods of food production, crowding and stress on the animals can increase the likelihood of bacterial and viral shedding of zoonotic pathogens (e.g. *Salmonella* in cattle and swine). The increase in demand for animal protein also leads to methods of animal rearing that preclude the proper biosecurity precautions needed to prevent introduction of pathogens that have health significance for both animals and humans (e.g. H5N1 avian influenza in free-ranging

ducks and geese in Southeast Asia). Our changing global climate leads to extended periods of flooding and drought, which impact the vectors of transmission (e.g. the floodwater *Aedes* spp. of mosquitoes which serve as the vector of Rift Valley fever virus to animals). International travel can transport infected animals, infected humans and vectors much farther and more quickly (e.g. this may be the explanation for the emergence of West Nile virus [WNV] in North America in 1999). War and political unrest destroy the fabric of society and disrupt governmental infrastructures that serve to protect animal health. Encroachment by humans and agricultural species into wildlife habitats increases the likelihood that all three types of species could be infected with novel pathogens. The microbes themselves are very adept at finding ways to perpetuate themselves and bypass the animal immune system to infect animal cells.

Outbreaks of infectious diseases in animals come at great cost to society. In 2001, the foot and mouth disease outbreak in the United Kingdom (UK) led to the depopulation of 4.2 billion head of cattle, sheep, pigs, and goats at an estimated cost to the UK economy of over £6 billion (70). An inestimable cost was the mental stress to producers, their families, and their communities caused by the mass slaughter of healthy animals to control this outbreak. In light of the UK experience, the impact of consumers' attitudes towards euthanasia of healthy animals as opposed to animal-sparing approaches to outbreak control may impact future policy.

Therefore, the concept of animal vaccination to prevent emerging infections becomes of key importance. However, when a vaccine is deployed as a control measure for emerging infections, unique considerations must be given to its use. Will the vaccine be used only in an emergency? Is it fully licensed for use, or are special authorisations required for its use? What storage conditions are required to maintain the product safely in the field setting? Is it stored fully prepared or does it need to be reconstituted? What is the goal of vaccination – to prevent infection or disease? If vaccine is to be used in an emergency, does it have sufficiently early onset of protection to warrant its use? Are several doses required to establish sufficient immunity to prevent infection? Are sufficient quantities of vaccine available to vaccinate the entire herd or flock? Is it necessary to vaccinate the entire herd or flock to produce adequate immunity to interrupt transmission? What is the impact on human health, if the pathogen is zoonotic? Does the vaccine reduce pathogen shedding sufficiently to prevent morbidity and mortality in the animal, but still allow low levels of pathogen excretion, sufficient for humans in contact with the animals to be at risk of infection? What is the public opinion of vaccination as compared to their view of alternative control measures such as depopulation? Is there a marker in the vaccine such that a diagnostic test can differentiate vaccinated from

infected animals to permit trade? The lack of ability to distinguish between vaccinated and infected animals has historically been perceived as a barrier to the use of vaccination and should be continually reevaluated through scientific research and policy development.

The existence of animal mediators of zoonotic disease (both as vectors or reservoirs) offers significant potential for the development of control strategies for zoonotic disease that are not necessarily available for the control of disease transmitted directly from human to human or directly from the 'environment' to humans. Vaccination for emerging infections in animals is an important potential tool for control of zoonotic disease and may provide an alternative to much more drastic control measures, such as depopulation. In addition to prevention of human disease, vaccination of reservoir species may also protect important nonhuman species from disease as well.

In the following case studies, we chose four examples of emerging infections in companion animals, domestic poultry, and wildlife to highlight the important role that vaccination can play in disease prevention in the animal host or reservoir, and how these vaccines directly or indirectly impact prevention or control of emerging infectious diseases in humans.

Case study 1: companion animals

Vaccination of animals to protect animal health: West Nile virus vaccine in horses

West Nile virus (WNV), a flavivirus related to Japanese encephalitis, St. Louis encephalitis and Murray Valley encephalitis viruses, was responsible for outbreaks of encephalomyelitis in humans and horses in New York in 1999 (13). West Nile virus had previously been identified as a cause of infection and encephalomyelitis in horses in Egypt and France in the early 1960s (53, 63). Risk factors that may have contributed to the emergence of WNV in North America included international transportation of the infected mosquito vector, bird or human, and a climate favourable to the maintenance of the mosquito vector in nature. Thus, WNV is now considered to be endemic in North America.

Mosquito vectors become infected with WNV by feeding on infected wild birds. Occasionally infected mosquitoes, when biting to consume blood, can transmit the virus to people and horses. Humans and horses are thought to be incidental hosts, that is, once infected they cannot be a source of infection for mosquitoes or other animals. The only vector proven to be involved in transmission to birds

and humans is the mosquito. Scientists have identified at least 59 mosquito species infected with WNV, but species from the genus *Culex*, including the common house mosquito *Cx. pipiens*, seem to be the most common carriers (30).

Clinical signs of WNV in horses are associated with central and/or peripheral nervous system dysfunction. Most horses exhibit secondary central nervous system-derived neurologic manifestations such as ataxia, including stumbling, staggering, wobbly gait or incoordination, or at least two of the following: circling, hind limb weakness, inability to stand, multiple limb paralysis, muscle fasciculation, proprioceptive deficits, altered mental status, blindness, lip droop/paralysis, and teeth grinding. Fever is not a consistent finding (52).

Since the emergence of WNV in the USA, there has been concern among the scientific community about whether horses could serve as amplifying hosts for WNV, exacerbating the challenges faced by public health and veterinary sectors in controlling its spread. In a study conducted in 2002, Bunning *et al.* demonstrated that horses experimentally infected with WNV strains known to be pathogenic for birds and humans developed low levels of viraemia of short duration. Furthermore, mosquitoes that fed upon experimentally infected horses were negative for the virus, leading investigators to the conclusion that horses were unlikely to serve as important amplifying hosts for WNV in nature (7).

However, the impact on equine health has been profound. From 1999 to 2005, the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) National Animal Health Surveillance System reported WNV cases in horses as follows: 1999, 25 cases; 2000, 66 cases; 2001, 738 cases; 2002, 15,257 cases; 2003, 5,181 cases; 2004, 1,406 cases and 2005, 1,075 cases (73). Among the 15,257 equine cases in horses reported in 2002, approximately 33% died from the infection (72).

The high mortality rate observed in horses formed the impetus for vaccine development. Fort Dodge Animal Health manufactured the first WNV vaccine in the USA, produced from a killed virus. Because of the emerging nature of WNV and its impact on horses, in an effort to find an intervention for this devastating disease, field safety trials of the killed vaccine were conducted among approximately 650 horses in eight states. Preliminary product purity and field safety data submitted to the USDA Center for Veterinary Biologics (CVB) led to the issuance of a conditional license in 2001. Subsequent efficacy data yielded from experimental challenge studies led to the issuance of full licensure of the killed vaccine in 2003. In addition to the inactivated monovalent product, three

other WNV vaccines are licensed by CVB: a live canarypox virus-vectored vaccine manufactured by Merial and licensed in 2003; a deoxyribonucleic acid (DNA) vaccine developed in collaboration with the US Centers for Disease Control and Prevention (CDC) and manufactured by Fort Dodge Animal Health, licensed in 2005 (further described below), and a live flavivirus chimeric vaccine manufactured by Intervet and licensed in 2006 (personal communication, M.B. Evans, USDA).

In 2001 in collaboration with Fort Dodge Animal Health, CDC began efforts to develop the world's first DNA WNV vaccine for horses (19). DNA vaccines use specific fragments of a pathogen's unique genetic material to stimulate a targeted immune response from the host, unlike traditional inactivated vaccine development that involves killing the virus or bacteria in such a manner that allows the pathogen to produce immunity but no disease (via replication) in the recipient. Studies to determine duration of immunity conferred by vaccination are ongoing. The vaccine label contains a caution that vaccinated horses may not be eligible for export, as current commercially used tests may not be able to differentiate among the DNA vaccine, conventional vaccines, and horses that have been exposed to the actual virus.

In areas of high vector activity, control of WNV in horses can present a challenge to their owners and veterinarians. A research study of immunologic responses in horses vaccinated with the killed vaccine demonstrated that a portion of horses may respond poorly to the vaccine and that WNV antibody titres conferred after two doses of vaccine have been administered can decline to low levels within 5 to 7 months, leading to the recommendation that vaccination every 6 months may be indicated (18).

Although not specifically recommended by the vaccine manufacturers, the American Association of Equine Practitioners has suggested that horses that are stressed, such as show and race horses, should have two boosters annually, in April and late July. Owners should recognise that horses vaccinated against Eastern, Western, and Venezuelan equine encephalitis are not protected against WNV. Control measures for WNV other than vaccination include reduction of mosquito vectors through use of topical repellents approved for horses and removal of standing water and old tyres from areas proximal to where horses are kept (3).

West Nile virus continues to emerge in horses in new parts of the world. In 2003, WNV outbreaks were reported in horses in Mexico and Morocco (44, 64). This case study is an example of the use of new technological approaches to devising useful interventions for the prevention of disease in humans; it also demonstrates how rapidly the research community and industry can respond to an emerging

infection, identify needs and collaborate to discover, evaluate and continually improve an intervention for an emerging infectious disease in animals. The DNA technology used to develop the equine WNV vaccine is serving as the foundation for an experimental human WNV vaccine (11).

Case study 2: domestic poultry

Vaccination of the animal reservoir to prevent disease in the animal, prevent slaughter of the animal, and reduce likelihood of transmission to people: avian influenza vaccine

Perhaps the best example of an emerging infectious disease affecting animals and humans today is the epizootic of highly pathogenic avian influenza A H5N1 (HPAI H5N1) that began in 1997 (21). Outbreaks of HPAI H5N1 have spread through three continents at an unprecedented rate, resulting in devastating health and economic consequences. From 1999 to 2003, poultry outbreak control measures in the European Union alone resulted in the depopulation of 50 million birds, at a significant cost to the global economy (9). From 18 March 2004 to 16 October 2006 the world has witnessed the occurrence of 256 laboratory confirmed human cases of HPAI with 151 fatalities associated with the epizootic of H5N1 in birds (82). In almost all the human cases, the primary risk factor for infection was close contact with infected domestic poultry or poultry products.

In the case of HPAI H5N1, the circumstances have indeed combined to create the perfect microbial storm. Agricultural practices, increasing human population with an associated increase in demand for animal poultry as a nutrient source, legal and illegal movement and transport of poultry, and risk behaviours of humans in their interaction with birds have all contributed to the emergence of a complex eco-epidemiologic picture that will not disappear in the near future. It is imperative that the veterinary sector seek opportunities to control HPAI in the animal reservoir, both to protect agriculture and peoples' livelihoods, but even more importantly to prevent the onset of a pandemic that could occur once the virus acquires the ability to transmit in a sustained and efficient manner from person to person.

Much effort has been placed into addressing control of HPAI H5N1 in the animal reservoir through the combined efforts of organisations such as the World Organisation for Animal Health (OIE), Food and Agriculture Organization (FAO), and World Health Organization (WHO). These organisations have jointly sponsored several international meetings to address this problem (24, 25, 26).

Each of these meetings highlighted the importance of poultry vaccination as an effective control measure. Information on the types of avian influenza (AI) vaccines that are available for use in poultry and on the technological advancements for vaccines developed for compatibility with laboratory diagnostic systems that can distinguish between vaccinated and infected poultry to allow trade is beyond the scope of this particular article and is discussed elsewhere in this volume.

However, a brief review of the advantages and limitations of poultry vaccination merits discussion, so the reader will appreciate the factors that should be taken into consideration in the decision to use vaccination as part of the containment strategy for the control of HPAI H5N1. Vaccination can play an important role in protecting poultry from development of clinical illness and from mortality, as well as reducing virus shedding and increasing resistance to infection. Vaccination is useful in situations where there is risk of major disease spread and where stamping out is not a viable option (i.e. in countries where the depopulation of birds will deprive the community of an important protein source). Vaccination strategies that include distinguishing infected from uninfected, vaccinated birds (DIVA) are critically important for surveillance, to show that disease control programmes are working. DIVA also represents a major advantage to a country's economy, since it can remove barriers to trade caused by restrictions on movement and sale of birds if they can be demonstrated to be free of infection (10).

In an intercountry consultation in Manila in 2005, experts from WHO observed that vaccination, if properly used, can have a positive impact on human health as well. It was noted that in places in Southeast Asia where infection in poultry has been controlled or eliminated, human cases no longer occurred. The WHO acknowledged that prevention of HPAI H5N1 avian influenza in humans is best achieved by controlling infection in poultry. The WHO supported FAO and OIE recommendations that control strategies for HPAI H5N1 should consider vaccination of poultry (81).

However, vaccination does have limitations that should also be considered. Even with vaccination, the virus is still able to replicate in clinically healthy vaccinated birds (10). This reduces the likelihood that disease eradication will be achieved and can elevate the risk to human health by leading to increased antigenic pressure for virus mutation in the poultry population. A recent publication by Savill *et al.* modelled impact of vaccination on silent spread of HPAI H5N1 between poultry flocks (62). The authors determined that 90% of birds needed to be successfully vaccinated to reduce the probability of an outbreak by 50%, but this could result in undetected outbreaks in birds. As the proportion of birds vaccinated rose, fewer

birds became infected but outbreaks became harder to detect. The use of sentinel birds could increase the likelihood of detection of outbreaks, especially at the end of a production cycle.

In the Savill model, elements of a successful vaccination programme for HPAI H5N1 include an effective vaccine, a high proportion of birds vaccinated, use of unvaccinated sentinel birds to ensure rapid detection of virus, good biosecurity practices and rapid removal of infected flocks once infection is detected. In the overall scheme of control of HPAI, vaccination should not be used as the sole control measure but as part of the overall control strategy. It should be carefully managed to ensure protection of poultry and human health.

Case study 3: companion animals

Vaccination of the carrier state in animals to prevent transmission to people: *Bartonella henselae* vaccine in cats

In March 2005, the CVB, in response to requests from industry, came to an agreement with the Department of Health and Human Services Food and Drug Administration in the USA to assume jurisdiction for vaccines intended to control the carrier state in animals. Notice No. 05-07 of the CVB, 'Biologics for Reduction of Colonisation and/or Shedding in Animals' informed stakeholders that USDA had changed its policy to permit licensing of veterinary biological products that claim to reduce colonisation or shedding of pathogens that may not cause significant clinical disease in animals, but may cause the animal to be a disease carrier (12).

The Notice stated that the jurisdiction for animal vaccines targeted at the reduction or elimination of a carrier state of organisms would lie with APHIS as long as certain criteria were met. Those criteria included the following:

- products must be indicated for administration to animals only and must act primarily through the direct stimulation of the immune system
- label claims must contain statements supported by data to show reduction of colonisation or shedding in the animal; no food safety or human health claims can be made
- products are required to show significant and clinically relevant efficacy as defined by APHIS
- products must demonstrate the ability to cause a substantial decrease in number of animals colonised and/or numbers of organisms shed by vaccinated animals.

The significance of this change should foster development and licensure of vaccines that will provide a novel approach for controlling significant zoonotic public health problems, for example, *Bartonella henselae* infections (cat-scratch disease).

An estimated 22,000 cases of cat-scratch disease (CSD) occur annually in the USA, ranking CSD as one of the most common zoonotic, non-foodborne infectious diseases and the leading cause of subacute unilateral adenopathy of children (83). *Bartonella* spp. infections are now recognised to be associated with several distinct clinical syndromes in people, including bacillary angiomatosis, bacillary peliosis, relapsing fever with bacteraemia, endocarditis, granulomatous hepatosplenic syndrome, retinitis and swelling of the optic nerve, arthritis, osteolytic lesions, and pulmonary granulomas (38). *Bartonella henselae* is frequently implicated in the onset of otherwise unexplained encephalopathy, including AIDS-associated encephalopathy (36, 37). Cats can be asymptotically bacteraemic for many weeks and develop detectable antibodies concurrently with bacteraemia (57, 58). The seroprevalence of *B. henselae* in cats varies throughout the USA and appears to be influenced by climate, with some areas showing in excess of 50% of cats having had prior infections (33). The recognition that human CSD is epidemiologically correlated with having been scratched by a cat predated the recognition of the causative agent by 50 years. Cat fleas are believed to play an important role in the transmission of *B. henselae* between cats (14, 33).

Because of the zoonotic origin of human CSD infections and the evidence that indicates that *B. henselae* infections are quite common in pet cats, vaccination of feline reservoirs of disease offers the opportunity to interrupt disease transmission and make a positive impact on public health, without negatively impacting the status of cats as companion animals. Both CDC and industry data show that vaccination can prevent *B. henselae* bacteraemia in cats challenged with infectious *B. henselae*. Future potential feline vaccines should therefore reduce the subsequent risk of transmission of *B. henselae* to humans, which is especially important among immunocompromised individuals.

Practical considerations may inhibit vaccine development and use for vector/reservoir species. These considerations might include:

- uncertain commercial profitability after the considerable costs for product development and licensure
- avoidance of vaccines for companion animals that produce unwanted side effects (e.g. use of adjuvants that might induce local reactions)
- competing commercial products that may reduce the perceived need for vaccination (e.g. effective flea treatment for cats).

In addition, if immunologically distinct microbes are responsible for what is clinically recognised as a single syndrome, either polyvalent vaccines may be required to prevent complete protection from multiple agents, or the public must be educated to understand that a vaccine based on a single agent, however efficacious for a target organism, may not prevent all disease associated with a clinically defined syndrome.

Case study 4: wildlife

Vaccination of reservoirs to prevent disease in other hosts: lyssaviruses and other emerging infections

The existence of known or suspected animal reservoirs handicaps disease eradication efforts, especially related to emerging human and animal pathogens (17). The major recent human medical successes in defeating smallpox, polio, measles, mumps, and most common paediatric diseases may owe much of their success to the fact that eradication efforts are unhampered by complications related directly to vector-borne or zoonotic issues (54). Historically, combinations of quarantine and importation policies, diagnostic test-and-slaughter programmes, proper use of antibiotics and parasiticides, and rational vaccine administration have been effective veterinary management practices.

These techniques are especially amenable to domestic species for the interruption of infectious disease cycles, as demonstrable in foot and mouth disease, hog cholera, brucellosis, tuberculosis, trichinosis, and many other diseases throughout the world (27, 65, 71, 74). However, strategies such as vaccination are often impractical for direct application to free-ranging wildlife because they are impacted by a multiple host-agent complex (22, 56, 80).

Although wildlife may pose substantial hurdles to disease eradication, concerted, multidisciplinary, international efforts have been responding gradually to this challenge. Perhaps one of the best modern paradigms concerning wildlife vaccination is also one of the oldest recognised zoonoses. Rabies is an acute, progressive encephalitis caused by ribonucleic acid (RNA) viruses in the family *Rhabdoviridae*, genus *Lyssavirus* (50). All mammals are believed to be susceptible. Nevertheless, members of the Carnivora, especially domestic dogs, represent the major global public health burden, with tens of thousands of humans dying annually and millions of people bitten by suspect animals each year, primarily in developing countries (35). Oddly, the historical application of the original human vaccination experiments performed by Pasteur and his colleagues at the end of the 19th century were rather slow in practical extension to animals (76). In

the 1920s, Japan became the first country to successfully apply mass rabies vaccination to domestic dogs. More routine veterinary use of rabies vaccination ensued, especially after World War II, and canine rabies control had progressed throughout developed countries by the mid-20th century. The concept and success of wildlife vaccination was borne out by several factors: the realisation that canine rabies could be eliminated by achieving herd immunity; the appreciation of the role of wild mammals such as foxes, raccoons, and other carnivores in dissemination of rabies; the recognition that oral vaccine administration is effective as a means of delivery; and continued progress in development of safe and effective biologicals and attractive baits (5). Beginning in the late 1970s, the tactical field application of rabies vaccine-laden baits over substantial regions in Europe and North America has led to the significant control, and in some cases selective elimination, of the disease among wild mammalian carnivores (15, 45, 67). In addition to self-replicating modified-live and recombinant viruses for oral use, inactivated rabies vaccines for parenteral administration have been used in trap-vaccinate-release programmes, particularly in urban areas (59). Such enterprises could be extended to other terrestrial mammals and diseases.

While the successes realised by wild carnivore vaccination against rabies have provided an important adjunct to traditional veterinary control techniques focused on domestic animals, any true disease elimination may be overshadowed in part by other relevant major reservoirs. For example, members of the Chiroptera represent an important source of rabies throughout the Americas, and a reservoir for emerging lyssaviruses in Africa, Australia, and Eurasia, some with considerable antigenic variation from conventional rabies vaccines (29, 39, 43, 50, 75). Moreover, bats are implicated in a number of other emerging viral diseases, including Ebola, severe acute respiratory syndrome (SARS), and Henipah virus infections (6, 8, 41, 42, 46, 48, 51). Could bat vaccination be considered for disease control and prevention, as implemented for wildlife rabies control in carnivores?

While this suggestion is intriguing, several barriers exist to immediate utilisation of similar vaccination strategies for bats. Whereas only a single species each of fox (*Vulpes vulpes*) and raccoon (*Procyon lotor*) are involved significantly for rabies in western Europe and eastern North America, respectively, bat species are highly diverse. As opposed to fewer than 300 described carnivore species (and few new additions), more than a thousand bat species are described, and nearly 50 new taxa have been suggested (77). Additionally, the relative comparative abundance of bats is high, with some local colonies estimated to consist of thousands to millions of individuals. Because bats are not terrestrial and can migrate over long distances, their dispersal ability creates challenges for vaccine

administration (16). Unlike the situation for domestic or wild carnivores, there are no currently licensed biologicals for the Chiroptera (49).

Given these difficulties, at first inspection, those searching for solutions to bat-related disease issues should perhaps initially consider other available prevention strategies (23). Viable approaches include public education to avoid direct contact with such wildlife; use of existing medical interventions if exposures occur; when available, pre-exposure vaccinations if warranted, and management techniques to minimise bat-human-veterinary conflicts. Traditional practices such as population reduction are not indicated because the extremely low turnover of bat populations may lower the population to a level from which it cannot recover. For example, vampire bats, which prey upon livestock and humans from Mexico to Argentina, have been targeted by specific applications of anti-coagulants, which exploit their hematophagous and social grooming activities (4). However, despite this particular scenario, significant other points related to efficacy, economics, ecology, and ethics argue against lethal means of disease control (61). Moreover, while vampire bat control may be perceived as useful, species eradication is not, because these bats are not only unique biologically, but can offer otherwise unrealised biomedical benefits (28). Today, in nearly all indications, lethal control of bat populations is not espoused by public health nor agricultural agencies in the USA (49). Thus, management techniques for bat-related diseases range from doing nothing, based upon risk assessment and practicality, to focusing only upon humans or affected domestic species, in an attempt to interrupt infectious chains of transmission.

Alternatively, some useful experience with bat vaccination already exists. Vaccination is a consideration because some bats that are brought into captivity for exhibition, applied research or conservation purposes may be incubating disease (66). As with other mammals, bats will respond to inactivated vaccines by parenteral administration (55). Commercial rabies biologicals have been applied to bats, not only for pre-exposure use, but also during outbreaks in captive colonies, in which CDC assistance was requested and provided in both public zoo and private research settings. Intramuscular or subcutaneous vaccination of bats may be quite safe in captivity, but is largely impractical for free-ranging animals.

Other techniques will be needed for field applications of vaccines to bats. In very large bat aggregations, such as in maternity colonies, it has been shown that the aerosol route of infection may be effective (16). This aerosol delivery system may be useful for the potential application of vaccines in bats (34, 78, 79). Oral recombinant vaccines have been tried in captivity for vampire bats (1). Application to one individual of a colony may be spread to

others via social grooming (2). For remote delivery, extended baiting may be envisioned, e.g. by adding vaccine to flavored liquids (as done for certain frugivorous or nectivorous bats), by including vaccine-laden bait in backyard feeders (as done for hummingbirds on a small scale), or by developing plant-based vaccines for consumption (69). As to potential vaccine candidates, given the revolution in reverse genetics, rabies virus itself can be used as an expression vector, for incorporation of foreign genes (20). Other vaccines 'on the wing' could be constructed for selected insectivorous bat species, by the creation of transgenic insects, expressing in appropriate context the immunogen of interest, such as the rabies virus glycoprotein (60). Extrapolating from the concept of both remote delivery and natural hypodermics, bat ectoparasites may be designed to harbour and administer vaccine vectors of interest. One area for potential focus is rhabdoviruses, as many are shared between invertebrates and vertebrates; one could imagine reverse-engineered rhabdovirus vaccines opening new arenas for discovery (40).

Conclusions

In this article, we have explored vaccination of the animal host or reservoir to protect animals against emerging diseases and how such vaccination can serve as a barrier to protect human health. We have reviewed the development of vaccines for a few emerging infections based on established and new technologies and examined their advantages and limitations; we have also looked at the concept of 'altruistic' vaccination of animals for emerging diseases which may not cause ill effect in the animal but which have an adverse effect on human health. Stemming from the realisation that zoonotic diseases are the predominant source of human emerging infectious diseases, it behoves academic, public health, and animal health agencies to consider creative constructive approaches to combat serious public health challenges (68). Veterinary vaccination remains a significant option for zoonotic disease control. Vaccination of vector/reservoir species, when efficacious vaccines are available (e.g. the currently licensed rabies vaccine), offers significant advantages for combating zoonotic human disease.

The concept of zoonotic vaccines is relevant not only for *B. henselae*, but also for other zoonotic pathogens of public health concern. Most notably, studies on the origins of food pathogens have identified that carriage of *Escherichia coli* O157:H7, *Salmonella enterica* and *Campylobacter jejuni* in food ruminants and poultry, as well as pet animals, is relatively common and serves as the ultimate source for human illness from these pathogens. These infections are a huge public health burden, estimated to be responsible for millions of human illnesses and hundreds of deaths each

year in the USA (47). Though much progress has been made in limiting the food contamination during processing through programmes such as hazard analysis and critical control point (HACCP) systems, control will also need to be applied at the farm level. Vaccines, probiotics and other biologics aimed at eliminating or limiting carriage of human pathogens in food animals are central to the next generation of zoonotic foodborne disease control programmes.

We have explored the exciting possibilities of vaccination of the wildlife reservoir for rabies, which ultimately could hold the key to prevention of other emerging diseases such as Ebola, SARS, and Henipah virus. However, for any practical application of the vaccine concept to bats for infectious disease control, multiple research needs abound. Intensive studies into the applied ecology, population biology and sociobiology of selected bat species are a prerequisite. Renewed pathogen discovery, community modelling, and host-agent dynamics must be appreciated. Basic investigations are needed to understand the relationship between bat physiology and immune response, akin to the investigations that have already been

carried out for other mammals. There is a clear need for development of specific biotechnological applications and methodology relevant to free-ranging bats. Such suggestions are not mere idle academic speculations, especially if one considers the alternative consequences of a lack of innovation, the pressures for an integrated response after the eventual establishment of a crisis, and the timeline for practical research and development within the modern regulatory framework. All must be balanced against the substantive public health, veterinary, and economic benefits that have been achieved to date from the oral rabies vaccination of wild carnivores, from original concept to tangible reality.

Acknowledgements

The authors acknowledge and thank Dr Nicholas Komar and Dr Robert Tauxe, Centers for Disease Control and Prevention, Dr Mary Beth Evans, US Department of Agriculture Animal and Plant Health Inspection Service, for their scientific contributions to this paper. ■

Les vaccins contre les maladies infectieuses émergentes

N. Marano, C. Rupprecht & R. Regnery

Les résultats et les conclusions exprimés dans cet article sont ceux des auteurs et ne reflètent pas nécessairement la position du Centers for Disease Control and Prevention.

Résumé

Les maladies infectieuses émergentes font peser une grave menace sur les populations humaines et animales, du fait de leur impact sur la santé mondiale, sur l'agriculture et sur l'économie. Les vaccins vétérinaires mis au point pour lutter contre ces maladies permettent de protéger la santé animale et d'empêcher la transmission à l'homme des maladies zoonotiques. A travers plusieurs exemples, cet article montre successivement comment la coopération entre la santé publique et le secteur pharmaceutique a permis de mettre au point un vaccin contre une maladie émergente des équidés (vaccin contre la fièvre du Nil occidental), comment la vaccination des volailles protège les animaux et prévient la transmission du virus à l'homme (vaccin contre l'influenza aviaire), comment les nouvelles réglementations ouvrent la voie à des vaccins qui contrôleront l'état de porteur des animaux et permettront ainsi de prévenir l'infection chez l'homme (vaccins contre *Bartonella henselae* chez le chat), et enfin comment des technologies innovantes permettent de vacciner des espèces sauvages servant de réservoir animal au virus de la rage. Sachant que les maladies zoonotiques sont la principale source des maladies infectieuses émergentes chez l'homme, il incombe aux institutions de recherche et aux instances de santé publique et de santé animale de concevoir des approches

créatives et constructives afin de lutter contre ces défis majeurs pour la santé publique. Lorsque des vaccins efficaces sont disponibles, la vaccination des vecteurs et des espèces qui servent de réservoir offre des avantages non négligeables pour lutter contre les zoonoses transmissibles à l'homme.

Mots-clés

Maladie infectieuse émergente – Santé publique – Vaccin antirabique pour les animaux sauvages – Vaccin contre l'influenza aviaire – Vaccin contre la fièvre du Nil occidental – Vaccination des animaux – Zoonose.



Vacunas contra infecciones emergentes

N. Marano, C. Rupprecht & R. Regnery

Los resultados y conclusiones expuestos en este artículo son responsabilidad de los autores y no corresponden necesariamente a los puntos de vista de los Centros de Control y Prevención de Enfermedades.

Resumen

Por sus efectos sobre la salud en el mundo, la agricultura y la economía, las enfermedades infecciosas emergentes representan una grave amenaza para las poblaciones tanto animales como humanas. Las vacunas fabricadas para luchar contra esas dolencias en los animales pueden no sólo proteger la salud de éstos, sino también prevenir la transmisión al ser humano de enfermedades zoonóticas. Valiéndose de una serie de ejemplos, los autores explican cómo la industria y la salud pública pueden trabajar concertadamente para obtener una vacuna capaz de prevenir una enfermedad emergente en el caballo (la provocada por el virus West Nile), cómo la vacunación de aves de corral puede proteger a los animales y prevenir el contagio de personas (en el caso de la influenza aviar), cómo los cambios reglamentarios pueden preparar el terreno para vacunas que permitan controlar a los animales portadores y prevenir así la transmisión al ser humano (vacunación de gatos contra *Bartonella henselae*) y cómo las nuevas tecnologías podrían aplicarse a la vacunación de especies salvajes que actúan como reservorio de la rabia. Una vez ha quedado claro que las enfermedades zoonóticas son la fuente básica de infecciones emergentes en el hombre, corresponde a los expertos y organismos de salud pública y sanidad animal encontrar soluciones creativas y constructivas para combatir estas graves amenazas que pesan sobre la salud pública. Cuando existen vacunas eficaces, su administración a las especies que sirven de vector o reservorio presenta considerables ventajas a la hora de combatir enfermedades zoonóticas.

Palabras clave

Enfermedad zoonótica – Infección emergente – Salud pública – Vacuna de la influenza aviar – Vacuna de la rabia en animales salvajes – Vacuna contra el virus West Nile – Vacunación animal.



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