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Abstract

Veterinary vaccines have had, and continue to have, a major role in protecting animal health and public health, reducing animal suffering, enabling efficient production of food animals to feed the burgeoning human population, and greatly reducing the need for antibiotics to treat food and companion animals. Prominent examples include rabies vaccines and rinderpest vaccines. Rabies vaccines for domestic animals and wildlife have nearly eliminated human rabies in developed countries. Thanks to the Global Rinderpest Eradication Program which involves vaccination, trade restrictions, and surveillance, rinderpest may soon become only the second disease (after smallpox) to be globally eradicated. Successful examples of new technology animal vaccines that are licensed for use, include gene-deleted marker vaccines, virus-like-particle vaccines, recombinant modified live virus vaccines, chimeric vaccines, and DNA vaccines. Animal vaccines also use a wide variety of novel adjuvants that are not yet approved for use in human vaccines. Animal vaccines can be developed and licensed much more quickly than human vaccines. The West Nile virus was discovered in the United States in August 1999. By August 2001, an Equine vaccine for West Nile virus was conditionally licensed. For animal vaccines to effectively protect animal and public health they must be widely used, which means they must be affordable. The regulatory process must meet the need for assuring safety and efficacy without increasing the cost of licensing and production to the point where they are not affordable to the end user.

Keywords

vaccine, immunization, public health, animal health, infectious diseases

Disciplines

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Veterinary vaccines and their importance to animal health and public health

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Abstract

Veterinary vaccines have had, and continue to have, a major role in protecting animal health and public health, reducing animal suffering, enabling efficient production of food animals to feed the burgeoning human population, and greatly reducing the need for antibiotics to treat food and companion animals. Prominent examples include rabies vaccines and rinderpest vaccines. Rabies vaccines for domestic animals and wildlife have nearly eliminated human rabies in developed countries. Thanks to the Global Rinderpest Eradication Program which involves vaccination, trade restrictions, and surveillance, rinderpest may soon become only the second disease (after smallpox) to be globally eradicated. Successful examples of new technology animal vaccines that are licensed for use, include gene-deleted marker vaccines, virus-like-particle vaccines, recombinant modified live virus vaccines, chimeric vaccines, and DNA vaccines. Animal vaccines also use a wide variety of novel adjuvants that are not yet approved for use in human vaccines. Animal vaccines can be developed and licensed much more quickly than human vaccines. The West Nile virus was discovered in the United States in August 1999. By August 2001, an Equine vaccine for West Nile virus was conditionally licensed. For animal vaccines to effectively protect animal and public health they must be widely used, which means they must be affordable. The regulatory process must meet the need for assuring safety and efficacy without increasing the cost of licensing and production to the point where they are not affordable to the end user.

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Keywords: vaccine; immunization; public health; animal health; infectious diseases

1. Introduction

Veterinary vaccines are important for animal health, animal welfare, food production, and public health. They are a cost-effective method to prevent animal disease, enhance the efficiency of food production, and reduce or prevent transmission of zoonotic and foodborne infections to people. Safe and effective animal vaccines are essential to

[#] The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods and the Interagency Coordinating Committee on the Validation of Alternative Methods

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modern society. It would be impossible to produce enough animal protein to feed the nearly 7 billion people on earth without vaccines to prevent epizootics in food-producing animals. Without companion animal vaccines (especially rabies vaccine), many people would not keep a pet in the household and would not experience the satisfaction of the human animal bond. Zoonotic diseases such as brucellosis and leptospirosis would be much more prevalent without effective vaccines. The impact of veterinary vaccines can be seen in the following examples.

Rinderpest is an example of how a disease that only affects animals can have a large public health impact. Rinderpest is an acute, highly contagious, viral disease of cattle, domesticated buffalo, and some species of wildlife. In 1889, cattle shipped from India carried the rinderpest virus to Africa, causing an epidemic that established the virus on the continent. Initially, approximately 90% of the cattle in sub-Saharan Africa died as well as many sheep and goats. Wild buffalo, giraffe, and wildebeest populations were decimated. The loss of draft animals, domestic livestock, and wildlife resulted in mass starvation, killing a third of the human population in Ethiopia and two-thirds of the Maasai people of Tanzania. The reduced number of grazing animals allowed thickets to form in grasslands. These thickets served as breeding grounds for tsetse flies, the vector for trypanosomes, resulting in an outbreak of trypanosomiasis (African sleeping sickness) in humans. This rinderpest epidemic is considered by some to have been the most catastrophic natural disaster ever to affect Africa. The Global Rinderpest Eradication Program is a large-scale international collaboration involving vaccination, local and international trade restrictions, and surveillance. This effort may be one of veterinary medicine's greatest achievements and rinderpest may soon become only the second disease (after smallpox) to be globally eradicated [1].

The rabies vaccine is another example of the impact of a successful animal vaccine. Rabies may be the oldest infectious disease known to man. Rabies vaccines for domestic animals and wildlife have nearly eliminated human rabies in developed countries. However, more than 55,000 people die of rabies every year in Asia and Africa and 98% of those cases are due to people being bitten by dogs that are not vaccinated [2]. This source of rabies in humans can be eliminated by adequate animal vaccination and control, educating those at risk, and enhancing access to appropriate medical care for those who are bitten. Affordability and availability of rabies vaccines, along with effective vaccination programs are key to changing the current situation.

2. Importance of veterinary vaccines

2.1. Safe and efficient food production

Veterinary vaccines are used in livestock and poultry to maintain animal health and to improve overall production. More efficient animal production and better access to high-quality protein are essential to feed the growing population. According to the United Nations Department of Economic and Social Affairs Population Division, the world population was approximately 6.9 billion in 2010, and is estimated to increase to just over 8 billion in 2025 and to reach 9.1 billion people in 2050 (**Figure 1**). The United Nations Food and Agriculture Organization (FAO) estimates that 1.02 billion people were undernourished in 2009, in both developed and developing countries (**Figure 2**). There have been dramatic increases in world meat and egg production between 1961 and 2007 (**Figure 3**). An FAO High-Level Expert Forum reported in September 2009 that in order to feed a projected world population of 9.1 billion people, the overall food production will need to increase by 70% between 2005/07 to 2050 [3]. Vaccines that preserve animal health and improve production are important components in meeting this need.

2.2. Control of zoonotic diseases

Vaccines to control zoonotic diseases in food animals, companion animals, and even wildlife have had a major impact on reducing the incidence of zoonotic diseases in people (**Table 1**). Without rabies vaccines, it is unlikely that families would be willing to keep cats and dogs as pets. Recombinant vaccinia-vectored rabies vaccines have also been used successfully in baits for oral vaccination campaigns to reduce the incidence of rabies in wild animals [4]. Vaccines for Brucellosis were instrumental in the *Brucella abortus* eradication program in the United States. Many countries have severe problems with Brucellosis in cattle, small ruminants, and people due to a lack of available Brucella vaccines for animals [5].

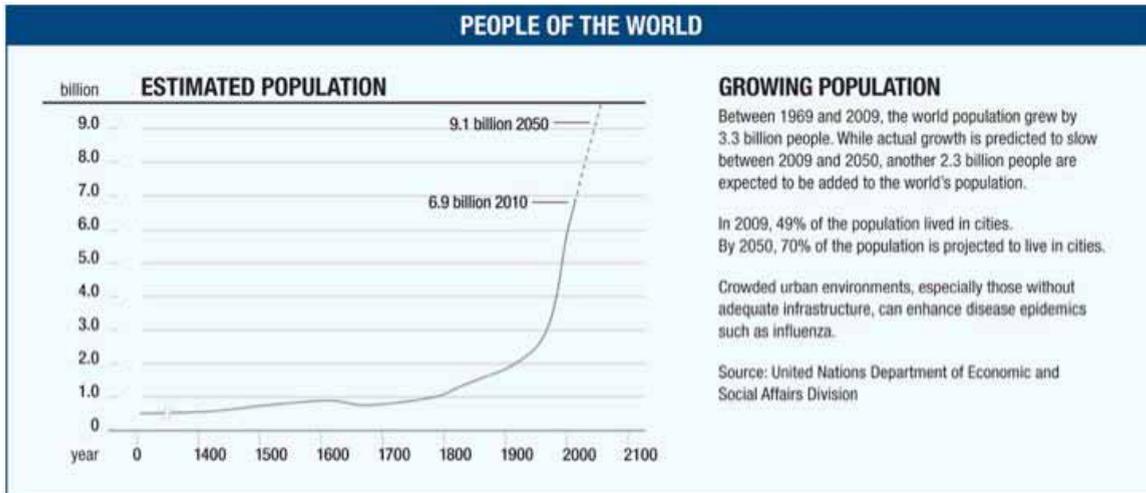


Figure 1. Estimated population of the world from approximately the last 2000 years through 2050. (Reprinted with permission from: Roth, J. A., Galyon, J., Stumbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals: Role of the Veterinarian. *In* Emerging and Exotic Diseases of Animals, 4th Edition, 2010, Rovid-Spickler, A., Roth, J.A., Galyon, J., Lofstedt, J. Editors. Center for Food Security and Public Health, Ames, IA. USA.

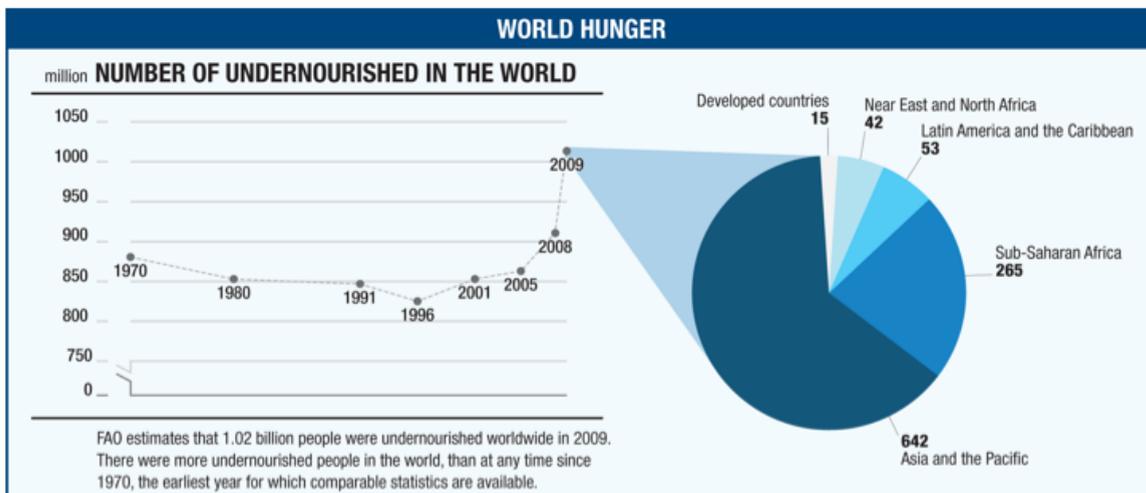


Figure 2. Estimated number and distribution of undernourished people in the world from 1970 through 2009. (Reprinted with permission from: Roth, J. A., Galyon, J., Stumbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals: Role of the Veterinarian. *In* Emerging and Exotic Diseases of Animals, 4th Edition, 2010, Rovid-Spickler, A., Roth, J.A., Galyon, J., Lofstedt, J. Editors. Center for Food Security and Public Health, Ames, IA. USA.

2.3. Control of emerging and exotic diseases of animals and people

Emerging and exotic animal diseases are a growing threat to human and animal health and jeopardize food security (**Figure 4**). Increases in human and animal populations, with accompanying environmental degradation and globalized trade and travel, enhance opportunities for transfer of pathogens within and between species. The resulting diseases pose enormous challenges now and for the future. In most of the world, increased demand for animal protein has resulted in intensified commercial food animal production and/or expanded “backyard”

production. Both types of production present unique challenges for disease emergence and control. Emerging zoonotic diseases of both food and companion animals are a major threat to public health. It is inevitable that the world will continue to experience emerging disease outbreaks in the coming decades. Rapid development of animal vaccines can play a key role in controlling emerging diseases.

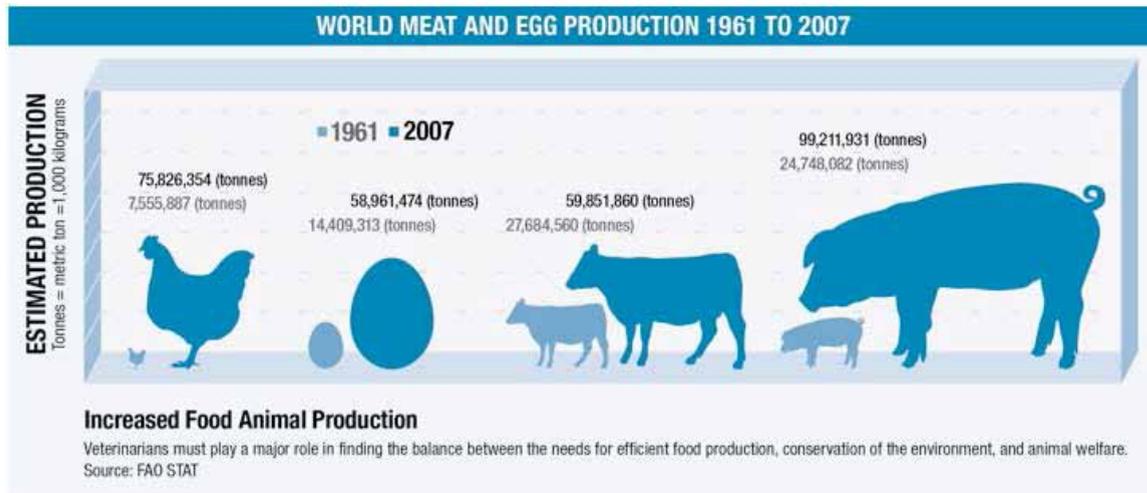


Figure 3. Estimated world meat and egg production in 1961 and 2007. (Reprinted with permission from: Roth, J. A., Galyon, J., Stumbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals: Role of the Veterinarian. *In* Emerging and Exotic Diseases of Animals, 4th Edition, 2010, Rovid-Spickler, A., Roth, J.A., Galyon, J., Lofstedt, J. Editors. Center for Food Security and Public Health, Ames, IA. USA.

2.4. Reduction of the need for antibiotics

Veterinary vaccines reduce the need for antibiotics to treat infections in food producing and companion animals. There are increasing concerns related to antibiotic resistance associated with the extensive use of antibiotics in veterinary and human medicine [6]. Producers may choose either vaccines or antibiotics to control some diseases based on cost, if both options are available. For example, swine dysentery due to *Lawsonia intracellularis* can be controlled by either vaccination or antibiotics, along with good management practices. Swine producers will use the approved control method that is most cost effective. If regulatory requirements for a biologics company to obtain and maintain a license to produce the vaccine were to increase, then the cost of the vaccine would increase and producers would opt to use less vaccine and more antibiotics. Affordable and available vaccines reduce reliance on antibiotics for animal health.

2.5. Food safety vaccines

Recently, vaccines have been developed to reduce the shedding of organisms that cause food borne diseases in people. Vaccines for *E coli* O157:H7 in cattle and *Salmonella enteritidis* in chickens are available. These vaccines typically do not improve the health of the vaccinated animal, but they reduce the shedding of pathogens that may contaminate animal products for human consumption. The severity of the *S. enteritidis* outbreak in people in the United States in 2010 due to consumption of contaminated eggs could have been reduced or prevented if the chickens had received the *S. enteritidis* vaccine.

Table 1. Veterinary vaccines for the following zoonotic diseases have been, or could be, used to control infections in animals, thereby reducing transmission of the infectious agent to people

Rabies
Brucellosis
Leptospirosis
Influenza
Rift Valley fever
Nipah and Hendra
Japanese encephalitis
Q fever

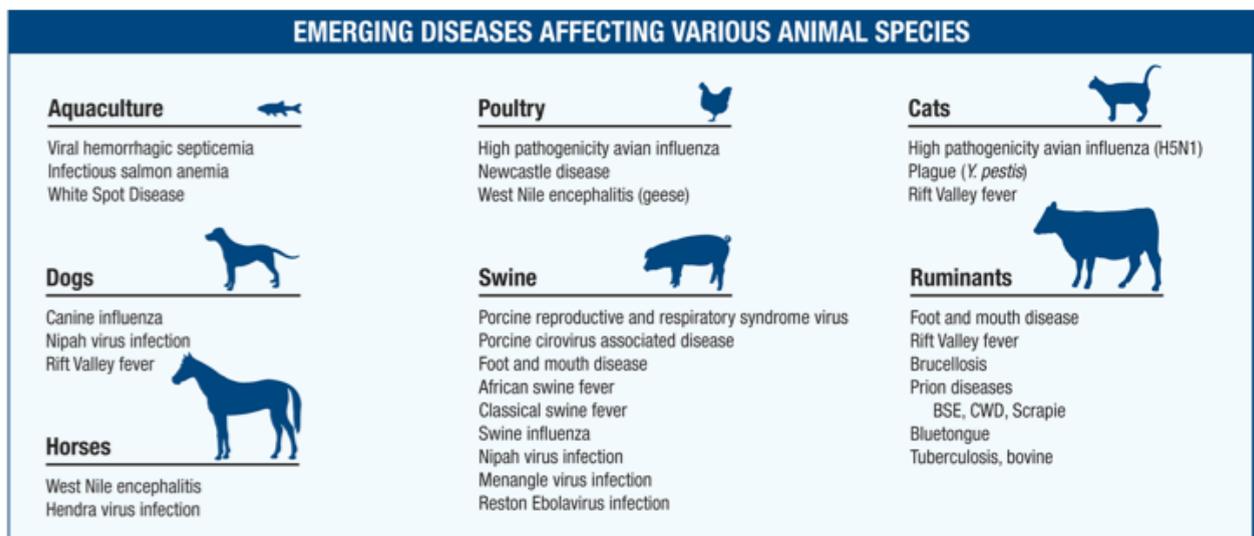


Figure 4. Emerging and re-emerging diseases affecting companion animal and food animal species. (Reprinted with permission from: Roth, J. A., Galyon, J., Stumbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals: Role of the Veterinarian. *In* Emerging and Exotic Diseases of Animals, 4th Edition, 2010, Rovid-Spickler, A., Roth, J.A., Galyon, J., Lofstedt, J. Editors. Center for Food Security and Public Health, Ames, IA. USA.

2.6. Control of diseases of companion animals and horses

Vaccines for diseases of companion animals (**Tables 2,3**) and horses (**Table 4**) have greatly enhanced the ability to keep animals in the household and to own horses. The human-animal bond that develops enriches the lives of both the animals and the people.

3. Diversity of veterinary vaccines

Animal vaccines are developed and licensed for a variety of purposes. Most are used to prevent infectious diseases. Livestock vaccines are used for different purposes than human vaccines. Livestock vaccines are primarily used to improve the efficiency of production of food animals. The cost of the vaccine is an important consideration as to whether the vaccine will be used. It must contribute to profitability for the producer in the long run to be widely accepted. Companion animal vaccines are similar to human vaccines in that the health and welfare of the

individual animal is often the primary consideration. Vaccination against zoonotic diseases and foodborne pathogens can be used to reduce or eliminate the risk to people. Wildlife vaccines are generally used for zoonotic diseases (e.g., oral bait vaccines for rabies), or in some cases in conjunction with disease control programs in domestic species (e.g., Brucellosis vaccine for bison and elk).

Table 2. Canine vaccines licensed for use in the US by the USDA Center for Veterinary Biologics (AAHA Canine Vaccine Task Force (2003, 2006)

<http://www.aahanet.org/PublicDocuments/VaccineGuidelines06Revised.pdf>

Canine Distemper virus
Canine Parvovirus
Canine adenovirus 2
Rabies
Canine parainfluenza 3
Leptospira (5 serovars)
<i>Bordetella bronchiseptica</i>
<i>Borrelia burgdorferii</i>
Canine distemper/measles
<i>Giardia</i> spp.
Canine corona virus
Rattlesnake venom
Periodontal disease

Today in the United States, there are 1,958 veterinary biologic products that cover 213 different animal diseases. These products are manufactured in 161 different facilities and by 97 licensees or permittees [7]. Licensed animal vaccines are available for diseases where vaccines are not available for analogous human diseases, such as feline immunodeficiency virus, and feline leukemia virus. Other examples include a vaccine to protect dogs from rattlesnake venom, a vaccine for periodontal disease in dogs, and a nucleic acid-mediated vaccine for treatment of malignant melanoma in dogs [8].

Table 3. Feline vaccines licensed for use in the US by the USDA Center for Veterinary Biologics (The 2006 AAHP Feline Vaccine Advisory Panel Report; Journal of the American Veterinary Medical Association 2006;229:1405-1441)

Feline panleukopenia Virus
Feline Viral Rhinotracheitis
Feline Calicivirus
Rabies
Feline Immunodeficiency Virus
Feline Leukemia Virus
<i>Bordetella bronchiseptica</i>
<i>Chlamydomphila felis</i>
Feline Infectious Peritonitis
<i>Giardia</i>

Veterinary vaccines have a distinct advantage in that they can be developed and licensed much more quickly and at much less cost than human vaccines. The ability to conduct safety and efficacy studies, including

vaccination/challenge studies in the target species greatly facilitates licensing of veterinary vaccines. Liability issues associated with adverse reactions for manufacturers of veterinary vaccines are much less than for manufacturers of human vaccines.

Table 4. Equine vaccines licensed for use in the US by the USDA Center for Veterinary Biologics (AAEP Guidelines for the Vaccination of Horses (2008); http://www.aaep.org/vaccination_guidelines.htm)

Tetanus
Eastern and Western Equine Encephalomyelitis
West Nile Virus
Rabies
Anthrax
Botulism
Equine Herpes Virus
Equine Viral Arteritis
Equine influenza
Potomac horse fever
Rotaviral diarrhea
Strangles

The equine West Nile virus vaccine is an example of how an animal vaccine can be developed and licensed quickly to meet an emergency situation. The West Nile virus was discovered in the United States in August 1999. The veterinary vaccine industry, working in cooperation with the USDA Center for Veterinary Biologics, quickly developed an effective vaccine to prevent the disease in horses. By August 2001, an equine vaccine for West Nile virus was conditionally licensed by the USDA. West Nile virus vaccine is now considered one of the core equine vaccines in the United States. [9]. The vaccine has also been used off label to protect some endangered birds, such as California condors. Porcine circovirus 2 vaccines and swine influenza pandemic H1N1 vaccines are additional examples of newly emerging diseases for which vaccines were developed and licensed quickly.

A disadvantage of veterinary vaccines is that the potential financial returns are much less than for human vaccines. Veterinary vaccines have lower sales prices and smaller potential market value. Consequently, there is a lower investment in research and development for animal vaccines than human vaccines, although the range of hosts and pathogens are greater.

4. Advances in vaccinology

The science behind vaccines changed little until about 20 years ago when the first genetically engineered veterinary vaccines were developed and licensed. These vaccines were able to successfully control Aujeszky's disease in pigs [10] and rabies in wildlife [11]. In the United States there are 15 licensed live vector vaccines (including chimeric vaccines), seven non-replicating recombinant antigen vaccines (including virus-like-particle vaccines, and vaccines derived from genetically engineered plants), four live-gene-deleted vaccines and two nucleic acid-mediated vaccines (**Table 5**) [8].

Another example of a novel vaccine that is currently licensed in other countries, but not the United States, is a vaccine that induces antibodies to gonadotropin releasing hormone to prevent the need to castrate male pigs.

5. Vaccine needs

The USDA and Department of Homeland Security have recognized the need to have licensed vaccines for important animal diseases that are not currently present in the United States. Since the diseases are not present in the United States, there is no market for the vaccines. Consequently, no biologics companies have gone to the expense

to license vaccines for those diseases. However, US animal agriculture is highly vulnerable to the introduction of these diseases. Homeland Security Presidential Directive (HSPD) 9 mandated the establishment of a National Veterinary Stockpile (NVS), a national repository that can deploy within 24 hours “sufficient amounts of animal vaccine, antiviral, or therapeutic products to appropriately respond to the most damaging animal diseases affecting human health and the economy” [12].

Table 5. USDA-APHIS-Veterinary Services Center for Veterinary Biologics active biotechnology products.

Non-replicating recombinant antigen(s)-vaccine:
Feline Leukemia Vaccine, Killed Virus
Avian Influenza Vaccine, H5N3 Subtype, Killed Virus
Porcine Circovirus Vaccine, Type 1 -Type 2 Chimera, Killed Virus
Porcine Circovirus Vaccine, Type 2, Killed Baculovirus Vector
<i>Escherichia Coli</i> Bacterin-Toxoid
<i>Borrelia Burgdorferi</i> Bacterial Extract
Feline Leukemia Virus Antigen
Nucleic acid-mediated (not synthetic)-vaccine:
West Nile Virus Vaccine, DNA
Canine Melanoma Vaccine, DNA
Live gene deleted:
<i>Escherichia Coli</i> Vaccine, Live Culture
<i>Salmonella Dublin</i> Vaccine, Live Culture
Pseudorabies Vaccine, Modified Live Virus
<i>Salmonella Typhimurium</i> Vaccine, Live Culture
Live vectored:
Marek's Disease Vaccine, Serotypes 1 & 3, Live Herpesvirus Chimera
Avian Influenza-Fowl Pox Vaccine, H5 Subtype, Live Fowl Pox Vector
Distemper Vaccine, Live Canarypox Vector
Equine Influenza Vaccine, Live Canarypox Vector
Canine Distemper-Adenovirus Type 2-Parvovirus Vaccine, Modified Live Virus, Canarypox Vector
Canine Distemper-Adenovirus Type 2-Parainfluenza-Parvovirus Vaccine, Modified Live Virus, Canarypox Vector
Rabies Vaccine, Live Canarypox Vector
West Nile Virus Vaccine, Live Canarypox Vector
Feline Leukemia Vaccine, Live Canarypox Vector
Rabies Vaccine, Live Vaccinia Vector
Newcastle Disease-Fowl Pox Vaccine, Live Fowl Pox Vector
Fowl Pox- <i>Mycoplasma Gallisepticum</i> Vaccine, Live Fowl Pox Vector
Fowl Pox-Laryngotracheitis Vaccine, Live Fowl Pox Vector
Bursal Disease-Marek's Disease Vaccine, Serotype 3, Live Marek's Disease Vector
Marek's Disease-Newcastle Disease Vaccine, Serotype 3, Live Marek's Disease Vector

The NVS advisory committee has identified the 17 highest priority foreign animal diseases for which vaccines, diagnostics and/or other countermeasures are needed (**Table 6**). The research and development needs for these countermeasures differ. There are significant challenges associated with meeting the licensing requirements mandated in Title 9 of the Code of Federal Regulations for biologics for these foreign animal diseases [13]. However, through collaborative efforts of the Department of Homeland Security, the USDA Center for Veterinary Biologics, and the biologics industry, significant progress is being made in licensing biologics to meet the mandate of HSPD 9.

6. Challenges

Much progress has been made in vaccine development in recent years; however, significant challenges remain. Animal and human infectious disease experts need to work together to prepare for new and emerging diseases. Veterinary vaccines must be pure, safe, potent and effective and they must be economical or they won't be widely used. Proper standards and production controls in the manufacture of veterinary vaccines are essential for ensuring quality products for animal disease control. The regulatory process for evaluation of vaccines must ensure adequate evaluation of biologicals but be efficient for both the regulatory agencies and the biologics manufacturers. Keeping the costs of animal vaccines low will encourage more use of vaccines and less use of antibiotics. It will also enable the use of food safety vaccines that do not have an economic advantage for the producer or health advantage to the animal, but have important public health benefits.

Table 6. Damaging animal diseases in priority order for inclusion of countermeasures into the National Veterinary Stockpile [10].

Agroterror Agent	Animal Industries Affected	Public Health Threat?
1 Highly pathogenic avian influenza	Poultry	Yes, may be lethal
2 Foot-and-mouth disease	Cattle, swine, sheep, and other cloven-hoofed livestock	No
3 Rift Valley fever	Cattle, sheep	Yes, may be lethal
4 Exotic Newcastle disease	Poultry	Yes, minor effects
5 Nipah and Hendra viruses	Swine (Nipah), horses (Hendra)	Yes, may be lethal
6 Classical swine fever	Swine	No
7 African swine fever	Swine	No
8 Bovine spongiform encephalopathy agent	Cattle	Suspected
9 Rinderpest	Cattle, sheep	No
10 Japanese encephalitis	Swine, equine	Yes, may be lethal
11 African horse sickness	Equine	No
12 Venezuelan equine encephalitis	Equine	Yes, may be lethal
13 Contagious bovine pleuropneumonia	Cattle	No
14 <i>Ehrlichia ruminantium</i> (heartwater)	Cattle, sheep, goats	No
15 Eastern equine encephalitis	Equine	Yes, may be lethal
16 <i>Coxiella burnetii</i>	Cattle, sheep, goats	Yes, may be lethal
17 Akabane	Cattle, sheep, goats	No

7. Conclusion

The fact that so many people depend on livestock and poultry for their livelihoods and as a source of food limits policy options, complicates local and global trade decisions, and raises political sensitivities. It is inevitable that the world will continue to experience the emergence of new human and animal diseases in the coming decades. This

challenge mandates the need for the medical, veterinary, and public health communities to work together locally and internationally. Veterinary vaccines will continue to be an important tool to protect human health, animal health, food safety, and food security and must be accessible and economical.

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