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Review

Vaccines against diseases transmitted from animals to humans: A one health paradigm

Thomas P. Monath[a,b,c,*]

[a] One Health Initiative Pro Bono Team, United States[1]
[b] Austria
[c] PaxVax Inc., United States

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ABSTRACT

This review focuses on the immunization of animals as a means of preventing human diseases (zoonoses). Three frameworks for the use of vaccines in this context are described, and examples are provided of successes and failures. *Framework I* vaccines are used for protection of humans and economically valuable animals, where neither plays a role in the transmission cycle. The benefit of collaborations between animal health and human health industries and regulators in developing such products is discussed, and one example (West Nile vaccine) of a single product developed for use in animals and humans is described. *Framework II* vaccines are indicated for domesticated animals as a means of preventing disease in both animals and humans. The agents of concern are transmitted directly or indirectly (e.g. via arthropod vectors) from animals to humans. A number of examples of the use of Framework II vaccines are provided, e.g. against brucellosis, *Escherischia coli* O157, rabies, Rift Valley fever, Venezuelan equine encephalitis, and Hendra virus. *Framework III* vaccines are used to immunize wild animals as a means of preventing transmission of disease agents to humans and domesticated animals. Examples are reservoir-targeted, oral bait rabies, *Mycobacterium bovis* and Lyme disease vaccines. Given the speed and lost cost of veterinary vaccine development, some interventions based on the immunization of animals could lead to rapid and relatively inexpensive advances in public health. Opportunities for vaccine-based approaches to preventing zoonotic and emerging diseases that integrate veterinary and human medicine (the One Health paradigm) are emphasized.

Contents

* Correspondence to: 295 Townsend Hill Road, Townsend, MA 01469, United States. Tel.: +1 978 549 0708; fax: +1 967 383 0226.
E-mail address: tpmonath@gmail.com
[1] www.onehealth initiative.com

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1. Introduction

Zoonoses (diseases transmissible from animals to humans) account for approximately 60% of all infectious pathogens of human beings and 70% of all emerging infectious diseases [1,2]. The origins of these diseases, and underlying factors (including man-made factors) in their emergence have been the subject of considerable interest [3,4]. Certain zoonotic diseases have the potential for pandemic spread by human contagion, such as avian influenza, SARS and the Middle East Respiratory Syndrome coronavirus, and others for regional cross-border epizootics, such as yellow fever, Venezuelan equine encephalitis and Rift Valley fever. The cost of a short list of zoonotic disease emergences in the interval between 1997 and 2009, including bovine spongiform encephalopathy, SARS, highly pathogenic avian influenza, West Nile, and pneumonic plague (India), was estimated to exceed $80 billion [5]. Of 32 major emergencies that concerned public health (including hurricanes, earthquakes, and terrorist attacks) occurring between 2001 and 2013, more than 25% were zoonotic disease outbreaks [6]. However, the toll on public health is much greater than that caused by such dramatic outbreaks. It is estimated that 56 different zoonotic diseases are responsible annually for 2.5 billion cases of human disease with 2.7 million deaths and substantial reductions in livestock production [7]. Animals, including livestock and companion animals, also suffer illness and death following infection with many zoonotic infections, and livestock and poultry are subject to large-scale intentional destruction as a means of preventing human infections, resulting in huge economic losses. Wild animals, including endangered species, may also be mortally affected, examples being West Nile disease in birds, yellow fever in neotropical monkeys, plague in black-footed ferrets, and Ebola in the great apes.

Vaccines are an important means of prevention and control of zoonotic infectious diseases in humans and domesticated animals. However, the target for vaccination is, in almost all cases, the directly affected species, and there are few practically implemented illustrations of the potential for indirectly preventing human disease by immunizing the domesticated or companion animal sources of infection. The concept of immunizing wild animal reservoirs for the prevention of disease in humans or domestic animals is even more challenging and has received limited attention. Moreover, human and animal health divisions of the biopharmaceutical industry are generally separate and segregated, and there is no organized approach to the development of new vaccines indicated for the prevention of spread of diseases from domestic or wild animals to humans. In addition, the major funding sources for research in human and animal diseases tend to be stove-piped into different government agencies, stifling cross-cutting approaches.

The purpose of this review is to stimulate the science and policy communities to seek innovative ways to interdict zoonotic diseases by integrating human and veterinary medicine and vaccine development, and by creating new streams of funding aimed at the intersection of human and animal health. These aims are consistent with the One Health Initiative, which seeks to establish "collaborative efforts of multiple disciplines working locally, nationally and globally to attain optimal health for people, animals and our environment" [8]. A framework for considering One Health vaccine interventions is provided, as well as a brief review of past and current efforts, including a few successes. It will be obvious to the reader that this is a wide-open field with many opportunities that deserve more attention than they have received. The complexity, timeline, and cost of development of animal vaccines and the regulatory hurdles for product approval are far less than for human vaccines. Thus some interventions based on the immunization of animals could lead to rapid and relatively inexpensive advances in public health. It is obvious that the benefit to human health deriving from vaccination of animals is far easier to justify when there is also a benefit to animal health, the latter often being closely linked to economic value.

2. The epidemiology of zoonotic diseases in relation to vaccination

Causative agents of zoonotic diseases, including viruses, parasites, bacteria, fungi, and prions, have extraordinarily varied life cycles and modes of transmission. Some may persist between periods of active transmission in soil or invertebrate species. Many have silent transmission cycles involving wild animals that have coevolved with the infectious agent and exhibit no signs of disease. Some zoonotic diseases occur when a causative agent harbored by a wild animal reservoir jumps species to domesticated animals and thence to humans. Others are primarily diseases of domesticated animal species. Humans may be infected by direct contact with wild or domesticated animals, or indirectly by ingestion of contaminated milk or meat, inhalation of aerosolized secretions or excreta, fomites, or hematophagous insect or tick vectors. Despite this complexity of epidemiological patterns, the opportunities for intervention often boil down to a few simple bottlenecks in the transmission process. For example, milk-borne diseases can be prevented by pasteurization, certain meat-borne diseases by inspection and animal husbandry improvements (e.g., trichinella, bovine tuberculosis), and other diseases avoided by limiting contact with known high risk species (e.g., tularemia, turtle-borne salmonellosis, exposure to bats carrying henipaviruses). Where the risk of infection is high, or the resulting disease severe, vaccines may be the most efficient and cost-effective means of prevention and control. Alternative methods for control of zoonotic diseases have generally employed trapping, poisoning, or other means of destroying the offending animal reservoir/vector; these methods have a mixed (often negative) record of success and are in any case becoming socially unacceptable. This review focuses on the use of vaccines for animals as an acceptable means of interdicting zoonotic disease in both animals and humans.

3. Frameworks for vaccine-based interventions

Three major epidemiological frameworks are identified for the control of zoonotic disease by means of vaccination of animals (Table 1). The scope of this review encompasses only those diseases for which a strategy targeting vaccination of animals is actually used or is under development. There are many diseases of

Table 1
Frameworks for vaccine development and utilization as a means of preventing zoonotic diseases, and status of approval of existing vaccines for humans and animals.

Framework (epidemiology)	Target of vaccination	Purpose of vaccination	Opportunities	Example	Status	Animal species
I. Humans and domestic animals are dead-end hosts (do not contribute to transmission cycle)	Domestic animals and humans	Protect humans and domestic animals against the disease	Potential for development of a similar vaccine for humans and animals, industry cooperation, shorter timelines, lower cost. Animals serve as model for human disease applicable to FDA Animal Rule	West Nile	Human vaccines: investigational, Phase II Animal vaccines: licensed	Horse, goose, alligator, some zoo animals
				Eastern equine encephalitis, Western equine encephalitis	Human vaccines: investigational, Phase II Animal vaccines: licensed	Horse, donkey, mule Other susceptible species (off label): emus, pheasants, chukars, camelids (llama, alpaca)
				Japanese encephalitis	Human and animal vaccines: licensed	Horse
II. Domestic animals play a major role in transmission of the disease to humans (and domestic animals)	Principally domestic animals. Secondarily, humans at high risk	Protect domestic animals against infection (disease) Prevent transmission from domesticated animals to humans (by contact, vehicle, or vector).	Same as Framework I Vaccination may provide herd immunity, decrease transmission. Potential support from public health agencies and human regulatory authorities to promote animal vaccines for preventing human diseases	*Bacillus anthracis* (Anthrax)	Human and animal vaccines: licensed	Cattle, other spp.
				Avian influenza	Human and animal vaccines: licensed	Poultry, swine
				Bartonella henselae (cat scratch fever)	Animal vaccine: investigational	Cat
				Brucella melitensis, B. abortus, B. suis	Animal vaccines: licensed	Cattle, sheep, goat, swine, dog
				B. canis (Brucellosis)	Animal vaccines: investigational	
				Burkholderia mallei (Glanders)	Animal and human vaccines: investigational	Horse, donkey, mule
				Campylobacter jejuni	Animal vaccines: investigational (advanced development)	Chicken
				Chlamydophila abortus (Chlamydiosis)	Animal vaccines: licensed	Sheep, goat
				Chlamydophila felis (feline pneumonitis, keratoconjunctivitis)	Animal vaccines: licensed	Cat
				Chlamydophila psittaci (Parrot fever)	Animal vaccines: investigational	Psittaciform pet birds. Poultry
				Cryptosporidia parvum Cryptosporidiosis	Animal vaccines: investigational	Cattle, sheep, goat
				Escherischia coli O157	Animal vaccines: licensed	Cattle
				Hendra virus	Animal vaccines: licensed	Horse
				Hepatitis E	Human vaccines: licensed	Pig
				Leishmania infantum (Visceral leishmaniasis, humans; visceral & cutaneous in domestic animals)	Animal vaccines: licensed	Dog
				Leptospirosis	Animal vaccines: licensed Human vaccines: investigational	Dog
				Middle East Respiratory Syndrome (MERS)	Human vaccines: investigational	Camel (if confirmed as intermediate host)
				Nipah virus	Animal vaccines: investigational	Pig
				Pasteurella multilocida	Animal vaccines: licensed	Sheep, goats, cattle, swine, chicken, rabbit
				Rabies	Human and animal vaccines: licensed	Dog, cat, sheep, horse, ferret Camelids (llama, alpaca: off label)

Table 1 (*Continued*)

Framework (epidemiology)	Target of vaccination	Purpose of vaccination	Opportunities	Example	Status	Animal species
Rift Valley fever	Human vaccines: investigational, Phase II Animal vaccines: licensed	Cow, sheep, goat				
				Salmonella spp.	Animal vaccines: licensed	Chicken
				Q fever	Human and animal vaccines: licensed	Sheep, goat
				Toxoplasmosis	Animal vaccine: licensed	Sheep Cat
					Animal and human vaccines: investigational	
				Venezuelan equine encephalitis	Human vaccines: investigational, Phase II Animal vaccines: licensed	Horse, mule, donkey
				Vesicular stomatitis	Animal vaccines: licensed (Central, South America)	Horse, cow, pig (sheep, goat, llama)
III. Wild animals play a major role in transmission of the disease to humans and domestic animals	Wild animals; humans and domestic animals at high risk	Prevent transmission to humans, domestic animals		*Borrelia* spp. (Lyme disease)	Human vaccines: investigational, Phase II. Domestic animal vaccines: licensed Wild animal vaccines: investigational	Dog (cat, horse) *Peromyscus* mice
				Brucella abortus	Wild animals: Investigational use of approved vaccine	Bison, elk
				Mycobacterium bovis	Wild animals: Investigational use of approved vaccine	Badger, deer, marsupials, wild boar, etc.
				Rabies	Wild animal vaccines: Licensed	Fox, raccoon, raccoon dog, coyote
				Yersinia pestis (plague)	Wild animals: investigational	Prairie dogs

animals transmissible to humans for which vaccination of animals is not feasible using currently available technologies, due to the complex ecology of the disease, a role of multiple wild animal species in transmission cycles, and difficulty of access to the host. For these diseases, the most practical and successful approach bypasses animals and is human immunization. Examples include yellow fever (acquired from mosquitoes infected by wild monkeys); hantavirus diseases (acquired by direct/indirect contact with rodents); and Ebola, Marburg, and severe respiratory coronavirus infections (acquired from contact with or aerosols generated by bats or from intermediate animal hosts infected by bats).

3.1. Framework I. Humans and domestic animals are dead-end hosts

The first major framework includes zoonotic infectious diseases that affect both humans and economically important animals, where wild animals are the source of infection. Livestock and humans are dead-end hosts, and neither contributes to the transmission cycle. In this case, vaccines are required to prevent disease in both humans and economically important animals, but do not interrupt transmission of the disease in nature. For Framework I diseases, there is an important opportunity to accelerate the development of new vaccines by concurrent veterinary and human product research (Table 2). Moreover the affected animal species represents a natural disease model of infection, pathogenesis and immunity that may be useful in testing efficacy and immunological correlates of protection of a new vaccine intended for human use, and thus provide data supporting regulatory approval under FDA's Animal Rule [9]. A list of Framework I diseases and vaccines is shown in Table 1, and an example is given below.

3.1.1. West Nile virus disease

West Nile virus is a mosquito-borne, single strand, positive-sense, enveloped RNA virus (genus Flavivirus, family *Flaviviridae*), closely related to Japanese encephalitis virus. West Nile virus is a recognized cause of human disease ranging from mild fever-rash-headache syndromes to lethal encephalomyelitis. Horses, domesticated geese, farmed alligators (as well as a number of wild birds and mammals) are also susceptible to severe and fatal disease. Although recognized as a cause of disease as early as the 1940s, West Nile became an increasing problem in the 1990s, with outbreaks affecting humans and/or horses in northern Africa, Western Europe, the eastern Mediterranean, the Black Sea region and the Volgograd Oblast of Russia [10]. The most dramatic development was the introduction of West Nile virus into North America in 1999 [11–13], the occurrence of large outbreaks in 2002 and 2003, rapid spread across the US, and subsequent introduction to the Caribbean and South America. Horses and a number of wild bird species, notably crows and jays, were affected in addition to humans. Between 1999 and 2012, a total of 37,008 cases of West Nile fever and 16,196 cases of neuroinvasive West Nile disease were reported in the US, with the highest incidence in the middle of the country from Texas north to the Dakotas [14]. The incidence of neuroinvasive disease in the US has varied between 0.1 and 1.0 per 100,000 in this interval [15]. Over 25,000 horses have been affected since 1999, and in these animals the disease is more severe (33% case-fatality, 40% of survivors with neurological sequelae) than in humans (4–9% case fatality, 30% of encephalitis survivors with sequelae) [16]. Moreover, the incidence of West Nile in horses (~700 per 100,000) is substantially higher than in humans [17].

The animal health industry rapidly responded to this veterinary emergency, and multiple West Nile vaccines were rapidly developed, including a live vaccine (discussed below), whole virion inactivated, DNA, and poxvirus vectored vaccines. The first vaccine for horses was marketed in 2001, only 2 years after introduction of the virus into the US. Multiple human vaccine development programs were also initiated, but many of these efforts were discontinued or decelerated due to the high market risk associated with low incidence, a slackening of public concern with the disease, and the uncertain regulatory pathway for vaccine approval. Although efficacy of a vaccine for equids is established [18], field trials to prove vaccine efficacy in humans would be large, expensive, and difficult due to the unpredictable occurrence of West Nile outbreaks. The application of the Animal Rule to licensing a West Nile vaccine, while plausible, has not been adjudicated by the FDA with a sponsor.

Although approaches to developing veterinary and human vaccines against West Nile were technologically similar, in only one case was a concurrent development program undertaken by a single company. This fact illustrates the current status of stove-piped and separate animal and human health biopharmaceutical industries. The exceptional case is of interest as a model of how vaccine development for zoonotic diseases could be improved. In 1999, within 2 months of the identification of West Nile as the etiological agent of the initial outbreak affecting humans and horses in New York, Acambis, a publically traded human-vaccine biotechnology company, applied its platform technology for yellow fever 17D-vectored vaccines to the development of a West Nile vaccine, with the intent to develop both vaccines for both horses and humans. This technology involved replacing the gene encoding the yellow fever 17D vaccine virus' envelope (E) protein with the corresponding gene of West Nile virus. This chimeric vector vaccine platform had been previously used by the company to construct a chimeric vaccine against the closely-related Japanese encephalitis virus [19]; at the time, that vaccine had proven to be highly effective, protecting non-human primates against intracerebral challenge with virulent Japanese encephalitis virus [20]. Two new vectors were engineered, one with the wild-type West Nile NY99 strain E protein gene and one with an E gene containing three attenuating mutations [21–23]. The former was neurovirulent in mice, while the latter was more attenuated and thus deemed more suitable as a human vaccine. The principal question was whether the yellow fever 17D vector would infect and immunize horses, since yellow fever is a host-restricted primate virus. To find out, studies were sponsored by Acambis in early 2000 at the Colorado State University School of Veterinary Medicine. Horses were vaccinated with the West Nile/yellow fever chimeric virus or with yellow fever 17D vaccine, and viremia and antibody responses were determined [24]. In addition, vaccinated and control horses were challenged by the intrathecal injection of a high dose of virulent West Nile virus, following the same model referred to above for protection studies of the chimeric Japanese encephalitis vaccine wherein monkeys were challenged by the intracerebral route. These studies showed that horses inoculated with chimeric vaccine developed neutralizing antibodies against West Nile and were protected against a severe intrathecal challenge. A similar development plan was successfully followed for the mutated human vaccine version, using non-human primates as the test host. The veterinary and human vaccine candidates were developed side by side, and the data obtained in both programs were designed to support transition to advanced clinical trials in horses and humans. In 2002, Acambis licensed the veterinary vaccine technology to a major animal health company (Intervet), and in the same year clinical trial materials were made for human trials. Intervet completed development of the veterinary vaccine (PreveNile®) [25], which was approved by USDA in 2007, and Acambis brought the human vaccine (ChimeriVax-WN02) into clinical trials in the same timeframe [26], subsequently outlicensing the technology to Sanofi Pasteur. As expected, development of the veterinary vaccine and its progression through the regulatory pathway substantially outpaced the human vaccine; importantly, the veterinary application significantly informed the human vaccine

Table 2
Strengths and limitations of vaccination of animals as a means to control of zoonotic diseases.

Framework (See Table 1)	Strengths	Limitations
I	Benefits to human and animal health Potential for accelerated development of new vaccines Collaborations between animal and human health industry Reduced development costs Additional models for Animal Rule Lack of commercial incentive	DIVA requirements Liability concerns Segregated regulatory pathways Inadvertent exposure of humans to live vaccines
II	New approaches to disease control Benefits to human and animal health Short development times and relatively low cost Accelerated regulatory pathway Potential for disease control without need for human vaccines Collaborations between animal and human health industry Improved food safety	DIVA requirements Wild animal reservoirs Persistent environmental source of infection Durability of immune response inadvertent exposure of humans to live vaccines Low commercial value, reliance on government funding Feral animals or small farm operations inaccessible to vaccination High vaccine coverage required for herd immunity
III	New approaches to disease control Control of infections acquired from wild animals Accelerated regulatory pathway Potential for disease control without need for human vaccines Collaborations between animal and human health industry Control of wildlife diseases	GMO issues Safety for non-target species Role of animals other than target species in transmission Very high or very low target species density Difficulty in designing and delivering oral vaccines Vaccine stability under conditions of use Low commercial value, reliance on government funding

development program in providing useful information on safety, durability of immunity and immune correlates or protection.

Co-development of the veterinary and human West Nile vaccines is as a potential model for other vaccines. There are a few other examples where vaccines were co-developed for animals and humans, including vaccines against Venezuelan equine encephalitis and Rift Valley fever (described below). Certain issues arise, however, that may need to be considered in the context of such integrated efforts. First, a safety problem arising during use of a veterinary vaccine could provoke regulatory concerns or a liability problem for the human analog. Although a safety issue did arise briefly due to anaphylaxis type reactions in horses, resulting in temporary withdrawal of PreveNile® from the market [27], there were no repercussions for the human analog vaccine (ChimeriVax-WN02). This raises the interesting question whether the human and veterinary regulatory agencies are integrating information that might be of value, either during development of similar vaccines for different species or after marketing approval. This is an obvious overlooked area for application of One Health principles. Second, the immune response to veterinary vaccines generally should *d*ifferentiate naturally *i*nfected from *v*accinated *a*nimals (DIVA) on the basis of a laboratory test, which allows compliance with trade restrictions. This is, of course not a concern for regulatory approval of human vaccines, although it can be useful in seroepidemiological and vaccine coverage studies. An example of problems associated with DIVA is the off-label use of commercial horse vaccine to protect emus against eastern equine encephalitis (EEE), since some combination vaccines against EEE contain equine influenza antigen and such vaccines elicit cross-reactive antibodies to avian influenza resulting in quarantine. The chimeric West Nile vaccine described above potentially allows for DIVA testing (using responses to the yellow fever nonstructural proteins expressed by the vector) [28].

3.2. Framework II. Domestic animals play a major role in transmission of the disease to humans (and domestic animals)

A number of important diseases are transmitted between domesticated animals and thence to humans. Vaccination of domesticated animals has the potential to protect humans against these zoonoses, either indirectly by interrupting transmission where domesticated animals are amplifying hosts in the transmission cycle or directly by preventing spread from infected animals to humans. A list of Framework II diseases and vaccines is shown in Table 1. Selected examples are used to illustrate the role of vaccination of domesticated animals in preventing human disease.

3.2.1. Brucellosis

Brucella spp. are facultative, intracellular Gram-negative bacteria, pathogenic for domestic animals and humans. Brucellosis, caused mainly by *Brucella melitensis* (which infects sheep and goats), *Brucella abortus* (cattle), and *Brucella suis* (swine), occurs worldwide, with the highest prevalence in the Middle East, Asia, Africa, tropical America, and the Mediterranean region [29,30]. The annual incidence of human infections is estimated at 500,000 cases but the disease is widely acknowledged to be underreported [31]. *Brucella canis*, an infection of dogs, occurs worldwide with highest prevalence in tropical America. *B. canis* disease in humans has been reported, especially in persons handling breeding dogs and in immunosuppressed individuals. Human brucellosis is acquired by contact or aerosol spread from infected animals, fomites, or ingestion of unpasteurized milk or undercooked meat. Not surprisingly, *Brucellae* survive for long periods in dust, animal excreta, soil, meat and dairy products. Wild animals are also affected and can be the source of infection of livestock and humans. In animals, brucellosis causes epididymitis in males and abortion, placentitis, infertility and reduced milk production in female animals. The human disease is protean, manifested by chronic fatigue, relapsing fever, endocarditis, spondylitis, osteomyelitis, arthritis, and meningitis [32]. Prevention of human disease by control of brucellosis in livestock has long been a public health priority [33].

Control of brucellosis relies principally on surveillance, testing, removal of infected animals, import/export animal and animal product control provisions, protection from exposure to wild reservoirs (such as elk, deer, and bison), and vaccination. Antibiotic treatment of animals is regulated and discouraged due to the large doses and long treatment required and concern about resistance. Old, empirically developed live attenuated vaccines, *B. melitensis* rev1 vaccine for goats and sheep; *B. abortus* S19 and RB51 vaccines for cattle; and the oral *B. suis* S2 vaccine used widely in China for multiple species, elicit cellular immunity against the intracellular pathogen and are more effective than other types of vaccine [34]. The RB51 vaccine (a spontaneous rifampin-resistant rough mutant) is approved in the US [35]. However, the live vaccines have a number of drawbacks. The latter include lack of the ability to differentiate S1 and rev1 vaccine immunity from natural immunity (DIVA) and interference with surveillance and export control

procedures; pathogenicity (especially abortion when animals are vaccinated during pregnancy); antibiotic resistance of the vaccine strains; and modest efficacy. Live vaccines used in livestock can also cause illness in humans. Vaccination as a stand-alone strategy has rarely been carefully evaluated, in large part due to concerns over the quality of the existing vaccines. However, vaccination is largely credited with elimination of brucellosis in the US [36,37] (The US was declared free of brucellosis in cattle in 2009) and for control of brucellosis in China [38]. A recent study in Greece showed that a mass vaccination program with the *B. melitensis* rev1 vaccine resulted in a decrease in human infections [39]. A number of new vaccine approaches, including DIVA vaccines, designed to induce Th1 oriented cellular immunity are under investigation, including safer rationally designed, mutated live vaccines [34]; recombinant, invasive *Escherischia coli* [40]; recombinant subunit microencapsulated vaccines; and DNA vaccines [41]. Experimental *B. canis* vaccines have been investigated in mice.

Where brucellosis-free status has been achieved, as in the US, wild animal reservoirs (especially bison and elk) threaten to reintroduce the disease. Vaccination with existing vaccines is feasible, but delivery is challenging [42].

3.2.2. *E. coli O157*

This Vero cytotoxin secreting Gram-negative bacteria is an important cause of sporadic and epidemic food-borne illnesses of humans, including gastroenteritis and hemorrhagic colitis, with potentially lethal complications (hemolytic-uremic syndrome). Cattle and sheep are the principal reservoirs of infection and transmission to humans occurs via food (meat, seeds and vegetables) contaminated with animal feces. Undercooked ground beef is a source of infection in approximately one-third of human cases and recalls are a significant economic threat to the meat packing and distribution industry. Animals concentrated at feed lots and slaughter that shed bacteria can produce lots of meat with high rates of O157 [43,44], but there is considerable variability in the occurrence of contaminations [45]. In developed countries, various sanitary measures and testing have been instituted to reduce the risk to consumers, but these remain imperfect. Vaccination of feed lot cattle has been proposed as a measure to reduce the prevalence and duration of shedding and the risk to consumers. O157-specific bacterial extract vaccines containing protective outer membrane proteins have been conditionally approved by USDA (manufactured by Epitopix, Willmar, MN) and fully approved by the Canadian Food Inspection Agency (Bioniche Life Sciences, Belleville, Ont.). Feedlot cattle receiving 2 or 3 doses of the Bioniche vaccine 3–4 weeks apart had 59–98% reduction in colorectal colonization or fecal shedding and significant reduction in magnitude and duration of shedding [46–48].

Hurd and Malladi [49] modeled the impact of vaccinating cattle on human health outcomes. Assuming 80% efficacy of the vaccine and 100% adoption rate, the model indicated a 60% reduction in the incidence of *E. coli* O157-related human illness. The model also predicted significant reductions in the number of lots of contaminated ground beef and detection by USDA, which would have substantial economic benefit to packers and distributors. Vaccine effectiveness under conditions of field use will be highly dependent on adoption rate (vaccine coverage), and in part by whether cattle complete the 3-dose vaccination series on the proscribed schedule [46]. An interesting question is: who will pay for vaccination of feedlot cattle? Is the economic benefit there for the meat industry, and will vaccination reduce the cost of other preventive measures and testing or will vaccine costs simply be on top of other costs? Will government agencies concerned with human health subsidize the cost, without empirical demonstration of a human health benefit? Since ground beef only contributes about one-third of human infections, how could vaccines be used as a means of reducing other sources of food contamination? Another issue for use of the current vaccines is the role of other enterohemorrhagic *E. coli* (e.g. O26, O11, and O103) in human disease.

3.2.3. *Cat scratch disease*

This disease is caused primarily by the Gram-negative bacterium, *Bartonella henselae*, transmitted between domestic cats by the agency of cat fleas, *Ctenocephalides felis*. Human infection occurs by contact spread from cats, including scratches by claws contaminated with blood or flea feces, or possibly by flea bite [50,51]. The prevalence of infection in household cats in the US is approximately 28%, but in stray animals it is 81% and high prevalence rates have been found in developing countries [52,53]. Disease in humans is manifest by fever, a papule followed by a pustule at the site of infection and lymphadenopathy. Rare complications include meningitis, encephalitis, endocarditis, glomerulonephritis, osteomyelitis, neuropsychiatric abnormalities, and relapsing fever and splenomegaly. Human infections in immune-compromised individuals are particularly severe. Approximately 22,000–24,000 cases and 2000 hospitalizations caused by cat scratch disease are estimated to occur annually in the US. In the late 1990s, Heska Corporation, an animal heath company in Colorado, initiated a program to develop a vaccine for household cats, with the goal of limiting the potential for transmission of the bacteria from cats to humans. Unfortunately, the program was not completed and no vaccine is available at present. Given the fact that cats rarely become ill with *B. henselae*, this would have been an unusual product providing protection to pet owners, with marginal if any real benefit to the target species. Moreover, it would likely have been extremely challenging to demonstrate a health benefit to humans.

3.2.4. *Rabies*

Rabies is a fatal infection of the central nervous system caused by rabies virus, a member of the Lyssavirus genus, family *Rhabdoviridae*. It is estimated that up to 40,000–60,000 cases of human rabies occur annually, and dog bite is the cause of over 98% [53]. Successful vaccination of dogs and humans against rabies was first demonstrated in 1885 by Louis Pasteur, using crude nerve tissue preparations. However, until the first decades of the 20th Century in developed countries, and continuing in many developing countries today, the ancient practice of dog population reduction campaigns have been the main approach to rabies control, a method that has repeatedly proven to be ineffective. Dog licensing and vaccination requirements were introduced in the United Kingdom in 1910, and gradually at the local and then state levels in the US beginning in the 1920s, with national requirements attained by 1955 [54]. Many successful dog vaccination campaigns have been reported in Latin American countries and Asia [55]. Some countries have declared eradication of canine rabies, notably the United Kingdom in 1922, Japan in 1956, the US in 2007, as well as Malaysia, Singapore, Taiwan, Hong Kong. In 2007, the first World Rabies Day event, the ultimate vision was promulgated of canine rabies elimination through systematic vaccination. However, rabies remains a significant public health problem, due to absent or incomplete dog vaccination in many areas of the world. More than 7.5 million post-exposure treatments with rabies vaccines are given annually, at a cost of over $1 billion worldwide [56,57]. In China, due to the low prevalence of canine vaccination, the sales of rabies vaccines for human post-exposure prophylaxis outstrips any other human vaccine, accounting for 14% of all annual vaccine sales, i.e. 12 million doses costing $244 million [58]. The requirement for human post-exposure vaccination at this scale represents an obvious failure of public health, since it plays no role in containing the spread of rabies in the canine vector.

A very high rate of vaccine coverage in the dog population (exceeding 75%) is required for interruption of the rabies

transmission cycle [59]. The development of oral rabies vaccines has allowed vaccination of free-roaming dogs that could not be restrained and vaccinated by injection, as well as the vaccination of wild animal species that are the source of infection in dogs [60]. Oral bait vaccine for dogs has been successfully deployed in trials in many countries, including Turkey, Thailand, Sri Lanka, South Africa, and the Philippines [61]; the World Health Organization has supported this approach as a supplemental program where there are substantial populations of free-ranging or feral dogs [60]. Significant increases in canine vaccination coverage have been achieved when oral rabies vaccine was added to a program of standard parenteral vaccination. Oral vaccination of dogs has been accomplished using commercial baits containing live modified rabies vaccines, such as the Street-Alabama-Dufferin (SAD) strain, variant B19 [62] and the attenuated Copenhagen strain of vaccinia expressing the rabies glycoprotein gene (G protein) [63].

A more detailed review of oral rabies vaccines is provided below (Framework III).

3.2.5. Hendra virus disease

Hendra virus disease, a severe and fatal infection of horses and humans in Australia, has been noted as an example illustrating One Health principles in disease prevention and control [64], and is especially relevant now that a new vaccine for horses has been introduced. Hendra is a member of the Henipavirus genus, family *Paramyxoviridae*. The reservoir hosts are fruit bats (*Pteropus* spp.), and the virus is spread from bats to horses by contact (including respiratory droplets), by food or fomites contaminated with bat urine, or by contact with sick horses. All reported human infections have resulted from contact with infected horses [65–67].

Hendra virus disease was first described in 1994. Human and equine cases have occurred in coastal Queensland and New South Wales and positive bats have been detected in the Northern Territory. A total of 81 deaths in equids have been reported in 14 outbreaks, with a very high case-fatality rate (75%), and 8 cases (4 fatal) have occurred in humans, including horse trainers and veterinarians, all of whom had contact with sick horses [68]. The disease is manifested by severe systemic illness, respiratory symptoms or acute and relapsing encephalitis [69]. Swine appear to be susceptible to experimental infection. Nipah virus, a closely related bat-borne agent in SE Asia has caused outbreaks of severe and fatal disease in swine and humans [65–67].

In November 2012, Pfizer Animal Health launched Equivac®HeV, an adjuvanted subunit protein vaccine for the prevention of Hendra virus disease of horses in Australia [70]. Since horses are a major source of contact spread of Hendra virus to humans, the vaccine promises to make an important contribution to human health as well. Fear of acquiring the disease has also constrained equine veterinary practice in Australia [71], and the vaccine should mitigate this problem.

Development of Equivac®HeV was a collaborative effort between Pfizer and CSIRO's Australian Animal Health Laboratory. However, support for the development program was also provided by human medical researchers in the US, at the Uniformed Services University of the Health Sciences supported by the Henry Jackson Foundation for the Advancement of Military Medicine. A provisional approval for limited use of the vaccine was obtained in early 2012, with full approval in November.

The vaccine is a soluble, recombinant glycoprotein (G) of Hendra virus, the ligand for cell attachment and antibodies to the protein neutralize cell receptor binding of the virus [72,73]. The vaccine protects horses and ferrets against experimental infection [73], and appears to cross-protect against Nipah virus [74].

The availability of Equivac®HeV should lead to rapid uptake by horse owners in Australia. The equine and horse racing industry in Australia is large, contributing billions of dollars, and over 1% of total Gross Domestic Product [75]. Hendra virus in horses is a notifiable disease in all Australian jurisdictions; the property where the horse cases are located is quarantined and animals that are infected are euthanized. The occurrence of at least one Hendra virus outbreak annually since 2006, and the high lethality of the disease have raised considerable awareness in Australia. Since all human cases of this zoonosis have resulted from contact with infected horses, vaccination of horses against Hendra virus promises to be a highly effective strategy for preventing human cases.

3.2.6. Rift Valley fever

Rift Valley fever is an enveloped, single-strand, segmented RNA virus belonging to the Phlebovirus genus, family *Bunyaviridae*, occurring in Africa, with intermittent extensions to the Arabian Peninsula. Rift Valley fever virus causes explosive and economically damaging outbreaks of disease in cattle and sheep, with stillbirth, abortion, and very high mortality of young animals; in adult animals, it causes 30% mortality in sheep, 10–15% in cattle, and 5–10% in goats [76]. Humans typically develop self-limited nonspecific febrile illness, but 1–2% have a complicated course with hemorrhagic fever syndrome, encephalitis, hepatitis, renal failure, or retinitis, and case-fatality rates in severely ill and hospitalized patients is as high as 20% [77,78]. The virus is transmitted between livestock and from livestock to humans by the agency of mosquito vectors. In addition, humans commonly acquire infection by contact and aerosol routes when handling, treating, or butchering infected livestock, and the virus can persist in meat for weeks. The ecology of Rift Valley fever and the reasons behind its periodic emergences have been the subject of intensive study. In brief, the reservoir of infection is *Aedes* mosquitoes, especially *Ae. linneatopennis*, which maintain the virus by transovarial transmission [79]. The dessication-resistant ova containing virus remain in depressions in the earth ('dambos') that are flooded during the rainy season, with the subsequent emergence of infected adult *Aedes* mosquitoes. Infected, viremic, livestock in turn served as source for amplified virus transmission by a variety of mosquito vectors [76,80].

There are no approved vaccines for prevention of Rift Valley fever in humans, although a number of candidates are in development by academic and government laboratories. Vaccination of cattle and sheep represents a strategy for preventing disease in these species, and thereby for interrupting virus transmission to humans. Rift Valley fever epizootics are to some extent predictable based on rainfall patterns and surveillance of disease in livestock [81]. Surveillance provides opportunities for rapid intervention, particularly with a single-dose vaccine (most likely a live, attenuated vaccine) that would protect against viremia in cattle and sheep and prevent mosquito infection. In addition, routine vaccination of livestock in inter-epizootic periods with a product capable of inducing durable protective immunity is a long range goal supported conceptually by modeling [82]. However, there are many obstacles to livestock immunization in Africa, including access, policy, regulatory approval, cold chain, and commercial viability. Additionally, DIVA requirements are driven by regulations prohibiting export of livestock or meat by countries experiencing Rift Valley fever [82].

Some of the obstacles to vaccination implementation could be overcome by development of improved vaccines. Two old veterinary vaccines, the live Smithburn vaccine, developed using techniques of serial passage in mouse brain similar to that applied to the early development of the French Neurotropic Vaccine against yellow fever [83,84], and a formalin inactivated vaccine [85] are commercially available from the Onderstepoort Institute in South Africa. However, the Smithburn vaccine, now produced in BHK-21 cells, is reported to cause teratogenicity and abortion when used in pregnant animals [84] and is used only in countries endemic for Rift valley fever due to concerns about reversion. The

inactivated vaccine, also grown in BHK-21 cell culture, requires multiple doses to be effective and probably has relatively short durability [86], making it less desirable for the interventions proposed above. Nonetheless, the inactivated vaccine was successfully used to interrupt a Rift valley fever outbreak in South African sheep [79]. Indeed, following a large epidemic of Rift Valley fever in Egypt in 1978–79, the Veterinary Serum and Vaccine Research Institute (Cairo, Egypt) produced a formalin-inactivated vaccine in BHK-21 cells using the epidemic strain (ZH501), which matched locally circulating strains compared to the South African strain [87]. Another inactivated vaccine (TSI-GSD 200) developed by the US Army for human immunization and grown in diploid fetal rhesus lung cells was tested clinically and shown to be well tolerated and immunogenic. Ninety % of the subjects developed a neutralizing titer >40, which was shown to be higher than the protective level in a passive immunization-challenge study in hamsters [88,89]. In addition to the requirement for multiple doses for primary and booster immunization, inactivated Rift Valley fever vaccines have the disadvantage of requiring high biocontainment facilities for manufacturing.

In recent years, there has been substantial progress in development of newer vaccines, and some of these vaccine development projects have been collaborations between human and veterinary research groups. Additionally, there has been a moderate level of support from the US government because Rift Valley fever is a credible threat of natural or intentional (bioterrorist) introduction. Nevertheless, despite very promising technical results, there has been insufficient support from industry and government to propel any of these new vaccine candidates into use.

Because of the obvious advantages of rapid onset and durable immunity associated with live vaccines, development of an improved live vaccine has been the focus of research. US Army investigators attempted to induce attenuating mutations in two Rift Valley fever virus strains isolated during the 1978 Egyptian epidemic [90]. MP-12 is a live vaccine that was developed from the virulent ZH-548 strain by 12 passages in MRC-5 cells in the presence of the mutagen, 5-fluorouracil, resulting in a temperature sensitive virus with 9 amino acid mutations. Attenuation was demonstrated in multiple animal models, and reassortment studies showed that attenuating mutations were redundant and resided in all three gene segments [91,92]. Development of MP-12 was undertaken by the US Army Medical Research Institute of Infectious Diseases with the intention to produce a vaccine for both human and animal immunization. The vaccine was clinically tested in 62 human volunteers and shown to be well-tolerated and highly immunogenic [93]. Army investigators, in collaboration with USDA, conducted a number of studies of MP-12 vaccine in sheep and cows, including neonatal, pregnant and lactating animals. These studies showed that MP-12 caused a low viremia, but with no attendant clinical signs; there was no virus secretion in milk, and no abortions or teratogenicity when vaccine was given in in mid- to late term pregnancy. MP-12 was highly immunogenic and protected livestock against virulent challenge [94,95]. However, ewes vaccinated with MP-12 early in pregnancy showed a low incidence of abortion and teratogenicity, indicating some residual virulence of the vaccine [96]. To improve genetic stability and safety of MP-12, reverse genetic techniques were used to introduce deletions in the S and M RNA segments in genes encoding, respectively, NSs and NSm proteins [97,98]. Two deletion mutants were evaluated for safety and immunogenicity in pregnant ewes [99] and in calves (Morrill JC personal communication, 2013) with positive results for the NSm deletant, making it an attractive candidate as a veterinary and human vaccine. There were no clear safety signals when ewes were inoculated in early-mid pregnancy. Further safety studies are required to rule out the low incidence of abortion/teratogenicity seen with parental MP-12 in early-term ewes. Unfortunately, human trials have not yet been performed with the rationally designed MP-12 derivative.

A third live vaccine designated Clone 13, is a plaque-derived clone of a Central African strain of Rift Valley fever isolated from a human subject, and was found to be naturally attenuated for mice and to have an in-frame deletion of most of the NSs gene [100]. This observation was the basis for modifying the MP-12 vaccine by NS gene deletion, as described above. Once again, a collaboration between the human and veterinary researchers led to a study in ewes, showing that Clone 13 was highly immunogenic but did not cause abortions [101,102]. Another attenuated vaccine designated R566, has been developed by reassorting clone 13 and MP-12 so that it contains the S segment of clone 13 and the L and M segments of MP-12. This strain has attenuation domains from both parental vaccine candidates.

A number of live, replicating, and non-replicating heterologous viral vectors expressing Rift Valley fever G1 and G2 glycoproteins and nonstructural proteins have been have been investigated in mice, elicited immune responses and protected against challenge. The vectors included lumpy skin disease (capripoxvirus) [103], alphavirus (VEE and Sindbis) replicons [104], Newcastle disease virus [105], adenovirus, and Modified Vaccinia Ankara. Several of these constructs were used to immunize sheep and/or cattle (lumpy skin disease virus, Newcastle disease virus, and Sindbis replicons) with somewhat variable success. For a more comprehensive review see Indran and Ikegami [106] and Boshra et al. [107]. Live vectors are a promising approach for new Rift Valley fever vaccines, particularly veterinary vaccines, but may have problems for homologous boosting in light of anti-vector immunity. Various prime-boost strategies have been proposed, as for plasmid DNA vaccines (see below), but these would be exceptionally difficult to implement for immunization of livestock in the field, and are thus impractical.

Subunit protein produced in insect cells, virus-like particles [108], and DNA vaccines [109] against Rift Valley fever are also in early stage development. These approaches have potential advantages of safety and thermostability during storage and distribution, but may require multiple dosing and provide less durable immunity than live vaccines, and thus are less desirable products for Framework II implementation.

Overall, it remains to be seen which of the many Rift Valley fever vaccines in development progress to regulatory approval and whether an integrated veterinary and human health policy based on the immunization of livestock in Africa together with predictive surveillance, can abort impending outbreaks, and lead to long range control of this important disease.

3.2.7. *Venezuelan equine encephalitis (VEE)*

VEE is a mosquito-borne single strand, positive-sense, enveloped RNA virus belonging to the Alphavirus genus, family *Togaviridae*. Other medically important members of the Alphavirus genus include eastern and western equine encephalitis viruses. There are 6 VEE virus subtypes identified by antigenic and genomic analyses, and a number of additional varieties. Subtype IAB and IC cause epizootic disease in equids and associated zoonotic infections of humans [110]. During epizootics, horses and donkeys infected with these strains develop high viremias, serve as the primary hosts for infection of mosquito vectors and therefore are the indirect source of human infections acquired by mosquito bite. In contrast, the enzootic subtypes II–VI, are maintained in nature in cycles involving rodent species and mosquitoes, are not amplified by equid viremic hosts, and cause sporadic illness in humans and equid dead-end hosts. Epizootics of IC virus are the result of mutation and selection of virulent equine-competent viruses from enzootic strains, particularly the ID variant [111].

In the 1930–1940s VEE IAB viruses caused large epizootics in South America, with associated human epidemics of encephalitis.

Between 1962 and 1969, a series of major subtype IAB and IC epizootics occurred in northern South America, and between 1969 and 1971 the virus spread north to Central America, Mexico, and Texas [112]. The cumulative economic and medical impact of VEE outbreaks between 1935 and 1971 was devastating, with over 150,000 equid and 50,000 human cases. Some of the VEE IAB epizootics are believed to have been spawned by the injection of horses with inactivated veterinary VEE vaccines containing residual live virus [113]. This likely occurred in Trinidad in 1943 and again in Nicaragua in 1970, but probably was a widespread problem in the past. Between 1992 and 1995, VEE IC re-emerged in Venezuela and Colombia, with an estimated 4000 equid deaths and over 100,000 human cases of which 3000 had encephalitis [114,115].

Since VEE causes an acute incapacitating illness in humans and the virus efficiently infects via the aerosol route, it was developed by both the US and Soviet Union as an offensive biological weapon [116]. As part of these programs, vaccines for the protection of military personnel were also developed. In the US, a live, attenuated virus (TC-83) was developed by the US Army Medical Research & Development Command (USAMRDC) by empirical passages of the prototype Trinidad donkey (subtype IAB) virus in fetal guinea pig heart cell culture [117]. The development of the live vaccine followed poor experiences with chemically inactivated vaccines; in animal models, only the live vaccine protected against aerosol challenge. However, TC-83 vaccine has a number of drawbacks as a human vaccine, including failure to immunize about 18% of vaccinees, and moderate-to-severe reactogenicity in about 25% of subjects. In humans, it remains an investigational product, used solely for the protection of laboratory workers [118], with approximately 7000 persons vaccinated since 1963. The TC-83 virus acquired 12 mutations during the empirical passage series in guinea pig heart cells, but attenuation appears linked to only 2 of these, in the 5′-noncoding region and the E2 envelope glycoprotein, and these substitutions appear to be subject to reversion in the vaccinated host [119]. In addition, TC-83 has been isolated from mosquito vectors during field use, illustrating the potential for secondary spread and mutation and recombination events. An investigational formalin-inactivated TC-83 vaccine (designated C-84) was also developed by USAMRDC and used following TC-83 priming to seroconvert TC-83 non-responders.

Since horses and related species are severely affected during epizootics and are the source of mosquito vectors infecting humans, there is an obvious need for a single dose veterinary vaccine that evokes rapid immunity. US Army investigators explored the use of TC-83 live, attenuated human vaccine for immunization of equids beginning in 1962 [120], and there was limited field use of the vaccine in Colombia in 1967. However, when epizootic VEE appeared for the first time in Central America (Guatemala) in May 1969, and then spread southwards to Costa Rica and northwards to the US, there was considerable urgency to utilize a vaccine strategy for control of the disease in horses, donkeys and mules. In 1969, the US military responded rapidly to requests for TC-83 vaccine from Guatemala and El Salvador. The vaccine had been produced and stockpiled at the Merrell National Laboratories, Swiftwater PA under contract to the USAMRDC for the purposes of biological defense. By 1972, over 10 million doses of TC-83 had been given to equidae in the US, Mexico and Central America [106]. Collaborative studies were also undertaken by agencies concerned with human and animal health (USAMRDC, NIH and USDA) to fully explore the biology of the vaccine in horses [121,122], ultimately leading to licensure and commercialized by the animal health industry, both as a live vaccine and then an inactivated vaccine combo with eastern and western equine encephalitis vaccines. TC-83 vaccine was credited with a rapid curtailment of the 1969–71 outbreak. The history of VEE exemplifies many One Health principles, including the prevention of human cases through domesticated animal vaccination, use of a single vaccine product for animals and humans, and an agency (the US Army) concerned with human health engaged in both veterinary and human vaccine development, and providing a solution for curtailing an emerging zoonosis. After the large epizootic in the 1970s, TC-83 vaccine was again deployed during the epidemic in 1995 in Colombia to create an immune barrier to spread of the virus.

Recent efforts have focused on development of improved VEE vaccines for humans that are less reactogenic and more immunogenic than TC-83, can be manufactured in a more acceptable substrate, and have a lower risk of reversion to virulence and of mosquito transmission [123]. In addition, vaccines that cross-protect against the enzootic VEE subtypes are needed. VEE ID is endemic in Colombia, Peru, Venezuela, and Ecuador, and the IE subtype circulates in southern Mexico. Aguilar et al. [103] postulated that disease caused by VEE is confused clinically with dengue, and that, in endemic areas, up to 10% of dengue cases may actually be due to VEE enzootic subtype viruses. Subtype ID poses the ever-present risk of mutational change to produce high viremia and epizootic transmission in equids, as happened in the 1990s.

V3526 vaccine is a rationally designed vaccine from the epizootic Subtype IAB genome, with insertion of a PE2 cleavage-signal mutation combined with an E1 gene resuscitating mutation. V3526 had a good safety profile and was immunogenic and protective in laboratory animals, including nonhuman primates [124]. While retaining a degree of neurovirulence for suckling mice, V3526 is not virulent when inoculated intracranially in juvenile monkeys [125]. V3526 has also been evaluated in horses [126]. The vaccine was safe and highly immunogenic, with subcutaneous doses as low as 100 plaque-forming units shown to protect horses against challenge with virulent subtype IAB virus. Unfortunately, V3526 proved to be too reactogenic for humans in a Phase 1 trial [127], and thus development for both human and veterinary use has stopped. The V3526 virus was subsequently formalin inactivated and has been investigated with adjuvants replacement for the C-84 vaccine.

Other live and live vector approaches to improved VEE vaccines have been investigated only in laboratory animals, including a chimeric virus constructed from nonstructural genes of Sindbis and the structural genes from VEE [128], VEE replicon vaccines, and vaccinia recombinants. None of these approaches have reached advanced development.

It is only a matter of time before another VEE outbreak emerges in tropical America, and there is a substantial risk of cross-border spread. The prospects for vaccine interventions have diminished with dwindling support for new vaccines and increased concerns for vaccine safety.

3.3. *Framework III. Wild animals play a major role in transmission of the disease to humans and domestic animals*

Most zoonotic diseases are maintained in transmission cycles involving wild mammals or birds. However, because of the difficulties in vaccinating specific host species, wildlife immunization as a means of preventing spread to domestic animals and humans has been applied in only a few diseases. Some of the barriers to implementing wild animal vaccination include (i) involvement of multiple species in natural transmission cycles; (ii) safety concerns for non-target species; (iii) high reproductive rates and population turn-over; (iv) fastidious feeding behaviors and difficulty in designing effective baits; (v) difficult delivery due to very high or, conversely, very low population densities of the target species; (vi) environmental concerns, and release of genetically modified organisms; (vii) difficulty in designing an effective formulation for oral immunization; (viii) instability of a vaccine or vector under prevailing environmental conditions; and (ix) requirement for low unit cost and government funding for vaccine purchase and delivery.

Nevertheless, targeted immunization of wild animal reservoirs is a subject of considerable interest for future research, not only for control of infectious agents affecting domestic animals and humans but also for control of wildlife diseases. One example of the latter was the effort to develop a means of immunizing great apes affected by Ebola virus in Central Africa with vaccines previously developed for human use.

Aside from rabies vaccines delivered in oral baits, which is well-established, wildlife vaccination has had limited success. Two promising examples of early-stage vaccine applications are described below (Lyme disease and *Mycobacterium bovis*). In addition experimental immunization and protection of prairie dogs (*Cynomys ludovicianus*) using a raccoon poxvirus recombinant oral bait vaccine [129], and ballistic vaccination of bison against *B. abortus* [130] have been described. Plague, a global but localized zoonotic disease with rodent wildlife reservoirs, would appear to be a target of particular interest for future research [131]. There are many other possible targets for new Framework III vaccines, and future research in this field is encouraged.

3.3.1. Lyme disease

In the United States, Lyme disease is the most common vector-borne disease and the 7th most common infectious disease overall. It is also a major and increasing public health problem in Europe. Approximately 30,000 cases are reported in the US annually, and the number has doubled in the last 15 years [132]. However, at a meeting in August, 2013, the Centers for Disease Control and Prevention (CDC) reported that the annual incidence of infection is believed to be 10-fold higher, i.e. 300,000 cases. Although Lyme disease occurs across the country, the incidence is highest in the northeast and north central states. In the US, Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is amplified each spring and summer in a cycle principally involving *Ixodes scapularis* ticks and field mice. Mice are persistently infected and represent the reservoir of infection in nature [133]. *B. burgdorferi* is passed transtadially to nymphal and adult ticks which infect humans and dogs; these species develop clinical disease but are dead-end hosts. The human disease is manifested by a protean syndrome, starting with a localized skin infection (*erythema migrans*), and progressing to a multisystem disease variably with lassitude, arthritis, carditis, meningitis and other neurological manifestations [134]. Because of the increasing incidence and geographic expansion of Lyme disease, the high incidence of tick exposure, and the difficulty in recognizing and removing attached ticks due to their small size, difficult differential diagnosis, troublesome and potentially severe clinical manifestations and medical controversies over treatment and chronicity of the disease, Lyme disease has emerged as a high priority for public health interventions [135].

Vaccination of humans would appear to be a logical and cost-effective means to prevent the disease [136], and veterinary vaccines for dogs are widely used and have proven to be modestly effective [137]. However, whereas safe and highly effective vaccines for humans have been developed, none is available for distribution today. Glaxo SmithKline's Lymerix® vaccine was approved in 1998, but withdrawn in 2002 by the company, principally for commercial reasons, a decision that is lamentable given the increasing incidence of the disease [135,138,139]. A new Lyme disease vaccine for humans active against both *B. burgdorferi* and species causing Lyme disease in Europe developed by Baxter Bioscience is now in Phase II development, but it is uncertain whether it will reach the market. Nevertheless, these vaccines established critical immunological principles; the human vaccines are composed of recombinant OspA protein, the dog vaccines of both OspA and OspC, and work via antibody-mediated mechanisms. OspA is expressed by the *Borrelia* spirochete in the midgut of infected ticks. Since the tick vector only begins to transmit *Borrelia* 24–36 h after initiating blood feeding, OspA specific antibodies imbibed in the blood meal of a vaccinated host kill the bacteria and block transmission [140,141].

If a similar OspA antibody response could be evoked in the natural reservoir hosts of *B. burgdoferi* (*Peromyscus* spp. field mice), it may be possible to interrupt the transmission cycle and reduce the prevalence of infected nymphal and adult ticks responsible for human and canine infections. Proof of concept was obtained in a field study where *Peromyscus leucopus* mice were trapped and vaccinated by subcutaneous injection of OspA; a reduction in the prevalence of *B. burgdorferi* in nymphal ticks was seen in the following year [142]. However, practical vaccine delivery and effective immunization of mice in the wild, requires a thermostable oral bait vaccine matched to the high population density and rapid population turnover of the reservoir hosts, the effects of which are not diluted by non-targeted species that play a role in *B. burgdorferi* transmission [135]. Two promising live oral vaccine approaches have been investigated in the laboratory: a bacterial (*E. coli*) vector [143,144] and a viral vector (vaccinia) [145,146] expressing OspA. The *E. coli* vector contained in an oral bait formulation and ingested multiple times elicited anti-OspA antibodies and protected laboratory and wild *P. leucopus* mice against needle and tick challenge. A 5-year field study of the oral bait vaccine, sponsored by CDC, has been performed and results are anticipated with interest. A company, US Biologics Inc., is engaged in bringing this vaccine to market. The vaccinia technology, which rests on the shoulders of the successful oral bait vaccine against wildlife rabies (see below), has been tested in the laboratory. Laboratory mice immunized by gavage with vaccinia expressing OspA were successfully immunized after a single dose and were protected against tick challenge. *Peromyscus* consuming oral bait vaccine were also significantly protected against challenge with infected ticks. Although the vaccinia vector looks promising, no commercial endeavor has yet emerged to support development. Both the *E. coli* and vaccinia oral vaccines require specialized formulations in baits that incorporate the vaccine in the bait itself, rather than in a liquid sachet embedded in the bait used for delivery of rabies vaccines.

Many questions surround the application of an oral bait vaccine targeting the reservoir host, including efficacy of this approach in the field, the high density of baits required, cost and sustainability of local and state funded programs aimed at distributing baits, and the role of species not targeted by the vaccine in Lyme disease maintenance cycles. If only partially effective, the risk of acquiring Lyme disease may be reduced, but the public would still need to take precautions against tick bite. Nevertheless, given the lack of a vaccine for humans, the high level of public concern about Lyme disease, the high risk to children, the localized nature of *B. burgdorferi* transmission allowing geospatially focused control efforts, and the possibility that homeowners may be motivated to play an active role in distributing baits, the idea has appeal.

3.3.2. M. bovis

M. bovis is the cause of tuberculosis in a wide array of domesticated and wild animals, and it remains a major veterinary health problem worldwide, causing severe economic losses from livestock disease, death and export restrictions. Humans become infected by ingesting raw milk or undercooked meat, or by the aerosol route from infected animals or humans. In developed countries where pasteurization and test-and-slaughter programs have controlled the disease, zoonotic infections are relatively rare, accounting for 0.3–7.2% of tuberculosis cases [147–149]; in developing countries which do not practice these measures, it remains more common, although few data on prevalence exist.

Wild animals are a major source of infection of domestic livestock [150]. Control measures aimed at control of *M. bovis* by culling wildlife reservoirs is problematic, with inconsistent results and

ethical concerns. Vaccination of wildlife is an attractive alternative control measure, especially since the traditional tuberculosis vaccine (Bacille Calmette-Guerin, BCG) derived from *M. bovis* is effective when orally administered [151]. Examples of wildlife that serve as maintenance hosts of *M. bovis* and sources of infection in livestock, include white-tail deer in the US [152]; wild boar, red and fallow deer in Europe [153]; badgers in the United Kingdom [154]; African buffalo (*Syncerus caffer*) in South Africa [155]; and brushtail possums (*Trichosurus vulpecula*) in New Zealand [156].

Brushtail possums have been experimentally vaccinated using oral BCG and shown to be resistant to challenge with *M. bovis* [157]. Proof of concept has been provided by a field study in an endemic area of New Zealand. Possums were trapped, manually vaccinated using orally delivered BCG in a lipid matrix formulation, and vaccinated and control animals were recaptured at intervals [158]. Vaccinated animals received 1–3 vaccinations during the 2-year study. At the end of study, the 14 ha study area was depopulated, and all animals assessed for clinical and subclinical *M. bovis* infections. Vaccine efficacy against naturally acquired tuberculosis was 95–96%. The authors concluded that oral vaccination of possums could be a practical strategy contributing to elimination of *M. bovis* in livestock. Although the field study did not demonstrate control via freely consumed bait vaccine, captive possums have been shown to consume vaccine in flavored baits [159].

3.3.3. Rabies

Rabies is transmitted between specific wild carnivore reservoir hosts, which serve as a source of spill-over infections of other wild carnivores, and infection of domesticated animals and humans. Oral rabies vaccine was initially deployed in Europe for control of rabies in the red fox (*Vulpes vulpes*), using modified live virus vaccine [160,161]. The concept began in the 1960s with the work of George Baer at the CDC, which showed that foxes could be orally immunized with modified live virus [162]. The live, attenuated Evelyn-Rokitnicki-Abelseth (ERA) vaccine or Street-Alabama-Dufferin (SAD) viruses were employed in experimental and field studies. Numerous studies in the 1970s confirmed that captive and wild foxes could be orally immunized with a variety of baits containing vaccine [163]. In 1978, Steck and colleagues initiated a wild fox rabies control program in the Swiss Alps using oral bait vaccine consisting of chicken heads with vaccine and tetracycline biomarker in a container made of polyvinyl chloride and aluminum foil inserted under the scalp [164]. The trial demonstrated that 60% of foxes had ingested bait. Over the next 20 years, successful fox rabies control programs were carried out in many European countries, after the late 1980s using baits distributed by fixed wing aircraft and helicopters rather than by ground [165], and resulting in elimination of terrestrial rabies in several countries [166,167]. For large scale distribution, the laborious chicken head method bait gave way to commercially manufactured molded or extruded baits of various kinds, consisting of fish meal or bone meal, fat, and a pouch or blister containing liquid vaccine virus [168]. The vaccines currently used in Europe are (1) SAG2 (e.g., RABIGEN®, Virbac Laboratories, France), a modified live attenuated rabies virus derived from the original SAD vaccine and having an additional mutation in the codon for amino acid 333 of the rabies G protein, which increases genetic stability of the virus [169]; and (2) recombinant vaccinia virus (Copenhagen strain) expressing the ERA® strain rabies G protein (Raboral®, Merial Corp.) [170]. The rabies G protein gene has been inserted into the thymidine kinase gene of vaccinia, which results in further attenuation compared to the parental virus [171,172]. Duration of oral rabies immunity, at least 18 months in adult red foxes, is sufficient to provide herd immunity and reduce the reproductive rate (R_0) to less than 1.

The modified live virus vaccines are more thermolabile than vaccinia, require −20°C storage, retain some pathogenicity for non-target species, and pose safety risks to humans exposed inadvertently. Consequently, recombinant vaccinia is the only oral rabies vaccine approved for wildlife immunization in the US. This vaccine consists of fishmeal and fish oil bound by a polymer (ethylene vinyl acetate) and containing the vaccine in a plastic pouch held in place by a wax mixture.

Immunization with vaccinia or modified live virus occurs in the buccal mucosa and tonsils, and vaccines are poorly effective after ingestion [173]. In one study, consumption by red foxes of a single bait containing vaccinia resulted in protection against virulent rabies in only half of the animals [174]. This observation suggests that high bait densities and repeated vaccinations are important to effective control in the wild. Bait densities distributed in Europe generally range between 10 and 20 baits/km^2, resulting in 50–80% of animals potentially immunized (positive for the tetracycline biomarker) [161]. In addition to distribution density, feeding habits may also be important, since animals have been observed to pick apart baits and consume only the bait portion.

While control of terrestrial wildlife rabies has been successful in parts of Europe, it has been more challenging in other areas due to the diversity of carnivores involved in transmission of different rabies virus variants. In the arctic regions, a specific rabies variant is maintained in the arctic fox, with spill-over infections of red foxes, skunks, and raccoon dogs. Where vaccination is not practiced in domesticated sledge dogs, these animals may be severely impacted by contacts with rabid foxes, and human dog owners placed at considerable risk. While experimental oral vaccination of arctic foxes has been successful, there is limited experience in the field [175]. In Ontario, Canada control of arctic rabies variant in red foxes using oral bait vaccine has been successful, but the virus still occurs as a result of spill-over transmission to skunks, which are not efficiently immunized with recombinant vaccinia vaccine [176,177].

Oral bait recombinant vaccinia vaccine has been primarily used to control raccoon rabies, which expanded beginning in the mid-1970s from enzootic areas in Florida northwards and westwards to involve many states in the eastern US, as well as New Brunswick and Quebec, Canada [178,179]. The control program relies on distribution of vaccine baits specific zones of rabies activity, particularly along the Appalachian Ridge, enhanced surveillance and ring vaccination with evidence of spread of the disease. Judged from the absence of spread beyond the zones of vaccine distribution, the program has worked well, despite relatively low prevalence of rabies antibody (approximately 30%) in sampled raccoons [170]. It is possible that pre-existing immunity to raccoonpox virus may interfere with immunization with vaccinia [180]. The economics of large-scale oral vaccination programs in the US have been modeled and are generally favorable [181]. In addition to control of raccoon rabies, successful use of the vaccine has been made in the control of gray fox (*Urocyon cinereoargenteus*) variant rabies in west Texas [182]. In contrast to raccoons, a higher prevalence of rabies antibody (61%) attributed to vaccination is found in gray foxes. Rabies in coyotes (*Canis latrans*) was responsible for epizootic canine rabies in the 1980s and 1990s in parts of the US, and was controlled by an oral bait vaccination campaign, contributing to the elimination of canine rabies by 2007 [177].

Skunks remain a problematic species for vaccine control of rabies. Skunks are an important spill-over host for the arctic fox, raccoon rabies, and big brown bat rabies virus variants [183]. Although the vaccinia vector vaccine is not sufficiently effective in skunks [169], promising results were obtained with a replication-competent adenovirus type 5 vector expressing the rabies G protein [184]. Aerial distribution of this vaccine (ONRAB®, Artemis Technologies, Guelph) showed high rates of immunization of raccoons, and arctic foxes and modest seroconversion (17–51% in different plots) in skunks, probably due to lower rates of bait acceptance [185,186]. ONRAB® is approved by the Canadian regulatory

authorities for control of rabies in skunks, raccoons, and foxes, and is under investigation in the US.

4. Limitations and failures

There are some notable failures of animal vaccination as a means to preventing zoonotic diseases of humans, and these illustrate some of the limitations of the approach shown in Table 2.

Japanese encephalitis, a mosquito-borne flavivirus closely related to West Nile virus, is endemic in Asia, with nearly 2 billion people at risk of infection [187]. Horses and humans are dead-end hosts, and Framework I immunization of both is widely practiced in many parts of Asia, with a long record of success. Pigs are an important domesticated animal amplifying host for infection of rice paddy-breeding *Culex* spp. vectors, resulting in spill-over infections of humans. Moreover, infection of pregnant sows can lead to abortion and stillbirth, and infected boars may have reduced spermatogenesis and infertility [188]. Framework II immunization of swine was previously a major initiative in Japan, using live, attenuated vaccines. However, it was exceedingly difficult to vaccinate piglets born in spring and early summer during the narrow window between loss of interfering maternal antibody and contribution to virus amplification. The practice of vaccination was abandoned in favor of re-locating piggeries from areas of *Culex* breeding and biting activity. Elsewhere in Asia, other obstacles precluded consideration of Framework II vaccination against Japanese encephalitis, including the prevalence of small piggeries located near vector breeding sites and of feral swine, and the importance of wild ardeid birds and waterfowl in virus transmission. Moreover in many areas of Asia, less developed than Japan, and undergoing rapid urbanization, the locations of pig holdings are not controlled and are often located near rice paddies and urban centers [189]. Consequently, the focus has long been on human vaccination as the primary means of prevention. This case study exemplifies some of the factors that can limit application of Framework II vaccination: (1) the need to customize vaccination to the breeding and husbandry practices and timing of domesticated animal targets; (2) the role of wild animals and feral domesticated animals as additional amplifying hosts in the transmission cycle; and (3) difficult access given the very large scale and geographic complexity of domesticated animal populations.

Q fever is caused by the intracellular Gram-negative bacterium, *Coxiellla burnetii* and an important worldwide infection of ruminants, which serve as the source of infection of humans, especially where large numbers of animals are concentrated [190]. Q fever is a major occupational hazard of abattoir and farm workers, veterinarians, and persons involved in the handling and distribution of animals or animal products. A dramatic outbreak recently occurred in high-intensity goat farms in the Netherlands (2009), with 2361 human cases and 6 deaths [191]. Transmission of *C. burnetii* occurs between direct spread between domesticated animals, and from animals to humans. Infected animals shed bacteria in urine, feces, vaginal secretions and products of conception, and in milk. Ticks are also a reservoir of bacteria in nature and a source of infection of livestock. Ruminants, particularly goats and sheep develop pneumonia, abortion, stillbirth, premature delivery, and delivery of weak offspring, and herds can be affected for prolonged periods, causing significant economic losses [192]. There are two developmental stages of *C. burnetii*, a small-cell variant (SCV, the extracellular form) and the metabolically active intracellular large-cell variant. The SCV is highly resistant to degradation and can persist in the environment for long periods of time. Infection of humans is acquired principally by the aerosol route via dust containing spore-like SCV forms, with oral routes of infection (ingestion of unpasteurized milk) being secondary. The human disease is characterized by an influenza-like illness, and may be complicated by pneumonia, endocarditis, and (pregnant women) abortion and fetal death. Person-to-person transmission occurs, but is rare. Approximately 5% of infected persons may develop chronic infections, with various manifestations.

Prophylactic vaccines have played a role in the control of Q fever in livestock, but the practice is not a reliable means of preventing human infections. In Russia, a live, attenuated M-44 vaccine was used for many years in animals and humans, but causes a persistent infection and has not been considered safe for use elsewhere. In Europe, Coxevac®, a formalin inactivated strain RSA 493/Nine-Mile phase 1 bacterial form (smooth forms, with complete surface lipopolysaccharide) has been used in goats and cattle and reduced the incidence of shedding, but is not effective in pregnant or chronically infected animals [183,193]. The live and phase 1 vaccines are also not DIVA, which presents substantial issues for export controls. In Australia, an inactivated phase 1 vaccine prepared from Henzereling strain is marketed for humans by CSL Ltd (Qvax®) [194]. However, severe reactions occur in persons who have previously been naturally infected with C. *burnetii*, and skin testing to ensure absence of exposure is required [195]. Clearly, improved vaccines are needed for both livestock and humans, but various attempts at recombinant vaccines have been disappointing.

The problem for Framework II vaccination against Q fever is due to multiple factors, including imperfect vaccines, limited efficacy of vaccines in parous animals, the difficulty in recognizing the disease and intervening expeditiously, and the rapid and widespread contamination of the environment with SCV forms. The last problem is the major reason that livestock vaccination is not a reliable means of protecting humans against exposure. A 4 year study of sheep vaccinated with the phase 1 vaccine showed that the proportion of animals shedding bacteria in feces was markedly reduced after 1 year and then eliminated after 2 years, but *C. burnetii* was still present in environmental samples [196].

Finally, live veterinary vaccines may pose a risk of inadvertent infection of humans handling the vaccine or vaccinated animals. Examples include live Brucella and orf (contagious ecthyma) vaccines.

5. Immunization of humans to prevent disease involving animals

While this topic is beyond the scope of this review, it is important in several contexts, and indeed little is known about the risk of human pathogens to animals. Immunization of swine and poultry workers against influenza as a means of preventing introduction of human influenza viruses to these animals has been emphasized as a means of preventing emergence of reassortant strains [197]. Immunization of humans to prevent spread of viruses to captive nonhuman primates is often practiced, including vaccines for influenza, hepatitis A and B, and measles.

6. Economics of animal vaccines for public health, conclusions, and future developments

Prevention of animal diseases and human diseases by use of vaccines is a well-established principle, and there are potential synergies that can be achieved in concurrent delivery of human and animal vaccines in developing country settings [198]. For some diseases affecting both livestock and humans there is a clear commercial incentive to develop vaccine products (Framework I vaccines) (Table 2). However, such development efforts are generally segregated in the animal and human health divisions in industry and academia, and have separate regulatory pathways. This results in a potential waste of resources and duplicated

scientific endeavors. Interestingly, when one company (Akso Nobel), an animal health company, decided in 2003 on a strategic move into human vaccine development, it drew on its veterinary scientists to staff the program. As pointed out in this review, there have been isolated successful examples, e.g. a West Nile vaccine, of co-development of a vaccine for both veterinary and human indications, an obviously efficient strategy that broadened both the commercial and public health opportunity. Future efforts along similar lines should be considered on a case by case basis, depending on medical need, but in general there is value in closer connections between human and veterinary vaccines and regulatory science, and in the application of domesticated animals as models for development of infectious disease and cancer vaccines. Several issues related to DIVA requirements and liability concerns have been mentioned.

Prevention of zoonotic diseases of humans by means of vaccination of domesticated (Framework II) or wild (Framework III) animals is an attractive but under-exploited concept. An obstacle is that there may be limited commercial incentives (Table 2). Where a market exists, Governments may be the principal customers, as is the case for the approved oral bait rabies vaccines and the reservoir-targeted Lyme disease vaccine in development. Thus, the public health gains for such an intervention need to be compelling and must offset the cost of development and implementation. The goal is far easier to justify when vaccination also prevents disease in an economically valuable animal species, there is a profit incentive for animal vaccination or a clear social gain from improved animal health, and when the public health spin-off is an added benefit. Examples of the latter may include vaccines against Hendra and Nipah virus diseases, Brucellosis, *Chlamydophila felis*, Rift Valley fever, and Venezuelan equine encephalitis. The potential for elimination of a disease through vaccination (employed together with other strategies), as has been demonstrated for brucellosis in the US and terrestrial rabies in some European countries is a compelling economic concept, though applicable in only selected cases. The cost of preventative programs is almost always lower than emergency response programs, as illustrated by the significantly lower cost of oral wildlife rabies programs over contingency actions to control epizootic spread [199]. The recent announcement of a 10-fold higher incidence of Lyme disease than previously believed will lead to a reassessment of the economics of preventive strategies for this disease, including wildlife vaccines.

Economics represent the key determinant for development and utilization of Framework II and III vaccine strategies. A low unit cost of such vaccines will always be a requirement. The economic barriers are particularly relevant when considering vaccines for developing countries. On the positive side, the cost of developing a new animal vaccine through licensure is a small fraction, approximately 10%, of the cost of a typical human vaccine (the latter being $200–500 million by one estimate [200], but often far higher) [201]. The relatively lower cost and shorter timelines for developing animal vaccines reflects the simpler path to regulatory approval, and is driven by the significantly lower market potential for these vaccines. Despite the lower cost of developing new veterinary vaccines, high and middle income countries still pay higher prices until the fixed costs of development are paid off, there is an over-supply of vaccine, or competing products enter the market. To redress the pricing barriers in the case of human vaccines, there has been strong advocacy for new approaches to secure vaccine supply and access for developing countries where the burden of infectious diseases is greatest [202]. As part of this strategy, emerging market manufacturers provide access to low unit cost vaccines, and such manufacturers of veterinary vaccines could play a substantial role in a public health strategy for animal immunization. Indeed all of the principles being applied to human vaccines could be extended to vaccines for animals, particularly if there is both a clear rationale for public health and the "pull" of a potentially expanded market or of guaranteed purchase agreements. Up to now public-private financing for developing and distributing veterinary vaccines has represented a tiny fraction of support available for human developing-world vaccines, and has focused on vaccines for livestock as a means of improving animal production and protein supply rather than preventing zoonotic diseases [203]. Given the public health impact of zoonotic diseases described in the introduction to this review and the potentially lower cost of interventions targeting animals vs. humans, there should be a new emphasis on the public health improvements that could result from animal immunization. Zoonotic diseases that merit consideration because they occur at high incidence or are poorly controlled, include rabies, zoonotic leishmaniasis, brucellosis, Rift Valley fever, *M. bovis*, Lyme disease, and several enteric bacterial infections.

As mentioned above, the regulatory pathway for animal vaccines is considerably simpler than for human vaccines [201]. This is due to multiple factors, including less onerous requirements for manufacturing and control of veterinary products, the simpler and far less expensive clinical trial requirements for marketing approval, the ability to challenge animals to demonstrate vaccine efficacy, as well as an established regulatory mechanism for conditional approval allowing commercial sales while still gathering more definitive data. There is no requirement for large, statistically powered efficacy field trials to obtain marketing approval, as is the case for human vaccines. The development of veterinary vaccines is consequently far faster than for human vaccines. For example, West Nile vaccine for horses was commercialized 2 years after introduction of the virus into the U.S., whereas the first (Phase 1) human trial of a West Nile vaccine was completed 5 years after introduction.

The lower costs and accelerated timeframe for development of animal vaccines represent an important rationale for novel investments in public health, particularly in developing countries. To justify investments in a Framework II or III vaccine where an economic incentive for animal immunization is marginal and a public health benefit is a goal, it is important to plan for vaccine effectiveness studies showing that vaccination of animals actually reduces human disease prevalence, as was postulated in Greece following vaccination against *B. melitensis* [39]. Such demonstrations would really drive the field forward. Thus, while the deployment of TC-83 Venezuelan equine encephalitis vaccine was credited with the curtailment of the human epidemic in 1971–72, no controlled study to demonstrate an effect on human disease incidence was actually performed. Indeed, studies to confirm the attractive hypothesis that immunization of domesticated ruminants against Rift Valley fever in Africa would prevent intermittent outbreaks of the disease in animals and humans, while leaving the mosquito reservoir of infection intact, would be difficult to design and carry out. Because of its discrete epidemiology, Hendra virus (albeit a low-incidence disease) presents a unique opportunity to demonstrate the effectiveness of animal immunization on the occurrence of a disease in humans.

The increasing problem of emerging infections, the majority of which are the result of spill-over from animals to humans, is a compelling reason to consider novel vaccine interventions, and the collaborations between veterinary and human health institutions in the development of the Hendra, West Nile, VEE and Rift Valley fever vaccines described in this review serve as examples of the power of this approach. Other potential targeted vaccine interventions focused on animal reservoirs or intermediate hosts in order to control disease emergences include avian influenza, Nipah virus disease, and, possibly, Middle East Respiratory Syndrome.

Funding agencies and industry should be encouraged to seek integrated approaches to prevention of zoonotic diseases. The ultimate success of examples provided in this review, such as *E. coli* O157 vaccines for cattle, reservoir targeted Lyme disease vaccines

for field mice, and Rift Valley fever vaccines for livestock will require sustained efforts utilizing the One Health paradigm.

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