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ABSTRACT The One Health concept merges environmental, wildlife, domestic animal, and human health into a global, interconnected context. Though recently a popular catchphrase due to the emergence and reemergence of diseases such as foot-and-mouth disease (FMD), bluetongue, bovine spongiform encephalopathy (BSE), Q Fever, Rift Valley fever, Nipah virus, West Nile virus (WNV), severe acute respiratory syndrome (SARS), highly pathogenic H5N1 avian influenza, and plague, the One Health concept is not new. The One Health approach to managing infectious diseases aims to promote and implement meaningful collaboration and communication between multiple allied disciplines working locally, nationally, and internationally to attain optimal health for people, domestic animals, wildlife, and our environment. Rabies is an ancient disease that results in more than 55,000 human deaths worldwide each year. Historic and current emphasis on interdisciplinary approaches to rabies control provides a prime example of a zoonotic disease that is being managed more effectively via the One Health approach. In North America, a few meso-carnivores and bats serve as reservoirs of rabies, perpetuating continual infection of humans, pets, and livestock. Increased emphasis on surveillance and control of rabies in wildlife is the key to local, regional, and continental elimination strategies.

KEY WORDS framework, North America, One Health, rabies, disease management.

The One Health concept is a broad-based strategy for managing infectious diseases through multi-disciplinary communication and collaboration, with optimal environmental, human, domestic animal, and wildlife health outcomes at local, national, and global levels. The ideal of "One Health" was first proposed in the 19th century by William Osler and Rudolf Virchow, and revived by veterinary epidemiologist Calvin Schwabe in his 1984 text "Veterinary Medicine and Human Health" (Hesselgrave 2010). These early proponents recognized the interdependence of animal and human health; observations historically overlooked until the late-20th century when there was greater recognition and acceptance that an integrated approach for managing disease transmission between domestic animals and wildlife could ultimately improve the health of people (Osofsky et al. 2005). In the 21st century, increasing human and wildlife populations, and a greater convergence of animal and humans within a variety of ecosystems rendered the continued use of compartmentalized approaches toward health management an imperfect paradigm. The One Health concept offers a multidisciplinary, coordinated opportunity to improve our capacity to effectively manage existing disease across the landscape and better address and contain new emerging infectious disease.

In the past 30 years, approximately 75% of emerging infectious diseases affecting humans were zoonoses; approximately 60% of the 1461 diseases now known to affect humans are caused by zoonotic pathogens capable of interspecies transmission (Taylor et al. 2001, Woolhouse and Gowtage-Sequeria, 2005, Mahr 2007, AVMA 2008, King et al. 2008). For example, West Nile virus (WNV) emerged in the United States in 1999, infecting over 1.5 million people as well as a considerable number of horses and wild birds, and

is now a permanent threat to human and animal health (AVMA 2008). Bovine spongiform encephalopathy (BSE) is a neurodegenerative disease of cattle that causes new variant Creutzfeldt-Jakob disease in humans. Emergence of this disease in 1987 resulted in the culling of approximately 4.4 million cattle in the United Kingdom, and global changes in the standards of agricultural trade (FAO 2008). Foot-and-mouth disease (FMD) is a non-zoonotic viral disease endemic to areas of Asia, Africa, and South America. FMD outbreaks may result in significant agricultural and economic losses. For example, control of a FMD outbreak in the UK in 2001 resulted in the slaughter of approximately 7 million sheep and cattle, at an estimated cost of $16 billion. Projected trade losses to the U.S. economy are estimated at $37 billion, should this disease re-emerge in the U.S. (AVMA 2008). Nipah virus emerged in Malaysia in 1999 due to a combination of habitat destruction, changes in local climate, and agricultural practices, resulting in encroachment of livestock into wildlife habitat. The resulting outbreak destroyed that country's swine industry, and related human fatalities induced massive public panic (FAO 2008). SARS emerged in 2003, and approximately 8000 people in China, Canada, Singapore, and Vietnam were eventually infected. Economic costs in Asian countries associated with this outbreak are estimated at $30–50 billion (FAO 2008). Highpath H5N1 avian influenza (HPAI) remains a potential pandemic threat that could cost the global economy approximately $2 trillion (FAO 2008). Vector-borne diseases such as plague, bluetongue, and Q fever continue to emerge in various geographic locations and countries, serving as potential sources of new epidemics.

Increased interactions and conflicts among humans, domestic animals, and wildlife within an increasingly human-altered environment are likely to result in continued emergence and re-emergence of diseases, and an increase in disease transmission among these groups. The One Health concept is uniquely designed to address these contemporary health issues by combining the efforts of human and animal health specialists, wildlife biologists, and ecologists to better understand how interactions among people, animals, and management of natural resources affect the occurrence of disease and health outcomes (Osofsky et al. 2005). Experts working together, instead of independently, to develop a big picture approach to disease management that recognizes personal and professional interdependences will result in greater accomplishments in the improvement of global health (Osofsky et al. 2005, Mahr 2007, AVMA 2008). Such integration will expand scientific knowledge for all invested professions, contribute to agricultural industries and conservation management, improve public health outcomes, and reduce incidence of pathogen transmission among domestic animal, wildlife, and human populations.

HISTORY OF RABIES

Rabies is one of the oldest documented diseases. Ancient Greeks referred to it as Lyssa or Lytta, which meant "madness," and Aristotle noted that "dogs suffer from the madness" and "all animals they bite become diseased" (Steele and Fernandez, 1991). Works by Hippocrates, Homer, Virgil, Xenophon, and others describe an illness believed to be rabies. During the Middle Ages and well into the 19th century, Europe experienced large-scale rabies epizootics involving dogs and foxes as primary reservoirs (Blancou et al. 1991, Steele and Fernandez 1991).

Rabies in wildlife and domestic animals was documented during early colonization of North America, and in 1768, a major epizootic occurred when rabies spilled over from foxes and dogs to swine and other domestic animals (Steele and Fernandez 1991). Rabies was first documented in the Commonwealth of Puerto Rico in 1841, when an edict was issued to kill any animal exhibiting signs of hydrophobia (Tierkel et al. 1952, Everard and Everard 1992). In the continental U.S., rabies followed settlers westward, reaching the West Coast in 1860, and persisted throughout the country into the mid-20th century. Foxes served as the primary reservoir of rabies in areas extending south from Canada to Florida and Texas during the 1940s (Korns and Zeissig 1948, Steele and Fernandez 1991, Rupprecht et al. 1995). Skunks emerged as a major rabies reservoir at this time, and bat rabies would be documented in all contiguous 48 states and Canada by the 1960s (Baer and Smith 1991, Steele and Fernandez 1991). Raccoon variant rabies, initially localized in south-central Florida during the 1950s, became established in the Mid-Atlantic states during the 1970s as result of the translocation of rabid animals from enzootic areas (Nettles et al. 1979, Chipman et al. 2007), and is now considered a significant threat in both rural and urban environments from southeastern Canada west to Ohio

and south to Alabama in the U.S. (Steele and Fernandez 1991, Rupprecht 1995). Rabies control measures existed during the first half of the 20th century, but were typically unsuccessful until 1947 when effective canine rabies vaccines became available and a national rabies control effort was instituted (Steele and Fernandez 1991). A decade later, combined efforts of local and national educational campaigns, urban field operations targeting canine rabies, and rural rabies control programs targeting animals other than dogs resulted in the decline of domestic dog rabies cases below the number of wild animal rabies cases for the first time (Blancou et al. 1991). In Puerto Rico, where rabies has occurred continually since the 1950s, the small Indian mongoose continues to serve as the primary reservoir of the disease (Blanton et al. 2006).

Since the late 1990s the National Rabies Management Program (NRMP) of the USDA Animal and Plant Health Inspection Service Wildlife Services (WS), has provided federal leadership in managing rabies in wildlife. The focuses of management activities conducted by NRMP are to reduce rabies impacts to human and animal health, and reduce costs associated with living with rabies. Immediate program goals include stopping the spread of specific rabies virus variants in meso-carnivores, to increase public awareness of wildlife rabies, and develop new and better techniques to manage the disease, with long-term goals focused on the elimination of rabies in meso-carnivores. The National Wildlife Research Center (NWRC) conducts research in a variety of WS program focus areas including rabies. The NWRC Rabies Research Project is designed to conduct studies on a prioritization basis to improve the NRMP's capability to manage rabies in wildlife. Wildlife agencies also collaborate with colleagues from domestic animal and human health to address rabies in a holistic One Health manner.

CURRENT STATUS OF RABIES

Rabies is present on all continents except Antarctica, and is a neglected disease in many countries. Cases of rabies are substantially underreported in most developing countries (Krebs et al. 1995); however, the World Health Organization (WHO) estimates that approximately 3 billion people are at risk of infection (Bentivoglio et al. 2011) and more than 55,000 human deaths occur annually (Krebs et al. 1995, Rupprecht et al. 1995) with the majority (>50%) of deaths occurring in children under 15 years of age (Knobel et al. 2005, Bourhy et al. 2010). Up to 95% of these cases occur in Asia (primarily India), and 99% of cases are transmitted by domestic dogs (*Canis lupus familiaris*) (Rupprecht et al. 1995, Bourhy et al. 2010). It is estimated that up to 15 million people living in developing countries require post-exposure prophylaxis (PEP) annually (Rupprecht et al. 1995, Bourhy et al. 2010). Wildlife rabies is present in developing countries, but the magnitude, scale, and impact on humans and domestic animals is mostly unknown due to the overwhelming occurrence of canine rabies, and the lack of resources needed to document the occurrence of rabies in indigenous wildlife. Cases of human and canine rabies in developed nations are increasingly rare, making wild mammalian carnivores the predominant hosts for terrestrial rabies (Krebs et al. 1995). Globally, locations free of terrestrial rabies include Australia, New Zealand, Papua New Guinea, Japan, Taiwan, United Kingdom, Ireland, mainland Norway, Sweden, Portugal, most of Pacific Oceania, and some Atlantic and Caribbean islands as well as Hawaii in the U.S. (Krebs et al. 1995).

During the early 1900s, the annual number of documented human rabies cases in the U.S. exceeded 100 (Krebs et al. 1995) but current cases now average 1–3 per year (Balsamo and Ratard 2010). Rabies control and prevention programs responsible for this dramatic decline are funded by public and private sectors, and are estimated to cost between $300 million and $1 billion per year (Krebs et al. 1995, Rupprecht et al. 1995). In North America, rabies is maintained among wildlife with a few meso-carnivores and bats serving as primary reservoirs. In the U.S., enzootic rabies is present in every state, except Hawaii. Wildlife accounts for approximately 90% of reported rabies cases; primary reservoir species include raccoons (*Procyon lotor*), skunks (predominantly *Mephitis mephitis*), foxes (*Alopex lagopus, Vulpes vulpes, Urocyon cinereoargenteus*), mongooses (*Herpestes javanicus*) in Puerto Rico only (Blanton et al. 2010), and over 30 species of bats (primarily *Lasionycteris noctivagans, Pipistrellus subflavus, Tadarida brasiliensis)* (Mondul et al. 2003, Franka et al. 2006, Constantine et al. 2009).

In 2009, 4 human and 6,690 animal rabies cases in 49 states and Puerto Rico were reported to the Centers for Disease Control and Prevention (CDC), with wildlife accounting for 92% of reported cases (Blanton et al. 2010). Raccoon rabies is enzootic in the

northeastern, mid-Atlantic, and southeastern U.S. Raccoons are the most frequently reported rabid wild animal; accounting for approximately 38% of all wild animal rabies cases (Blanton et al. 2010). Bats were the second most frequently reported rabid wild animal, comprising approximately 26% of all wild animal rabies cases (Blanton et al. 2010). Skunk rabies is present in 22 north-central and south-central states and California, and collectively the three skunk rabies variants have the broadest geographic distribution in the U.S. Skunk rabies cases comprised approximately 26% of all wild animal rabies cases. Ten states (Arizona, Colorado, Iowa, Michigan, Missouri, Montana, Nebraska, New Mexico, South Dakota, and Wyoming) reported a 50% increase in cases from 2008 to 2009 (Blanton et al. 2010). Fox rabies accounted for approximately 8% of all wild animal rabies cases in 2009, the highest number of rabid foxes recorded since 2002 (Blanton et al. 2010). Puerto Rico reported a total of 43 cases of animal rabies, with 79% of cases occurring in mongooses, and 21% occurring in domestic animals or livestock (Blanton et al. 2010). A variety of other terrestrial mammals were also reported confirmed with rabies including: beavers (*Castor canadensis*), bobcats (*Lynx rufus*), a cougar (*Felis concolor*), coyotes (*Canis latrans*), fishers (*Martes pennati*), ground hogs (*Marmota momax*), a muskrat (*Ondatra zibethicus*), opossums (*Didelphis marsupialis*), a rabbit (*Sylvilagus sp.),* a ringtail (*Bassariscus astutus*), river otters (*Lontra canadensis*), squirrels (*Sciurus spp.*), white-tail deer (*Odocoileus virginianus*), and a wolf (*Canis lupus*) (Blanton et al. 2010). Rabid cats (*Felis catus*) and dogs accounted for the majority of cases in domestic animals (59.4% and 16%, respectively). The preponderance of rabies cases now occur in diverse meso-carnivores which affect pets and livestock, further underscoring the need for collaboration among veterinarians, wildlife biologists, and public health officials.

RABIES AND ONE HEALTH

Rabies is an excellent example of a disease that can most efficiently and effectively be managed through a strategic application of the concepts of One Health. The national rabies control effort initiated in the mid-20th century involved the integration of multiple professions including veterinary and human medicine; wildlife biology; public health; bio-pharmacological research; and the media. Rabies mitigation today continues to rely on the cooperation of such disciplines to protect human and animal health. For example, the NRMP and many state health departments collaborate to implement optimized strategies for mitigating rabies in wildlife following the procedural legal framework provided by the National Environmental Policy Act. WS and other collaborators from multiple agencies, universities, organizations and the private sector representing diverse disciplines have mutually developed the U.S. National Plan for Wildlife Rabies Management and the North American Rabies Management Plan to guide rabies surveillance, control, and research nationally and on the North American continent.

Ultimately, comprehensive control of rabies in wildlife populations requires a complex and evolving framework. The effects of anthropogenic factors such as an increasing human population; intensive agricultural practices; and wild and domestic animal translocation; as well as a variety of natural factors such as wildlife population biology; interactions among susceptible and rabies host species; animal movements; changing habitats; environmental degradation; and climate change requires development of an integrated contingency plan to prevent rabies from re-emerging as a major zoonosis (Rosatte et al. 2002). Increased emphasis on rabies surveillance and control in wildlife in addition to continued domestic animal vaccination and human PEP will be key while working toward elimination of terrestrial rabies in North America.

THE RABIES FRAMEWORK

Examining rabies surveillance and control through the lens of a One Health framework allows development of mitigation strategies focused on the interface between domestic and wild animals, humans, and the ecosystem. The objective of the framework is focus on the major factors required to achieve the overarching goals of improving public health and ecosystem health through multi-perspective rabies prevention, control, and elimination strategies. The key components of the framework are:

1. Recognize the Importance of the Human-Animal-Environment Interface

The disease ecology of rabies is a complex affected by host biological factors, ecosystem attributes, diversity of virus variants, and external factors such as changes in human, domestic animal, and wildlife populations; contact between livestock and wildlife; encroachment of humans into areas inhabited by wildlife; changing

agricultural practices; ecosystem degradation due to encroachment, pollution, climate change, land use, and other factors; and globalized trade in animals and animal products.

Develop an Integrated, Flexible, Multidisciplinary, and Multiagency Approach Toward Rabies Management

The holistic objective of a One Health approach to rabies is to minimize the impact of the disease while working toward elimination. This will require scientific, governmental, and private sectors—which often function in isolation—to function as a coherent system, integrating respective technical, social, political, policy and regulatory issues (Rosatte et al. 2002, Osofsky et al. 2005, FAO 2008). To fully develop an understanding of the epidemiology, maintenance, and transmission of rabies among reservoir hosts and incidental hosts, contributions from multiple professional sectors such as wildlife biology and behavioral ecology; natural resource management and ecology; livestock and agriculture science; veterinary and human medicine; virology; biotechnology; biomedical engineering; and epidemiology will be essential.

2. Increase Investment in Risk-Based Rabies Surveillance, Intervention, Outbreak Prevention, Control, and Elimination Programs in Primary Host Species

Long-term political and financial investments are essential for the development and maintenance of the surveillance, prevention, and control measures required for management of an epizootic disease such as rabies. Establishment and maintenance of long-term risk-based surveillance systems in areas where enzootic wildlife rabies is present will improve prevention and management strategies. Further development of comprehensive surveillance plans examining factors leading to human and domestic animal exposure will contribute to improved exposure prevention and intervention measures.

3. Increased Investment in Rabies Virus Research

Continued research examining the pathogenicity, species specificity, transmission dynamics, immunogenicity, and genetic construct of the different rabies virus variants is key to understanding the behavior of this disease in wildlife. Collective examination of these elements will lead to new perspectives on how and why enzootic rabies can persist and remerge in nature, leading to development of optimized control strategies.

4. Continue to Promote Public Health Education and Awareness

Continued support of rabies awareness campaigns will have positive effects on human and domestic animal health. Continuing to educate the public about the presence of enzootic rabies, the risk of wildlife rabies, and the preventive benefits of pet and livestock vaccination will contribute toward prevention and control of this disease. Improvement of current communication strategies will improve prevention, detection, and response to outbreaks. Transparency regarding management of wildlife rabies will improve the public understanding of oral rabies vaccines, ORV campaigns, and other wildlife rabies intervention methods.

5. Develop Prioritized, Targeted Control Programs through Strategic Research

The most successful rabies control programs worldwide are those that have taken a multiagency approach (Rosatte et al. 2002). Future efforts to control and eliminate rabies in the U.S. should combine traditional methodology with new, innovative, cost-effective solutions based on the identification of immediate and long-term priorities, and research-based identification of new risks. Sustained epidemiological studies are needed to determine the incidence and prevalence of the disease, characterize transmission dynamics, and determine demographic and geographic influences that affect occurrence. Enhanced rabies surveillance based on systematic and targeted sampling of animal populations, and timely and accurate diagnosis (Lembo et al. 2006) has already proven to provide greater confidence for management decisions (Slate et al. 2009) rather than relying solely on passive surveillance (Krebs et al. 1995).

6. Increase Investment in Vaccine Research

Oral rabies vaccination programs targeted toward control of raccoon variant rabies have been associated with significant reduction in the prevalence of raccoon rabies in some areas of the U.S. (Rupprecht et al. 1995). Continued development of new, novel oral vaccines must be supported through research examining their efficacy in all critical reservoir hosts and new baiting strategies need to be developed. Supporting research must evaluate the influence of the pathogenicity, immunogenicity, demographic effect of rabies reservoir host behavior, and metapopulation influences, and human demographic impacts to determine most appropriate strategies for bait distribution (Krebs et al. 1995, Rosatte et al. 2002).

7. Support a Global Perspective

The Manhattan Principles drafted by health experts from around the world in September 2009 expanded the original One Health concept to the global goal of "One World, One Health" and established priorities for an international, interdisciplinary approach for combating epidemic and epizootic disease for the benefit of humans, domestic animals, wildlife, and the global ecosystem (FAO 2009). Exchange of "local" knowledge and insights gained through continued research and development in all facets of rabies prevention, diagnosis, control and elimination in order to improve "global" rabies mitigation strategies must be championed.

DISCUSSION AND SUMMARY

The One Health concept recognizes the indelible connection between human, animal, and ecosystem health. It proposes an international, interdisciplinary approach for surveillance, prevention, control, and mitigation of disease, as well as environmental conservation. For the One Health concept to succeed, it must be embraced at local, national, and global levels, and include collaborative training at universities, along with respectful interdisciplinary partnerships among professionals in veterinary medicine, human medicine, public health, bio-medical engineering, animal science, wildlife biology, and environmental ecology sectors (Mahr 2007, King et al. 2008, Hesselgrave 2010). Potential outcomes include a large body of relevant research, shared resources, improved efficiency of disease surveillance, better reporting of disease occurrence, more concise preparedness and contingency planning, expedient responses to disease outbreaks, improved local and global human and animal health, and advancements in natural resource management (Mahr 2007, King et al. 2008, Hesselgrave 2010). Overcoming professional paradigms, which compartmentalize disease into specialized care, species-oriented approaches, and encourage clinically-based disease treatment mindsets instead of preventive medicine philosophies, will be paramount to the success of the One Health concept. Wildlife managers must promote better rabies management and become key partners in rabies surveillance and control that focuses on wildlife reservoirs with the goal of preventing the spread of rabies virus variants and encouraging the elimination of these variants from large geographic areas to reduce the human health and economic impacts of living with rabies. The short-term effort and expense required to concretely address rabies in wildlife is easily justified relative to the long-term savings and protection of health of the nation's wildlife, livestock, pets, and citizens locally, nationally, and globally.

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