Pre-spillover Prevention of Emerging Zoonotic Diseases: What Are the Targets and What Are the Tools?

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Abstract The uneven standards of surveillance, human- or animal-based, for zoonotic diseases or pathogens maintained and transmitted by wildlife H$_R$s, or even domestic species, is a global problem, readily apparent even within the United States, where investment in public health, including surveillance systems, has a long and enviable history. As of 2006, there appears to be little scientific, social, or political consensus that animal-based surveillance for zoonoses merits investment in international infrastructure, other than the fledgling efforts with avian influenza, or targeted nontraditional avenues of surveillance and research. National institutions charged with strategic planning for emerging diseases or intentional releases of zoonotic agents have emphasized improving diagnostic capabilities for detecting human infections, modifying the immune status of human or domestic animals through vaccines, producing better antiviral or antibacterial drugs, and enhancing human-based surveillance as an early warning system. With the possible exception of extensive human vaccination, each of these approaches target post-spillover events and none of these avenues of research will have the slightest impact on reducing the risk of additional emergence of viruses or other pathogens from wildlife. Novel schemes of preventing spillover of human pathogens from animal H$_R$s can only spring from improving our understanding of the ecological context and biological interactions of pathogen maintenance among H$_R$s. Although the benefit derived from investments to improve surveillance and knowledge of zoonotic pathogens circulating among wildlife H$_R$ populations is uncertain, our experience with HIV and the looming threat of pandemic avian influenza A inform us of the outcomes we can expect by relying on detection of post-spillover events among sentinel humans.

1
Introduction

Individual humans sickened or killed by an unknown infectious cause potentially indicate a zoonotic disease emergence has occurred, but, by themselves, are insufficient to document any instance of emergence. Incident cases of a new zoonotic

disease must come to the attention of local authorities and then be the target of clinical, epidemiologic, and microbiologic research prior to any determination that an outbreak was caused by an emerging or reemerging pathogen. Satisfactory fulfillment of Koch's postulates is a daunting process, involving the diagnosis of human disease, i.e., the isolation of the infecting pathogen in cell culture; the molecular and antigenic characterization of pathogens obtained from human or animal tissues; and establishing the novel pathogen's causal role as etiologic agent (Osterhaus et al. 2004).

These endeavors link forever an instance of emergence with a single time point and place, a pinpoint and date on a map [Fig. 2.2 in Institute of Medicine (2003)]. Such an accounting system is necessary, but belies the dynamic ongoing process of disease emergence. As with the invading species that perishes on a foreign shore before being identified and labeled by a knowledgeable biologist, countless cases of zoonotic disease go unrecognized and uncatalogued. These missing data limit comparative analyses of the qualities of successful invading species to the far larger outgroup of pathogens for which there are limited or negative, i.e., not detected, data (Daszak et al. 2000; Cleaveland et al. 2001; Dobson and Foufopoulos 2001; Kolar and Lodge 2001; see the chapter by Cleaveland et al., this volume). Irrespective of the limitations of such studies, coherent trends and suites of plausible traits associated with successfully emerging pathogens have been derived from comparative studies (Dobson and Foufopoulos 2001; Cleaveland et al. 2001; see the chapters by Cleaveland et al. and Holmes and Drummond, this volume), but offer little guidance on how and where to focus attention (but see the chapters by Daszak et al. and Merianos, this volume).

Zoonotic viral emergences surprise even the scientists who are most knowledgeable within a subject area. Witness the identification of a novel *Hantavirus* causing fatal disease in the southwestern United State, after decades of search for pathogenic hantaviruses in the United States (LeDuc et al. 1993), and the discovery of a novel *Lyssavirus* causing a disease indistinguishable from rabies, in supposedly rabies-free Australia (Hooper et al. 1997). Although the process of zoonotic pathogen emergence often begins with identification of a case or cluster of human disease, surveillance and monitoring systems are ill equipped to detect and then characterize the unknown (see the chapters by Merianos and by Stallknecht, this volume).

Once a new zoonotic disease is identified and a case definition is established, the systematic collection of information on incident cases of human disease is used to generate information in a usable form, through appropriate data analytic and publication processes conducted through personnel working through a central repository. When the information is disseminated back to health professionals, from the federal government to individual practitioner level, a surveillance system is established. The country of occurrence, the morbidity and mortality, and the preexisting public health infrastructure, mixed with a good portion of serendipity, influence the likelihood of detecting a newly emerged zoonosis.

2

Disease Detection and Surveillance: Prerequisites to Zoonotic Disease Emergence

Surveillance for zoonotic pathogens is largely based on detecting illness or infection in *Homo sapiens* (see the chapters by Merianos and by Stallknecht, this volume); humans serve as the sentinel species for zoonotic agents maintained in transmission cycles in which, fortunately, they rarely play other than an incidental role as a dead-end host. A variety of surveillance systems and data sources have been successfully, if sometimes unintentionally, employed to monitor existing zoonotic diseases or to detect new diseases (Table 1).

An example of a serendipitous outcome stemming from syndrome-based surveillance for a specific disease occurred in New York City in 2001, with the implementation of a system to detect bioterrorism-related cases of anthrax (Centers for Disease Control and Prevention 2001; Buehler et al. 2003; Paddock et al. 2003). The putative anthrax case definition included a febrile illness accompanied by either a rash or eschar. Rickettsialpox, caused by *Rickettsia akari*, had been an endemic, legally mandated reportable disease in New York City since the mid-1940s (Huebner and Jellison 1947; Huebner et al. 1946), but since the 1980s the median number of annual cases reported was approximately 1 (Paddock et al. 2003). The classical presentation of rickettsialpox includes a fever and one or more eschars at the bite sites produced by the infected mite vector transmitting *R. akari*. Over an 18-month interval, 34 cases of rickettsialpox were diagnosed through the syndromic-based anthrax-surveillance system in New York City; tissue biopsies from patients yielded the first isolates of *R. akari* from the United States in more than 50 years (Koss et al. 2003). Although rickettsialpox was a known entity, anthrax surveillance highlighted the under-appreciated level of disease caused by this endemic zoonosis.

Surveillance systems designed to detect and monitor a specific animal disease have also uncovered novel zoonotic pathogens. In the United States, two previously unknown rhabdoviruses have been isolated from dead birds collected for monitoring and forecasting WNV activity (Eidson et al. 2001b, 2001c; Mostashari et al. 2003; Garvin et al. 2004; Travassos da Rosa et al. 2002). While in Australia, laboratory workup of a sick pteropid bat collected in conjunction with Hendra virus (HeV) investigations following an outbreak of disease affecting horses and humans in 1994–1995 (Field et al. 2000, 2004; Halpin et al. 2000) yielded a new *Lyssavirus*, Australian bat lyssavirus (ABL), closely related to rabies virus (Fraser et al. 1996; Gould et al. 1998a). Within months of the isolation of ABL, this virus was demonstrated to be the cause of fatal encephalitis in humans (Gould et al. 1998b); until this time no rabies had been reported from Australia.

Effective, but informal, surveillance systems can be implemented rapidly following the identification of a novel zoonotic disease emergence within

Table 1 Examples of surveillance methods and data sources used to detect and monitor the emergence of zoonotic pathogens causing disease among human sentinels

Surveillance system or data source	Condition monitored
Individual physician	Hantavirus pulmonary syndrome (HPS) in Four Corners region of the United States[a]
Self-reporting of illness	Hot-line telephone reporting of suspect HPS coupled with trace-back for clinical records and samples for diagnostic testing[b]
CDC, Nationally Notifiable Diseases Surveillance System (NNDSS)[c]	West Nile fever and encephalitis[d], human and animal rabies[e], Rocky Mountain spotted fever[f] and others
CDC—Syndrome-based surveillance for anthrax fever, rash or eschar	Rickettsialpox described from New York City during surveillance for anthrax-first isolates of this rickettsia in 50 years[g,h]
EMERGEncy ID NET[i]	Appropriateness of rabies postexposure treatment in sentinel cities given recommendations of ACIP[j]
Automated rumor-tracking web-crawler[k]	Initial cases of severe acute respiratory disease (SARS) in China[l]
Community-based active surveillance, clinical practices and veterinary services	Human and animal rabies in Machakos District, Kenya[m,n]

[a] Duchin et al. 1994
[b] Tappero et al. 1996[3]
[c] Teutsch2000
[d] Centers for Disease Control and Prevention 2002
[e] Krebs et al. 2004
[f] Childs and Paddock 2002
[g] Paddock et al. 2003
[h] Koss et al. 2003
[i] Talan et al. 1998
[j] Moran et al. 2000
[k] A Report of the National Advisory Committee on SARS and Public Health 2003
[l] Heymann and Rodier 2004
[m] Kitala et al. 2000a
[n] Kitala et al. 2000b

countries with a highly developed public health infrastructure. The interplay of factors influencing initial detection and later development of systematic surveillance are illustrated by the outbreak of hantavirus pulmonary syndrome (HPS) in the southwestern United States in May 1993. An Indian Health Service physician noted a temporally and spatially linked cluster of cases of a severe,

often fatal, respiratory disease, affecting previously healthy, young-adult Navajo Indians residing on a reservation (Duchin et al. 1994). The physician notified local authorities and subsequently CDC was invited by state officials to help investigate the growing number of fatalities. Testing of patient sera at CDC revealed the presence of antibodies reactive with hantaviral antigens (Ksiazek et al. 1995). Facilitated by epidemiologic knowledge of hantaviruses and hantaviral diseases occurring in Eurasia, rapid progress was made in uncovering the natural history of this mysterious new disease. In a matter of weeks, investigators confirmed the disease was clinically distinct from Eurasian disease (Moolenaar et al. 1995), that the etiologic agent was a new *Hantavirus*, Sin Nombre virus (Nichol et al. 1993), and the reservoir host (H_R; for definition of terminology see the chapter by Childs et al., this volume) was a species of New World rodent, *Peromyscus maniculatus* (Childs et al. 1994).

A relatively crude but effective national surveillance program, capitalizing on media interest in the HPS outbreak, was established by June 1993. Six months later, private citizens or their physicians had reported and submitted clinical specimens for diagnostic testing from 280 persons; 21 confirmed HPS cases were identified from 11 states outside of the four-state region where the initial outbreak was localized (Tappero et al. 1996). This impromptu surveillance system was highly successful in rapidly identifying the widespread geographic distribution and sporadic incidence of HPS cases throughout much of the western United States.

Once a zoonotic disease is characterized, formal, systematic surveillance efforts can be initiated at the state or national level in countries possessing the requisite infrastructure. National surveillance programs coordinated through CDC, with rare exceptions, focus on the systematic collection of data on human disease. National surveillance and the global network for monitoring Influenza A activity among humans is the outstanding example of a system integrating epidemiologic data with the collection and characterization of influenza viral subtypes circulating throughout the world (Centers for Disease Control and Prevention 2004d; Cox et al. 1994). The unquestioned value of the global influenza surveillance program rests with the vaccines produced. Each year's new influenza vaccines are based on determinations of the currently circulating influenza subtypes and divining which subtypes should be incorporated into next season's vaccine cocktail.

A global early warning system to detect zoonotic pathogens transmitted to humans was launched in July 2006 by the UN Food and Agriculture Organization (FAO) and the World Health Organization (WHO) in collaboration with the World Organization for Animal Health (formerly the Office of International Epizooties or OIE) (http://www.who.int/mediacentre/news/new/2006/nw02/en). Specifically mentioned as examples are BSE and SARS; data from infected and diseased humans and animals will be gathered and assessed jointly. Plans to develop a global animal-based influenza surveillance program exist (Centers

for Disease Control and Prevention 2004d; Stohr 2003). It remains unclear if animal-based influenza surveillance will extend beyond domestic poultry and livestock to wild waterfowl and shorebird H_Rs, although this latter activity is strongly endorsed (Shortridge et al. 2003; Melville and Shortridge 2004; see the chapter by Webby et al., this volume).

3
Surveillance as Defined by Human and Veterinary Medicine

Surveillance for zoonotic diseases among wildlife, as opposed to domestic animals and livestock, falls through the cracks of both veterinary and human health practices (see the chapter by Stallknecht, this volume). Reviews of animal health monitoring systems mention wildlife disease surveillance only in passing and largely in reference to the difficulties of establishing population estimates (denominator data) for defining rates, such as disease incidence, or the obstacles to developing systematic surveillance programs coordinating with human disease surveillance (Ingram et al. 1975; see the chapters by Daszak et al., Merianos, and by Stallknecht, this volume).

Most regional or state systems collecting information on wildlife diseases are passive surveillance systems. Passive surveillance in the United States, as defined by public health professionals, is the systematic collection of data on human diseases, reportable through legal mandate in most states, obtained within specified time frames on conditions listed by National Notifiable Disease Surveillance System (NNDSS) (Teutsch 2000); data are reported to CDC by electronic submissions via the National Electronic Telecommunications System for Surveillance (NETSS) (Teutsch 2000). International regulations require reporting on quarantinable conditions, such as plague, yellow fever, cholera, and SARS (Teutsch 2000; Centers for Disease Control and Prevention 2002b). Diseases covered by the NNDSS are established through collaborations of the Council of State and Territorial Epidemiologists (CSTE) with the CDC and the nationally reportable diseases are reviewed at 3-year intervals, at which time case definitions are established or modified (Centers for Disease Control and Prevention 1997). By virtue of the population estimates provided by the US Census, human surveillance data collected via NNDSS are population-based. Summary statistics on nationally notifiable disease are published weekly in *Morbidity and Mortality Weekly Report (MMWR)* and summarized in annual reports (Centers for Disease Control and Prevention 2004c).

In contrast, for wildlife and domestic animal diseases, the OIE, situated in Paris, France, determines diseases reportable by its member counties

(Thiermann 2003). The diseases are divided into two lists: List A diseases are of major importance in international trade of animals or animal products and have the potential for very serious and rapid spread irrespective of national borders; List B diseases are of public health importance within counties (Thiermann 2003; http://www.oie.int). Within the United States, mandated reporting of animal diseases varies by state, and voluntary reporting by professionals is a major component of data collection (Salman 2003). At the federal level, information is collected by the Animal and Plant Health Inspection Service (APHIS) of the Department of Agriculture (USDA). Given the lack of accurate population estimates for many domestic animals and livestock, passive veterinary surveillance is not population-based.

3.1
Wildlife-Based Surveillance for Zoonotic Disease: Current Practices

Surveillance for wildlife diseases exists at some level in most developed countries. As with human, surveillance, the infrastructure for receiving, typing, and storing animal specimens and the diagnostic laboratory capacity for establishing diagnoses are minimal prerequisites (see the chapter by Stallknecht, this volume).

Within North America, the Canadian Cooperative Wildlife Health Center (CCWHC), supported by the four Canadian veterinary schools, was established in 1992 to promote nationwide surveillance of wildlife diseases. In Canada, disease detection is carried out by a wide range of professional and voluntary field personnel, including hunters, and specimen diagnosis is conducted at provincial and federal veterinary laboratories. The central repository for data is the CCWHC, which disseminates surveillance information to persons responsible for wildlife programs and policies, and to the public (Leighton et al. 1997).

In the United States, states have often taken the lead in monitoring wildlife diseases, such as WNV among dead birds, arboviral infections among sentinel bird flocks (Mostashari et al. 2003; Eidson et al. 2001a; Komar 2001), and transmissible spongiform encepahlopathy (TSE) associated with elk and white-tailed deer (Williams and Miller 2003). In several states, notably California and Florida, surveillance for arbovirus activity using sentinel flocks of birds have documented trends in the enzootic activity of western equine encephalomyelitis (WEE), St. Louis encephalitis (SLE), and eastern equine encephalomyelitis (EEE) linked to climatic and local weather patterns (Reeves1990; Shaman et al. 2002; Day 2001; Barker et al. 2003).

Surveillance for viruses transmitted from wildlife H_Rs to domestic poultry and livestock, such as avian influenza A, subtypes of which infect and cause disease in humans (Kermode-Scott 2004; Fouchier et al. 2004), is conducted through the USDA. Additionally, the USDA conducts mandated surveillance

for zoonotic infections of livestock, such as BSE, anthrax, and bovine tuberculosis (TB) (Anonymous 2004b; Myers et al. 2003).

Regional activities monitoring wildlife diseases, especially among game animals, such as white-tailed deer (*Odocoileus virginianus*), exist through cooperative efforts involving research and educational institutions, state fish and game departments, and hunters. A successful example is the Southeastern Cooperative Wildlife Disease Study (SCWDS) maintained at the University of Georgia, where programs collect regional data on wildlife, ectoparasitic and endoparastic infestations, and microbiologic and serologic evidence of past or current infections. Historical collections and independently funded research programs through SCWDS recently led to the rapid elucidation of the natural history of emerging tick-borne zoonoses caused by bacteria in the genera *Ehrlichia* and *Anaplasma* (Davidson et al. 2001; Little et al. 1998; Lockhart et al. 1996, 1997; see the chapter by Paddock and Yabsley, this volume).

Wildlife disease monitoring in Sweden and Northern Europe has existed since the 1940s, relying heavily on the cooperation and interest of hunters in the collection and submission of samples from game animals (Mörner 2002; Mörner et al. 2002). Surveillance for wildlife diseases in the UK and Ireland has included bovine TB maintained by badgers (see the chapter by Palmer, this volume); current plans call for increased surveillance of wildlife, notably birds for WNV, in England and Wales (Griffin et al. 2005; Gormley and Costello 2003; Crook et al. 2002; Duff et al. 2003; see the chapter by Palmer, this volume).

4
Zoonotic Disease Emergences and Targeted Surveys for Infected Wildlife H_Rs

4.1
Short-Term Surveys Following Zoonotic Disease Emergence

Short-term studies of wildlife H_Rs are the most common survey methods employed in response to specific instances of emergence or spread of zoonotic disease. Following an outbreak of human monkeypox in several US states (Centers for Disease Control and Prevention 2003a; see the chapter by Regnery, this volume), local populations of indigenous North American rodents were captured and examined for infection from areas around animal-holding facilities housing African rodents imported for the pet-trade and implicated as the source of monkeypox virus (Cunha 2004; Check 2004). Native American ground squirrels, coincidentally housed in the same buildings with the African rodents and purchased as pets, were implicated as the source of monkeypox virus transmitted to humans (Guarner et al. 2004; see the chapter by Regnery,

this volume). Short-lived studies identifying rabid raccoons were undertaken in Ohio, following the first reported case of raccoon-variant rabies in that state (Stefanak et al. 1999). Testing of trapped and road-killed raccoons helped define the geographic extent of the enzootic area of raccoon rabies in the state in preparation for the deployment of an oral rabies vaccine (ORV) in an effort to prevent the westward expansion of epizootic raccoon rabies into Ohio and west to other states (Kemere et al. 2002; Foroutan et al. 2002; APHIS Wildlife Services Factsheet 2002).

4.2
Long-Term Studies Following Zoonotic Disease Emergence

Long-term prospective studies of zoonotic pathogens circulating within wild-life H_Rs are critical to understanding factors mediating irregular increases and declines within animal populations, which can drive the risk of spillover to humans. The varying population dynamics of zoonotic pathogens and their H_Rs are, in some instances, as with rabies virus, driven by pathogen-induced host mortality (Anderson et al. 1981; Childs et al. 2000; Coyne et al. 1989); the risk of rabies virus spillover to domestic animals is closely, but not perfectly, mirrored by the temporal dynamics within the wildlife H_R (Gordon et al. 2004).

Examples of systematic wildlife disease studies that have exceeded several years in duration are few. One ongoing example is the investigations of the population dynamics of rodent H_Rs and SNV and other hantaviruses in the southwestern United States, which were established in the mid-1990s following the 1993 outbreak of HPS. Replicated and coordinated studies among universities in several states, using similar methodologies for population sampling, virological testing, and data management (Mills et al. 1995), have provided a wealth of information critical for unraveling aspects of the transmission and maintenance of hantaviruses (Mills et al. 1999a, 1999b). The knowledge base established by these efforts allowed increasingly elaborate hypotheses developed from field observations to be tested.

The modalities of hantaviral transmission were assessed by application of microsatellite markers to genetically identify familial relationships among individual mice; related male *P. maniculatus* were more likely to be SNV-infected (Root et al. 2004), providing clues to the chain of transmission events contributing to the male bias in hantaviral infection documented by several descriptive studies (Mills et al. 1999a). Ongoing research is providing clues as to the critical H_R population size required to sustain hantavirus transmission and is exploring the phenomenon of SNV disappearance and reemergence in H_R populations (Calisher et al. 2002), possibly through SNV maintenance within refugia of a special nature (Yates et al. 2002). These ongoing studies spanning more than

6 years, have been sufficient to capture occurrences and effects of environmental drivers, such as El Niño Southern Oscillation (ENSO), which occurs at semi-predictable intervals of approximately 5–10 years (Chen et al. 2004a). ENSO is a principal indicator of global climate which modifies local weather patterns; increasing rainfall associated with ENSO is hypothesized to drive a trophic cascade of events (Polis et al. 2000), ultimately leading to increases in local H_R populations and increased risk of HPS (Glass et al. 2002; Hjelle and Glass 2000). Remote sensing and GIS techniques, coupled to a household-based case–control methodology assessing rodent abundance around residences of HPS cases (Childs et al. 1995), predicted where *P. maniculatus* would be more abundant at future case houses. Analyses of annual satellite images to detect local environmental conditions supportive of rodent HR population growth has proven an effective tool for predicting the qualitative level of risk (low, moderate, high) for HPS over a sizable region of the southwestern US (Glass et al. 2006). Educational recommendations and field trials of rodent-proofing methods were incorporated into the long-term investigations (Glass et al. 1997), to provide readily available control measures in anticipation of increased risk of HPS (Childs et al. 1993).

5
Animal-Based Zoonotic Disease Surveillance: A Horse of Another Color

Animal-based surveillance is a process inherently different from human-based surveillance (Table 2). With the exception of surveillance efforts targeting livestock and poultry, run through the Center for Animal Health Surveillance of the USDA (King 1985), no formal sampling methodology exists for estimating animal population sizes at the regional or continental level (see the chapter by Stallknecht, this volume). Wildlife population estimates at the continental scale are few and generally restricted to tractable populations associated with conservation efforts, with the possible exception of national waterfowl surveys (Butler et al. 1995), or national hunter- or road-killed indices of white-tailed deer populations (Hayne1984).

Targeted ecologic studies directed at species that are endangered or threatened have in several instances provided population-based information complementing the objectives of wildlife disease research. The most notable examples involve species that are relatively easy to observe or for which population-based indices exist, such as carcass, nest, or scat counts (Leroy et al. 2004). Where estimates of animal numbers have been enumerated, the impact of fatal zoonotic viruses indicate certain wildlife species could serve as sentinels for monitoring viral activity; species conservation activities can

Table 2 Key differences in the terms "passive surveillance" and "active surveillance" and methods of data collection as used and defined by veterinary and human health professionals

Surveillance system or manner of data collection	Veterinary health[a]	Human public health[b]
Passive	"The passive collection of data involves the reporting of clinical or subclinical suspect cases to the health authorities by health care professionals at their discretion."	"A passive surveillance system is one in which a health jurisdiction receives disease reports from physicians, laboratories, or other individuals or institutions as mandated by state law."
Key characteristics	Voluntary	Legally mandated, systematically collected within specified time frames, voluntarily reported to CDC
	Not population-based	Specified by state and federal officials within the National Notifiable Disease Surveillance System (NNDSS). Population-based by virtue of the US Census
Active	"An active collection of data for any monitoring and surveillance system (MOSS) is the systematic collection or regular recording of cases of a designated disease or group of diseases for a specific goal of monitoring or surveillance."	"In contrast, an active surveillance system is established when a health department regularly contacts reporting sources (e.g., once per week) to elicit reports, including negative reports (no cases)."
Key characteristics	Not necessarily mandated by law Population-based	Not necessarily mandated by law Population-based Collects negative data

[a] Quoted from Salman (2003)
[b] Quoted from Birkhead and Maylahn (2000)

provide leverage to any additional surveillance investment (see the chapter by Daszak et al., this volume). Examples include great apes killed by Ebola virus (Leroy et al. 2004; Walsh et al. 2003; see the chapters by Gonzales et al., this volume), and rabies induced mortality among African wild dogs (Kat et al. 1995; Gascoyne et al. 1993b; Burrows 1992), and Ethiopian (Whitby et al. 1997; Sillero-Zubiri et al. 1996) and Artic wolves (Ballard and Krausman 1997; Weiler

et al. 1995; Chapman 1978). For other wildlife, the lack of population estimates precludes estimation of basic epidemiologic parameters, including rates such as incidence or mortality; these capabilities are beyond those of any existing surveillance system for a wildlife zoonosis.

Novel animal-based surveillance and control programs are being planned for zoonotic agents, such as BSE, SARS-CoV and influenza A subtypes which have realized or potential pandemic importance to humans or domestic animals (http://www.who.int/mediacentre/news/new/2006/nw02/en). The ultimate H_Rs for these agents includes domestic and wild animal species. For example, the H_Rs for influenza A subtype H5NI are among wild waterfowl and shorebirds, and perhaps other avian types, although, domestic chickens and other poultry serve as both the first secondary host (H_{S1}) or intermediate host (H_I)(see the chapter by Childs et al., this volume, for description of terms) and can develop as a novel H_R (see the chapter by Webby et al., this volume). Experts within the WHO and elsewhere, acknowledge a need ". . . to get rid of the natural reservoir of H5N1, but we need to do it safely" (quote attributed to Klaus Stohr, project leader of WHO's global influenza program; cited in Abbott and Pearson [2004]). However, even rough plans of how such an immense undertaking will be designed and integrated into the countries of greatest significance in Asia are lacking.

5.1
Obstacles to Animal-Based Surveillance

Even when infection within an animal H_R or H_S is relatively detectable, national surveillance programs for monitoring morbidity and mortality among wildlife and establishing the etiologic cause of infection through a system of diagnostic laboratories are rare (see the chapter by Stallknecht, this volume). If the zoonotic agent is a pathogen of domestic livestock, formal surveillance can target abattoirs or production facilities where food animals are processed, as is the major emphasis of BSE surveillance conducted both in the United States by the USDA (Kellar and Lees 2003; Anonymous 2004b) and within European countries (La et al. 2004). Among wildlife, animal rabies is the only disease within the NNDSS for which time-series data of reasonable duration, more than 50 years, quantity and quality has been systematically collected from all US states and territories (Childs et al. 2002).

Animal-based surveillance for pathogens causing emerging zoonotic diseases in humans is often hampered by the lack of clinical signs in infected individuals of the H_R (Table 2). Where zoonotic viruses cause fatal disease among wildlife and domestic animal H_Rs, H_Ss, or H_Is, tracking the spread of these agents is a simpler matter, although this remains a formidable challenge within countries lacking basic surveillance infrastructure. Tracking the spread of influenza A

subtype H5N1 of domestic chickens, ducks, and some wild waterfowl in south-eastern Asia (Chen et al. 2004b; Li et al. 2004; Lu et al. 2003; see the chapter by Webby et al., this volume), WNV in North America (Garvin et al. 2004; Guptill et al. 2003; Walsh et al. 2003; Larkin 2000), Ebola virus in central Africa (Leroy et al. 2004, 2005; Walsh et al. 2003; see the chapter by Gonzales et al., this volume), and rabies virus in North America, Europe, and southern Africa (Sabeta et al. 2003; Childs et al. 2000; Gordon et al. 2004; see the chapter by Nel and Rupprecht, this volume) has been facilitated by the mortality these viruses cause in wildlife and domestic species.

6
Benefits of Animal-Based Surveillance: Lessons from a Model System for Rabies

National surveillance for animal rabies is a model public health activity. As the CDC is charged with promotion of human health and disease prevention and control, animal-based rabies surveillance data are well integrated into national, state, and local human and veterinary public health programs (Childs et al. 2002). A brief examination of the objectives, types of data collected, and the practical use of the information disseminated through the national animal rabies surveillance program is illustrative of the potential benefits accrued from an animal-based surveillance system.

Surveillance for animal rabies collects information on the current status and level of rabies activity among wildlife and domestic animals at the county level within individual states. Monthly counts of rabid animals, and from some states the tally of negative results, designated to the level of animal species or taxonomic group, are submitted to the CDC (Krebs et al. 2004).

Surveillance information is analyzed, summarized, and disseminated back to the data providers in a timely manner through publications (Krebs et al. 2004) and additional communications, which are updated annually, such as The Compendium of Animal Rabies Prevention and Control (Centers for Disease Control 2005). Surveillance data on animal rabies are sufficiently detailed and accurate to allow human and veterinary health professionals to anticipate levels of rabies activity at the county or regional level, permitting some future planning for preventative activities, including procurement of human vaccine and human rabies immunoglobulin (HRIG) for postexposure treatment of potentially exposed persons (Centers for Disease Control and Prevention 2004b; Advisory Committee on Immunization Practices 1999); increasing vaccination levels of dogs and cats; and initiation of targeted control efforts to vaccinate wildlife using ORV (Krebs et al. 2004; Kemere et al. 2002).

Several species of terrestrial carnivore, raccoons (*Procyon lotor*), red foxes (*Vulpes vulpes*), and striped skunks (*Mephitis mephitis*) serve as H_Rs for particular

genetic variants of rabies circulating in the continental US; numerous rabies virus variants are also associated with different species of bats (Messenger et al. 2003). Rabies virus variants can be differentiated by limited sequence analysis or monoclonal antibody methods (Smith et al. 1995) and the enzootic area where rabies variants overlap the geographic range of their terrestrial mammalian hosts can be reasonably determined (Childs et al. 2002). Time-series surveillance data on wildlife rabies, analyzed by statistical algorithms defining and demarcating intervals of increased (epizootic) or diminished (interepizootic or enzootic) rabies activity, provide results concordant with predictions and outcomes based on numerical solutions to mathematical models of the population dynamics of rabies virus within a single H_R species (Childs et al. 2000; Anderson et al. 1981; Coyne et al. 1989). Time-series analyses have defined the temporal dynamics of disease in a wildlife H_R (Childs et al. 2000; Guerra et al. 2003) and demonstrated the close association of this relatively predictable process to the risk of rabies spillover to domestic animals (Gordon et al. 2004). Furthermore, these data can inform epidemiologic simulations and models predicting epizootic rabies spread (Russell et al. 2004, 2005), and have been modified to forecast the savings accrued by preventing rabies spread through the application of ORV (Gordon et al. 2005).

Additionally, local data have provided the raw material to explore formal methodologies for demonstrating and assessing the impact of long-distance translocations (LDTs) of infected animals on the rate and pattern of rabies spread in heterogeneous environments (Smith et al. 2005). The availability of remotely sensed or digitized maps, coupled with GIS-assisted partitioning of landscapes into habitats of varying quality, allow explorations of the impact of landscape heterogeneity on the characteristics of epizootics and the pattern of epizootic wavefront spread (Jones et al. 2003; Smith et al. 2005). Such analyses have been used to assess where remedial prevention activities should be focused when breaches in ORV barriers occur and where active surveillance might be considered as a complement to passive data collection where fine-scale knowledge of the presence of rabies is needed to guide interventions (Russell et al. 2005).

7
Generic and Specific Limitations to Animal-Based Surveillance: Lessons from Rabies

However, rabies surveillance reveals several inherent difficulties to conducting any form of wildlife-based disease surveillance and offers a sobering view of the hurdles to be overcome when considering such programs in other locations for other diseases. Animal rabies surveillance was implemented to provide humans with a measure of rabies risk in their communities and, other than relative

species counts over years, there is no information on the incidence or impact of rabies in any animal community. The nature of the human–animal interactions required by an animal-based surveillance system provides a distorted image of rabies as a community process (Fig. 1).
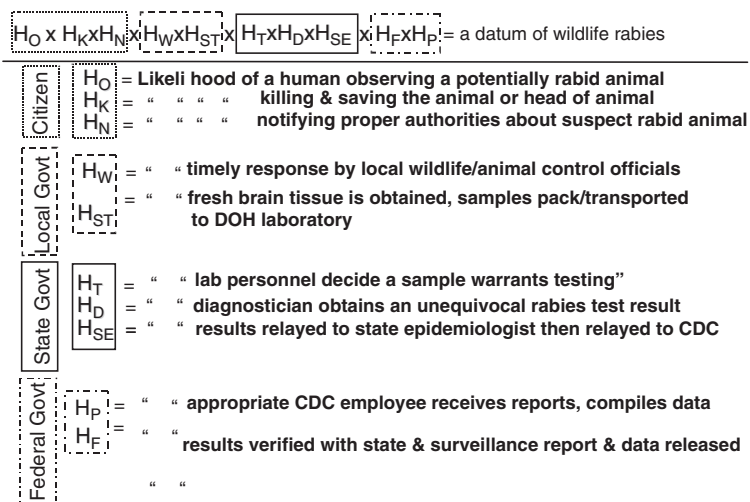
Biases inherent to data collected by animal rabies surveillance at the national level stem from the requirement of human participation in each step of the process culminating in a rabies diagnosis in an animal (Fig. 1a; Gordon et al. 2005). The impact of human demography, measured as absolute population size per county, on the surveillance process is sufficient to account for fully 70% of the variation in total animal specimens tested for rabies (Fig. 1b; Childs et al. 2007). Total county expenditure is almost as strong a predictor, accounting for 65% of the variation in total animal tests performed.

Pathobiologic features of rabies, human behavior, and the expense associated with diagnostic testing of specimens skew the types of animals observed, harvested, and tested for rabies. Medium-to-large-sized mammals are more likely to be observed by humans and reported to wildlife control officials. In a typical surveillance year, small terrestrial mammals, predominantly rodents, but some insectivores, weighing less than 1 kg account for less than 0.5% of the total animals tested and diagnosed as rabid (Real and Childs 2006), although small mammals provide the greatest species diversity and the overwhelming abundance of individuals and biomass of many mammalian communities (Bourliere 1975). Rodents are fully susceptible to rabies infection and are capable of transmitting the virus to other species (Childs et al. 1997; Winkler et al. 1972); in some countries, rodents have been implicated in natural maintenance cycles of the virus (Summa et al. 1987; Verlinde et al. 1975).

A major sampling bias occurs at the level of the rabies diagnostic laboratory where, in an effort to save money on personnel time and diagnostic reagents, rabies testing is typically restricted to specimens from animals directly involved

Fig. 1a, b (Continued) data integrating test outcome with information on the type of animal and date and place of origin produced at the state level and submitted to CDC. **b** Although data on each of the events partitioned in (**a**) are unavailable, a surrogate value of population size is used to measure the importance of human interaction in generating surveillance data, assuming that increasing numbers of humans increase the likelihood of many of the events in (**a**) occurring. There is a strong association between the absolute numbers of humans resident in the smallest surveillance unit (US Census figures), a county within a state, and the total numbers of animals tested for rabies from that surveillance unit. The relationship is a power function in which human population size accounts for 70% of the variance in median total tests conducted for rabies conducted over a decade from 713 counties in a region affected by the raccoon variant of rabies virus. (Adapted from Childs et al. 2006)
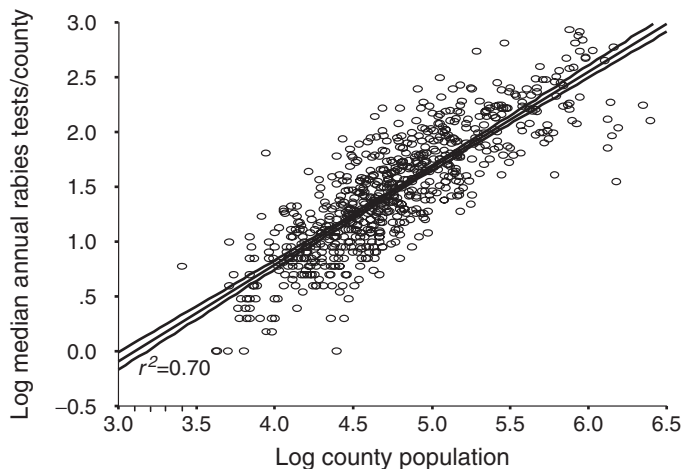
a)

$H_O \times H_K \times H_N \times H_W \times H_{ST} \times H_T \times H_D \times H_{SE} \times H_F \times H_P$ = a datum of wildlife rabies

Citizen		
H_O	=	**Likeli hood of a human observing a potentially rabid animal**
H_K	= " " "	**killing & saving the animal or head of animal**
H_N	= " " "	**notifying proper authorities about suspect rabid animal**

Local Govt		
H_W	= " "	**timely response by local wildlife/animal control officials**
H_{ST}	= " "	**fresh brain tissue is obtained, samples pack/transported to DOH laboratory**

State Govt		
H_T	= " "	**lab personnel decide a sample warrants testing"**
H_D	= " "	**diagnostician obtains an unequivocal rabies test result**
H_{SE}	= " "	**results relayed to state epidemiologist then relayed to CDC**

Federal Govt		
H_P	= " "	**appropriate CDC employee receives reports, compiles data**
H_F	= " "	**results verified with state & surveillance report & data released**
	" "	

b)

Fig. 1a, b The process of wildlife- and animal-based surveillance is interactive, involving multiple, and frequently independent, interactions between humans and wildlife to generate a single datum captured. Panel **a** depicts some examples of these interactions, which could be assigned a probability if information were available, between private citizens and local and federal agencies in the route to generating a datum on animal rabies. Each process involves some interaction with an animal, a tissue sample taken from the animal, test material derived from the sample, an outcome derived from the sample at the diagnostic laboratory, and the

in the potential exposure of humans or domestic animals to rabies virus (Fig. 1a); other specimens go untested (Torrence et al. 1992; Wilson et al. 1997). Many of these limitations and biases will be generic problems confronting any effort to monitor wildlife species anywhere in the world.

8
From Detection to Intervention: Human-Based Approaches to Zoonotic Disease Control

The most widespread approaches to zoonotic disease control completely ignore the ecology of wildlife and pathogen maintenance and transmission and, therefore, the potential for interrupting pathogen transmission prior to human spillover. Instead, prevention and control strategies focus on defensive measures for the human H_S.

National institutions charged with strategic planning for emerging diseases or intentional releases of zoonotic agents have emphasized improving diagnostic capabilities for detecting human infections, modifying the immune status of human or domestic animals through vaccines, producing better antiviral or antibacterial drugs, and enhancing human-based surveillance as an early warning system (Fauchi 2002; Centers for Disease Control and Prevention 1998). With the possible exception of extensive human vaccination, each of these approaches target post-spillover events and none of these avenues of research will have the slightest impact on reducing the risk of additional emergence of viruses or other pathogens from wildlife.

9
Limitations to Human-Based Intervention Programs for Prevention of Zoonotic Diseases

The current fixation on human vaccines, human diagnostics, human drugs, and human-based surveillance is the legacy of past successes. Landmark achievements for zoonotic disease prevention include vaccines for yellow fever and rabies, and other vaccines of human or veterinary importance exist, or are being developed, for tick-borne encephalitis, Rift-Valley fever, arboviral encephalitides, SARS, Ebola hemorrhagic fever, HPS, and many others (Chang et al. 2004; Cox et al. 2004; Lau 2004; Custer et al. 2003; Matsuoka et al. 2003; Nalca et al. 2003; Warfield et al. 2003; Hjelle 2002; Tomori 2002; Tesh et al. 2002; Stephenson 2001; Monath et al. 2001; Huang et al. 2004). New antiviral drugs can be designed, created, and screened with far better efficiency than at

any time in the past and novel candidates and methodologies for improving the delivery of drugs to infected cells are in development (Oxford et al. 2005; Duzgunes et al. 2005; Wu et al. 2005; Pastor-Anglada et al. 2005).

Additionally, traditional measures of case isolation, contact-tracing, and quarantine of exposed persons, banning of public gatherings, or curtailing individual access to international travel have proved highly effective in controlling the spread of zoonotic diseases with pandemic potential, as with SARS (Zhong 2004; Anderson et al. 2004; Speakman et al. 2003; see the chapter by Wang and Eaton, this volume) (Fig. 2). But SARS-CoV is not influenza A. Methods relying on increasing social distance are unlikely to prevent the spread of human-adapted pandemic influenza A (Fraser et al. 2004; Mills et al. 2004). Aerosol transmissibility of influenza virus in the subclinical patient precedes clinical signs by 24 h (Mills et al. 2004; Fraser et al. 2004), unlike the coincidence of clinical disease with the onset of infectiousness with SARS-CoV (Anderson et al. 2004). Influenza A vaccine production capacity and antiviral medication stockpiles to combat influenza spread are insufficient even in wealthy developed countries (Mills et al. 2004). Can we continue to prepare and respond to such pathogens by strictly defensive measures aimed at the human H_S?

So given the proven record of achievement of a medical or technological approach to defending humans from invasion by infectious organisms, is there much to be gained by examining processes, antecedent to human spillover, for potential vulnerabilities and as intervention targets, as a complement to ongoing efforts to improve human-based disease prevention activities? The answer is yes, but a qualified yes. Simply saying we need such systems glosses over the myriad of obstacles in developing programs. Designing and implementing wildlife-based surveillance and targeted interventions will not be achieved in the short term and establishing the infrastructure to support these efforts would be difficult and expensive (see the chapter by Merianos, this volume).

10
From Detection to Intervention: Targets for Wildlife or Domestic Animal Control

The maintenance and transmission cycles of zoonotic viruses within wildlife H_Rs offer many of the same targets for control as do human-based interventions, with the notable exception that population culling can be exploited for control of animal reservoirs, intermediate host populations and arthropod vector species. The ultimate prevention strategy for zoonotic agents affecting humans is to abrogate or greatly reduce cross-species transmission by disrupting transmission and maintenance cycles of zoonotic viruses within the H_R.
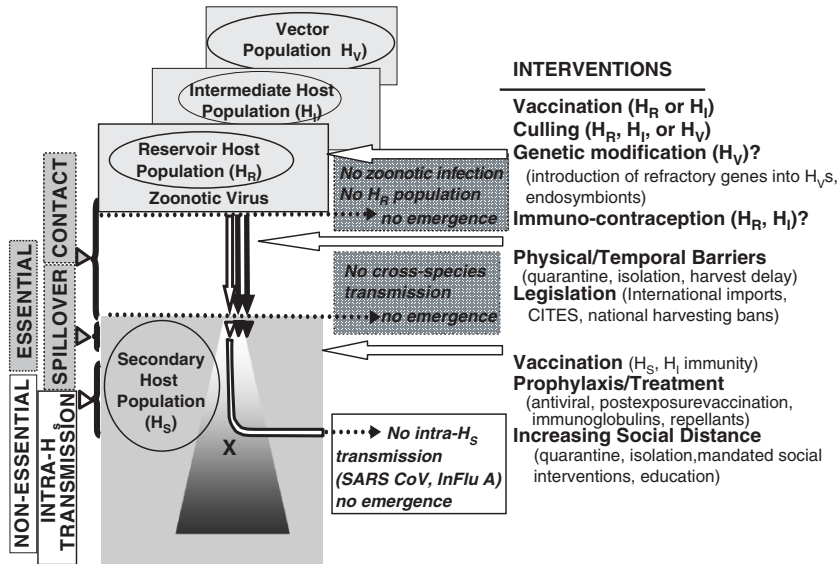
Fig. 2 The targets and types of intervention tools available for preventing spill-over of zoonotic pathogens to humans, or for mitigating the impact or spread of zoonotic disease should spillover occur. The *open arrows* leading from the list of intervention types indicate where the intervention acts, either directly at the population level of the reservoir host population (H_R), vector population (H_V), intermediate vertebrate host population (H_I), or at the secondary host population (H_S) assumed to be humans. Other targets are the processes or rates associated with spillover, such as reducing contact between infected H_R and susceptible H_S or between infected H_R and susceptible H_R, or infected H_S and susceptible H_S. The methods employed to reduce host populations are largely restricted to culling (vertebrates) or insecticides (arthropods). Vaccination of host populations is in use for some zoonotic viruses (rabies, influenza A, VEE, etc.) and new vaccines are in development (see Table 3). Animal quarantine, isolation of animals exposed to a pathogen, and legal bans to trade in animals or animal products originating from countries with enzootic disease act to increase social distance and decrease the likelihood of contacts between infected and susceptible hosts. Immunocontraception of H_Rs to reduce population size or genetic modification of H_Vs to render vector populations refractory to infection may play a role in prevention in the future. Human vaccination, treatment, and the prophylactic use of drugs are defensive measures that may prevent or reduce spillover and post-spillover spread, but will not reduce the likelihood of contact between infected H_R and individual humans. (Modified from Childs 2004)

However, rarely has the full force of human scientific creativity and funding been directed at understanding and interrupting vulnerable infectious processes prerequisite to, but intermediate from, the immediate circumstances leading to human infection.

10.1
Culling of Vectors and Wildlife

The most widespread approach to zoonosis control is the culling or killing of individuals of H_Rs, H_Vs, or H_Is, either through selected culling (largely restricted to domestic animals) or indiscriminate population reduction (Wobeser 2002). The most common example of culling is the use of insecticides to control H_V populations and nuisance populations of mosquitoes (Thier 2001; Leprince and Lane 1996; Mount et al. 1996); however, issues related to human and environmental health have limited enthusiasm for this type of control in many circumstances. Culling of wildlife H_R populations has been adopted, or is planned, to curtail transmission of several viral and bacterial zoonotic pathogens to humans or domesticated livestock, although the record of population control as an effective prevention strategy limiting spillover is mixed (Wobeser 2002; see the chapter by Palmer, this volume).

Targeted reduction of specific H_R populations for control of rabies virus variants has been employed in Europe and North America. On both continents, programs have targeted red foxes (Muller 1971; Debbie1991) and in North America raccoon and skunk populations have been targeted (Rosatte et al. 1986; Debbie1991). Efforts are ongoing in Central and South America to reduce vampire bat populations in an effort to curtail the enormous economic loses sustained from vampire-bat transmitted rabies to cattle. Anticoagulants applied topically or systemically by direct inoculation into livestock are the major methods of vampire bat control (Crespo et al. 1979; Fornes et al. 1974; Thompson et al. 1972). However, wildlife culling to control rabies has been deemed largely unsuccessful or unnecessary given the intensive use of ORV to vaccinate susceptible H_Rs (Centers for Disease Control and Prevention 2004b; Macinnes et al. 2001; Aubert 1999b; Brochier et al. 1995; Slate et al. 2005). However, mathematical modeling of different control strategies frequently identifies a combination of vaccination and targeted culling as the optimal strategy for rabies control (Smith and Wilkinson 2003; Anderson et al. 1981).

Culling has recently been halted as a control measure for badgers serving as H_Rs for bovine TB in England (Roper 2003; Gormley and Costello 2003; see the chapter by Palmer, this volume), although in Ireland data suggest badger culling is an effective measure in reducing the incidence of TB in cattle herds (Griffin et al. 2005). The removal of some 20,000 badgers in England from 1975 to 1997

failed to curb bovine TB spread among cattle (Delahay et al. 2003). Vaccination of badgers against TB is now being investigated as a part of an integrated control program that includes targeting specific sites for control and different herd management practices for high-risk regions (White and Benhin 2004).

China initiated culling of live captured and breeding stocks of several species of carnivores, the masked palm civet (*Paguma larvata*), the raccoon dog (*Nyctereutes procyonoides*), and the Chinese ferret badger (*Melogale moschata*), implicated in the transmission of SARS-CoV to humans (Watts 2004; Zhong 2004). The WHO questioned the appropriateness of culling wildlife species (Parry 2004) and it is now appears that wild carnivores are not the actual H_R for SARS-CoV. Current information suggests that bats of the genus *Rhinolophus* are the H_R for ancestral coronaviruses giving rise to SARS-CoV capable of infecting wild carnivores and humans (Li et al. 2005; see the chapter by Wang and Eaton, this volume). Irrespective of the culling of farm-raised animals, the enormous illegal trade in wildlife will continue to stock the wet markets of China, Vietnam, and other southeastern Asian countries, with meat and other animal products from wild carnivores and other wildlife species prized for their culinary and medicinal properties (Bell et al. 2004; Yiming and Dianmo 1998).

10.2
Domestic Livestock and Poultry Culling for Zoonotic Disease Control

Control of emerging zoonotic agents circulating among domestic poultry, livestock, and companion animals is often more finely targeted at specific infected subpopulations or demographic cohorts than methods applied to wildlife. For example, the mass elimination of seropositive dogs in Brazil has been used in control programs for zoonotic visceral leishmaniasis; although evidence suggests dog control has failed to reduce the number of human leishmaniasis cases (Moreira et al. 2004).

Different culling strategies have been used for the control of BSE. Herd culling involves destroying entire herds of cattle from which an index case of BSE originated; birth cohort culling targets the subpopulation of cattle born during a specific interval of time and considered at greatest risk for having acquired BSE before the prohibition of feed containing cattle-derived offal; maternal culling destroys offspring borne to high-risk cows as the risk of vertical transmission of BSE is approximately 10% (Anonymous 2000); a final subpopulation considered to be at high risk, but difficult to identify operationally, is the feeding cohort. In the UK selected culling of birth cohorts (years 1989–1993) and maternal cohorts have been the major methods employed (Donnelly et al. 1997), involving destruction of more than 80,000 animals (Anonymous 2000). France, Portugal, and Ireland have employed mainly herd culling, with

some maternal culling in France, with the destruction of approximately 10,000, 6,000, and 15,000 cattle, respectively (Anonymous, 2000). Additional culling methods may be employed as surveillance data accumulate (Calavas et al. 2004). Switzerland and Belgium have adopted both herd and birth cohort culling, with 2,000 and 1,400 animals destroyed as of 2000, respectively (Heim and Murray 2004; Anonymous 2000).

Culling of domestic poultry is the primary means of control for pathogenic influenza A subtypes, some considered to have pandemic potential as human viruses. Millions of chickens and other poultry were killed in Hong Kong in an attempt to prevent the spread of influenza A subtype H5N1 (Watts 2004a; Tam 2002), and in 2004 over 20 million chickens were killed in eight Southeast Asian nations as the threat of a human pandemic looms (Watts 2004a; Abbott and Pearson, 2004; see the chapters by Merianos and Webby et al., this volume). In April 2004, Canada ordered the killing of 19 million chickens and other poultry to contain an outbreak of influenza H7N3; 1 year earlier, the Netherlands culled 30 million chickens to control an outbreak of a related influenza subtype, H7N7 (Stegeman et al. 2004).

Livestock culling resulting in major economic losses accompanied the outbreak of NiV affecting swine and humans in Malaysia in 1997 (Stegeman et al. 2004; Paton et al.1999; see the chapter by Merianos, this volume), where more than 1 million swine were culled (Lam and Chua 2002; Uppal 2000). Nipah virus has since re-emerged in Malaysia, precipitating new rounds of culling (Ahmad 2000). Export bans and culling have enormous economic impacts and emerging zoonotic viruses, such as Influenza H5N1, NiV, WNV, and SARS-CoV, confront the stake holders in a global economy with unprecedented new risks (James 2005; von Overbeck 2003).

10.3
Alternatives to Culling as Population Control

In the future, population reduction by immune contraceptive programs could be used among certain populations of H_Rs or H_Is (Ferro 2002; Miller and Killian 2002; Lurz et al. 2002) (Fig. 2). There are ethical and practical limits as to how culling is, and will be, employed, as populations of game species and other wildlife species considered ecologically and esthetically important will be off limits, even if the species serves as H_R for a zoonotic pathogen. Exceptions occur where species overabundance becomes a nuisance problem or threatens vulnerable environments, as with white-tailed deer (*Odocoileus virgineanus*) in suburban environments or feral horses on barrier islands or federally controlled lands. In such instances, immune contraception may become the population reduction method of choice (Kirkpatrick et al. 1997). Where critical

species within a community become environmentally destructive when over-abundant, as with elephants within the confines of protected game reserves, controlled culling through hunting could generate income for indigenous peoples, but plans to use immune contraception may present a more acceptable choice (Fayrer-Hosken et al. 1999; Delsink et al. 2002).

10.4
Wildlife Vaccination

The second major approach to zoonotic pathogen control is through vaccination of individuals in the target H_R or H_I populations. Wildlife vaccination is currently limited to few species, although new vaccines are under development (Table 3).

Japanese encephalitis virus (JEV) transmission to humans often requires mosquito vectors which initially obtain a viremic bloodmeal from a swine H_I, alternatively referred to as an amplifying host (Daniels et al. 2002); vaccination of domestic swine to interrupt JEV transmission has been attempted (Daniels et al. 2002; Ueba et al. 1978). Similarly, vaccines for chickens serving as the H_R of influenza A virus subtypes are being employed to remove the intermediary avian host most closely associated with virus transmission to humans (Lee et al. 2004; Ellis et al. 2004b). Intermediate or amplifying vertebrate H_{S1}s, once infected by contact with a H_R, can directly transmit zoonotic viruses to the humans H_{S2}, as occurred with HeV and NiV transmission from pteropid bats initially to horses and swine (Hooper et al. 1998; Selvey et al. 1995; Field et al. 2001; Uppal 2000; see the chapters by Daniels et al. and Field et al., this volume) (Fig. 2). However, the wildlife vaccine with the widest distribution and greatest proven effectiveness is ORV for red foxes and raccoons.

The ORV most commonly in use for rabies control targeting wild carnivores is a recombinant vaccinia virus vaccine expressing the rabies virus glycoprotein gene (V-RG) (Rupprecht et al. 1986 1988); ORV was the first live-recombinant vaccine to be released in the field (Hanlon et al. 1998). The vaccine is distributed in plastic sachets, often covered with a polymer containing additives designed to preferentially attract the target H_R (Linhart et al. 1997, 2002), although nontarget species find these vaccine-laden baits attractive (Olson and Werner 1999).

Millions of ORV doses have been delivered to control red fox rabies in Europe and raccoon rabies in the United States (Aubert 1999a, 1999b; Hanlon and Rupprecht 1998; Slate et al. 2005); ORV has eliminated or reduced red fox rabies in many countries in western Europe (Hanlon and Rupprecht 1998; Aubert 1999b). In the United States, deployment of ORV to reduce enzootic levels of rabies, such as gray fox-associated rabies in Texas (Steelman et al. 2000), or to develop immune barriers to the spread of raccoon variant rabies and coyote/dog variant rabies, in Ohio, West Virginia, and Pennsylvania (the Ohio barrier), and in Texas, respectively (Foroutan et al. 2002; Farry et al. 1998; Slate et al. 2005),

Table 3 Examples of current, planned, or extraordinary interventions by vaccines targeting zoonotic viruses and bacteria among different classes of wildlife or domestic animal hosts

Type of host targeted	Specific example	Vaccine type	Achieved or desired purpose
Reservoir host (H_R)	Oral rabies vaccine (ORV) for red fox, raccoon, coyote, gray foxes[a-d]	Recombinant live vaccinia virus containing rabies glycoprotein gene (V-RG)	Eliminated substantial areas of enzootic red fox rabies in Europe Established an ORV barrier in Ohio to halt westward spread of raccoon-variant rabies virus
	Oral or parenteral vaccination of badgers (*Meles meles*) for TB[e]	Live vaccine, *M. bovis* BCG is main contender	Reduce transmission of TB from a sylvatic badger H_R to cattle
	Oral or parenteral vaccination of *Peromyscus leucopus* for *Borrelia burgdorferi*[f, g]	Recombinant protein A (OspA) from *B. burgdorferi* in *Escherichia coli* and other vectors for oral vaccination of mice	Reduce spirochetal load and prevalence in nymphal ticks to reduce human and domestic animal risk of Lyme disease
	Oral plague vaccine for prairie dogs[h]	Recombinant raccoonpox virus with F1 gene of *Yersinia pestis*	Eliminate plague foci by immunizing H_R among ground dwelling sciurids
Intermediate (H_I) or secondary host (H_S)	Rabies vaccine for domestic animals dogs, cats, ferrets[i]	Killed whole virus	Eliminate the domestic dog as the principal H_R for rabies virus throughout developing world Reduce human exposure to wildlife variants of rabies virus transmitted from a wildlife H_R to a companion animal (H_{S1}) and then to humans (H_{S2})
	Influenza A for chickens, domestic ducks[j, k]	Killed whole virus; recombinant virus vaccine using a Newcastle disease virus with inserted hemagglutinin (HA) gene from avian influenza virus	Prevent emergence and spread of potential pandemic influenza subtypes such as H5N1; prevent domestic poultry mortality from highly pathogenic influenza A viruses transmitted from waterfowl H_R

(*Continued*)

Table 3 Examples of current, planned, or extraordinary interventions by vaccines targeting zoonotic viruses and bacteria among different classes of wildlife or domestic animal hosts—cont'd.

Type of host targeted	Specific example	Vaccine type	Achieved or desired purpose
	Swine vaccinated for JEV[l, m]	Live attenuated Japanese encephalitis virus (JEV); Recombinant vaccine of pseudorabies virus (PRV) expressing NS1 protein of JEV	Prevent human disease from JEV infecting amplifying, intermediate, or secondary host in swine; prevent swine disease caused by JEV
	Horses, other livestock vaccinated for WNV, VEE, WEE, and EEE[n-p]	Inactivated mice brain-derived; live attenuated TC-83; multivalent inactivated VEE, EEE, and WEE viruses	Prevent veterinary losses and remove a H_I for transmission of zoonotic viruses to humans
Secondary host (H_S)	Distemper virus and rabies virus for African wild dog[q,r]	Live attenuated distemper virus and killed distemper and rabies virus vaccines	Protect endangered species from viral diseases introduced by humans through their domestic pets
	Plague vaccine for black-footed ferrets[s]	Recombinant raccoonpox virus with F1 gene of *Yersinia pestis*	Protect endangered and reintroduced species from zoonotic diseases maintained by prairie dog H_R populations
	Whooping cranes vaccinated for EEE[t]	Inactivated EEE virus	Protect endangered species from viral diseases

H_R reservoir host; H_S secondary host; H_I intermediate host

[a-d] Steelman et al. 2000; Fearneyhough et al. 1998; Roscoe et al. 1998; Brochier et al. 1996
[e] Gormley and Costello 2003
[f, g] Luke et al. 1997; Tsao et al. 2004
[h] Mencher et al. 2004
[i] Jenkins et al. 2004
[j, k] Ellis et al. 2004b; Swayne et al. 2003
[l, m] Xu et al. 2004; Ueba et al. 1978
[n-p] Weaver et al. 2004; Minke et al. 2004; Turell et al. 1999
[q, r] Gascoyne et al. 1993a; Van Heerden et al. 2002
[s] Rocke et al. 2004
[t] Olsen et al. 1997

have established zones where herd immunity is sufficiently high that rabies virus transmission is interrupted.

The Ohio barrier was effective in preventing or reducing raccoon rabies cases west of the vaccination border to a sporadic few, but after 6–7 years of success, a serious breach of the Ohio barrier, 11 km west of the vaccine zone, sparked what appears to be a new epizootic focus (Russell et al. 2005; Anonymous.2004a). Rapid and extensive remedial vaccination was employed and will be essential to contain this new focus from rapidly expanding into a full-blown epizootic (Russell et al. 2005).This long-term approach to rabies control is expensive and demands sustained public commitment (Kemere et al. 2002; Foroutan et al. 2002; Gordon et al. 2005); however, the alternative public health activities required should raccoon rabies become enzootic, are perhaps more expensive and also require sustained support (Gordon et al. 2005).

Although the risk for human exposure to vaccinia virus in ORV exists, relatively few instances of human exposure have been reported (Gordon et al. 2005). In the United States, a case of systemic vaccinia occurred in a pregnant women after she was bitten by her pet dog while trying to remove a vaccine sachet from the dog's mouth (Rupprecht et al. 2001).

10.5
Alternatives to Wildlife Vaccination

If ever fully developed and employed, genetic manipulation of H_V populations, or endosymbionts of H_V populations to establish vector refractoriness to infection by a zoonotic pathogen (Scott et al. 2002; Rasgon et al. 2003; Olson et al. 2002; Blair et al. 2000), will theoretically disrupt the transmission chain leading to human infection (Fig. 2). If refractory gene penetrance into a H_V population is complete, a pathogen could suffer extinction; if partial, the effect would be a mirror image to partial vaccine coverage of humans. Both strategies would reduce the probability of contact (see the chapter by Real and Biek, this volume) between an infectious vector and a susceptible human host, one reducing the proportion or number of infected vectors, the other decreasing the number or proportion of susceptible humans. As yet genetic engineering methods have no proven practical value in zoonotic disease control.

10.6
Quarantine, Isolation, and Legislation

Quarantine of animals arriving into a country from foreign countries, where certain diseases are enzootic, has a long history (Gensini et al. 2004). For example, dogs traveling from the United States to the UK were subject to a 6-month

quarantine as part of the UK's rabies prevention law; proof of vaccination and a positive serologic test now suffice (Shaw et al. 2003; Fooks et al. 2002).

National legislation can attempt to reduce within-country movement of species recognized to be H_Rs of zoonotic viruses. Laws pertaining to translocations of rabies H_Rs were passed following the outbreak of a coyote/dog variant of rabies virus in Florida following importation of infected coyotes from Texas (Centers for Disease Control and Prevention 1995). The CDC imposed a ban on the importation of African rodents destined for the US pet trade after the introduction of monkeypox virus and the outbreak of human monkeypox that resulted from transmission of virus through an indigenous North American rodent H_I infected by virus spillover where housed in the same building with the African rodents (Centers for Disease Control 2003b; see the chapter by Regnery, this volume). On the same day as the CDC ban was announced, the Food and Drug Administration initiated regulatory control of interstate transport of prairie dogs in an effort to limit further spread of monkeypox to humans and potentially other susceptible species (see the chapter by Regnery, this volume). In a similar attempt to control the transmission of SARS-CoV, China passed laws prohibiting trade in certain carnivore species following the outbreak of SARS (Zhong 2004).

International laws pertaining to facilitating animal trade, while reducing the risk of exporting diseased animals or animal products, were established by the sanitary and phytosanitary measures, the SPS agreement, coincident with establishment of the World Trade Organization (WTO) in 1994 (Zepeda et al. 2005). The international standards are set by the OIE (OIE 2003). National prohibitions have been instituted by various nations, as exemplified by bans on importing cattle or cattle products from countries where BSE has been detected, listed, and updated on the USDA website (http://www.aphis.usda.gov/lpa/issues/bse/trade/bse_trade_ban_status.html), and bans to importing poultry from countries with enzootic avian influenza (Hall 2004), also listed on the USDA website (http://www.aphis.usda.gov/lpa/issues/ai_us/ai_trade_ban_status.html).

11
Obstacles to Animal-Based Intervention Strategies to Control Zoonotic Disease

11.1
National and International Commitment and Training

Public health professionals have lamented the years of budgetary neglect that have weakened our federal and state infrastructure for conducting surveillance (Bryan et al. 1994). National capacities to collect surveillance data of quality,

which can inform prevention and intervention planning, are not developed over a year or even a decade. Any diminishment in support for human-based surveillance activities is a poor prognostic for implementing novel activities, such as designing and implementing regional programs to study zoonotic pathogens within their wildlife H_Rs, as any of these efforts require the same long-term, continuous support.

The United States has already lost much of its capacity to train scientists whose interests span field biology and laboratory sciences; the calls for increased training is a shrill mantra falling on deaf ears (Institute of Medicine1987, 2003, 1992; Centers for Disease Control and Prevention 1994). Even the emergences of SARS-CoV, HIV, WNV, influenza A subtype H5N1, SNV, and NiV have generated little movement toward training, encouraging, or promoting our professional capacity to explore the intricacies by which such pathogens have evolved and are maintained within their wildlife hosts; but by in large, the national response has been a handful of RO1s and a few training grants in vector-borne diseases and disease ecology. Additionally, there has been little success at cross-training of public health and veterinary professionals at the doctoral level; schools of public health tend to have few veterinarians as full-time faculty members, although at the postdoctoral level programs such as the Epidemiologic Intelligence Service (EIS) at CDC recruit veterinarians with each class.

As of July 2006, a joint and coordinated effort to establish an international surveillance network for the monitoring of animals and humans for zoonotic pathogens, or diseases caused by them, has been announced by the WHO and FASO in collaboration with the OIE (http://www.who.int/mediacentre/news/new/2006/nw02/en). The nature of this effort and details concerning program implementation in countries lacking adequate surveillance infrastructure have yet to be announced; any assessment of such a program designed to provide an early warning system for zoonotic pathogen emergence may be years in coming.

11.2
An International Problem with Equivalency in Veterinary Services

The role of veterinary medicine and veterinary epidemiology in support of the SPS agreement is severely hampered by the inequality of services available among nations (Zepeda et al. 2005). Developing nations face an enormous challenge to develop surveillance and monitoring systems, diagnostic laboratories, and the coordinating infrastructure to assure the validity and quality of the process for any domestic animal and livestock disease, much less emerging zoonoses (Zepeda et al. 2005).

11.3
Whose Problem Is It?

The bias toward human-based surveillance and post-spillover treatment of infected humans is firmly institutionalized, and too often the mission-boundaries of federal agencies preclude coordinated advancement toward any integrative policy. As an example of the problems inherent to different federal agencies' ability to cross traditional boundaries to promote integration of human and veterinary epidemiology is illustrated by a report issued by CDC in *Morbidity and Mortality Weekly Reports* in response to the discovery of BSE in cattle in the United States: "The occurrence of BSE in the United States reinforces the need for physicians to be aware of the clinical features of variant Creutzfeldt-Jakob disease (vCJD) and to arrange for brain autopsies in all decedents with suspected or probable CJD to assess the neuropathology of these patients" (Centers for Disease Control 2004a). Although efforts of the USDA to trace the origins of the infected animal were briefly alluded to in this report, the final recommendation focusing on the human consequences of BSE missed an opportunity to re-emphasize the critical component of veterinary surveillance. Perhaps a report, written in collaboration with the USDA, could have highlighted the means by which BSE surveillance in cattle was to be enhanced.

Research focusing on wildlife H_Rs and the human–wildlife interface is most often funded through year-to-year contracts or limited grants to research institutions, which often lack the infrastructure to preserve data, specimens, and, too often, trained investigators for durations exceeding the length of a grant. In addition, if there are no programs in place to disseminate and use the information generated by disparate research efforts, the results from such studies will remain within the confines of some academic journal, rather than translated into recommendations to prevent or reduce the risk of human disease. Currently, any products or recommendations stemming from such studies have little chance of diffusing into the public health culture (Childs 2006, in press).

The same problem exists with theoretical or mathematical approaches to infectious disease epidemiology. Once mathematical models are developed and validated by use of existing data sets (Russell et al. 2004, 2005; Coyne et al. 1989; Childs et al. 2000), the route to integrating insights gleaned from mathematical approaches into public health practice or specific control activities is unclear. Mathematical modeling as an aid to assist policy decisions has come under severe criticism from practicing veterinary professionals operating on the front lines of disease control. The disparate interpretations of the success of mathematical models in forming an effective control policy for an animal-disease disease outbreak are clearly illustrated by postcrisis reviews of the foot-and-mouth-disease (FMD) outbreak in the UK in 2001. Proponents and authors of

models saw the utility and predictions of models validated (Woolhouse 2003), while some veterinary practitioners and epidemiologists saw little to no benefit in the models as applied in a real-time crisis (Salman 2004). The serious and widening gulf between mathematical modeling and public health practice requires a systematic and purposeful effort on both sides to bridge these differences (Childs 2006, in press). If communications fail, the danger exists for one class of professional to dismiss the efforts of the other as either irrelevant or hopelessly unsophisticated. Whose problem is it?

11.4
Jumping Zoonoses: The Problems of Long-Distance Translocation

National and international long-range translocations of infected animals have played an extensive role in the emergence of viral zoonoses. The phenomenon is so common that it must be considered in conjunction with any control strategy based on legal restrictions to animal movement, bans to trade in wildlife, or when constructing vaccination barriers to limit pathogen spread.

Instances of transcontinental zoonotic viral spread reinforce the significance of LDTs and the recommendation that contingencies for their occurrence should be included in any strategic plan for zoonotic disease control. In 2002, SARS spread around the world in a matter of months, eventually affecting 27 countries on every populated continent (Heymann 2004). In 2003, monkeypox was introduced into the United States along with a shipment of African rodents destined for the pet trade (Cunha 2004; Centers for Disease Control and Prevention 2003a; see the chapter by Regnery, this volume). In 1999, WNV was recorded in the New World for the first time, introduced into New York City by an infected vector or human host (Lanciotti et al. 1999; Kilpatrick et al. 2005). In 1999, Singapore experienced outbreaks of NiV infection among abattoir workers after importing swine from Malaysia (Chew et al. 2000; see the chapter by Field et al., this volume).

The impact of a within-country LDT is well illustrated by the spread of raccoon rabies from a focus identified in the late 1970s along the Virginia–West Virginia border, a focus likely seeded by the translocation of raccoons incubating rabies from an enzootic region of raccoon-associated rabies virus in the southeastern United States (Nettles et al. 1979). The resulting rabies epizootic, as the disease spread into mid-Atlantic and northeastern states, was one of the most extensive and intensive wildlife epizootics recorded (Childs et al. 2001; Hanlon and Rupprecht 1998). A rabid bat stowaway onboard a ship originating from the west coast of the United States was discovered in Hawaii, which is a rabies-free state (Centers for Disease Control and Prevention 1992); other instances of LDTs of rabid bats, some transcontinental, have been reviewed (Constantine 2003). At a finer scale, quantitatively defined instances of raccoon

rabies epizootic foci developing in advance of the epizootic wavefront in Connecticut indicate local translocations influenced the spatial pattern of raccoon rabies spread through that state (Smith et al. 2005). The instance of a rabies virus variant of coyotes/domestic dogs from Texas being introduced into Florida with transported coyotes was described previously (Centers for Disease Control and Prevention 1995).

11.5
Animal Disease Detection and Compensation: How Close Is the Link?

Without adequate compensation for losses accrued through culling or exportation bans, countries attempting to implement animal-based surveillance programs for domestic species, much less wildlife, are likely to encounter problems with voluntary reporting (see the chapter by Merianos, this volume). In some instances, the mere threat of culling, as with swine in areas of Malaysia affected by NiV, can promote epidemic spread as farmers disperse valuable animals to protect their livelihood (Chua 2003; see the chapter by Field et al., this volume). In addition to the enormous economic losses facing individuals whose animals are killed or whose products cannot be sold, the consequences of reporting an outbreak of a new zoonotic disease can be politically unattractive, inviting delays in reporting, as may have occurred with SARS in China (Enserink 2003). Other hidden costs associated with zoonotic disease outbreaks may persist through the burden of surveillance and animal testing (Bradley and Liberski 2004) and the loss to veterinary services (Bennett and Hallam 1998).

11.6
H_R Identification and the Consequences of Getting It Wrong

Before implementation of any control activity, such as culling or vaccination, it is essential that the target species has been accurately and irrefutably identified as the H_R or H_I of importance. Identification of a H_R requires establishing epidemiologic plausibility using definable criteria, such as the temporal and spatial association of putative H_Rs to pathogen spillover, and molecular epidemiologic data linking virus recovered from a H_S to virus circulating among H_Rs (Haydon et al. 2002; Childs 2004). China initiated culling of some species of carnivores and other wildlife intended for human consumption (Watts 2004b), although no SARS-CoV has yet been isolated from wild civets obtained directly from the field (Bell et al. 2004; Guan et al. 2003). In 2005, a putative H_R for coronaviruses ancestral to those isolated and characterized from humans and palm civets was identified among three species of bats of the genus *Rhinolophus* (Li et al. 2005; see the chapter by Wang and Eaton, this volume). Molecular sequencing of SARS-CoV from

bats, palm civets, and humans indicates a common ancestor with rapid positive selection for virulent viral subtypes infecting humans and civets (Song et al. 2005; see the chapter by Wang and Eaton, this volume).

Removing carnivores near the top of ecological food chains can have many unforeseen, and in certain circumstances, potentially disastrous, consequences. By diluting, or severing important links in community processes, culling of top-level carnivores can cause changes in species richness and diversity in communities and increases in prey populations (Ostfeld and Holt 2004; Ostfeld and Keesing 2000), including wild rodent H_Rs of other potentially dangerous zoonotic agents, such as *Borrelia burgdorferi* and the arenaviruses and hantaviruses (LoGiudice et al. 2003; Mills and Childs 1998). Use of methods designed to control one species, such as anticoagulants topically applied to cattle to reduce vampire bat populations, can reduce populations of ecologically important species of bats unintentionally dosing themselves when roosting with vampire bats in confined spaces (Mayen 2003; Martinez-Burnes et al. 1997).

12
Priority Zoonoses: The Case for Enhanced Surveillance for HIV and Influenza A

Contrast the purposeful and highly successful surveillance for animal rabies with activities targeting other known or potential pandemic zoonotic threats with wildlife H_Rs. Subtypes of HIV I and HIV II have emerged independently from primate SIVs on at least eight independent occasions (Hahn et al. 2000; B. Hahn, personal communication to JEC). The number of SIVs described among nonhuman primates in Africa, as of 2004, was approximately 40 (Apetrei et al. 2004). Rapid replication, high mutability, and the elevated rates of recombination of lentiviruses (Zhuang et al. 2002; see the chapter by Holmes and Drummond, this volume) virtually assures that new strains of SIV-HIV will make the journey out of Africa. There appears to be little systematic effort to enhance or build the basic infrastructure in regions of West Africa that could begin to conduct surveillance for new emerging HIVs at the human level or monitor the dynamics of transmission of diverse and genetically chimerical SIVs transmitted among nonhuman primates. Detection of spumaviruses among hunters, although uncommon (~1%), signify the extent to which humans are exposed and infected with diverse primate retroviruses (Wolfe et al. 2004). Although some of the countries of importance are war zones and politically unstable, it is unclear that given an improving situation, surveillance for SIVs spilling over to humans would be regarded as a priority among funding institutions concentrating on HIV vaccine trials.

How are we surveilling and preparing for the next pandemic of influenza? Currently influenza A subtype H5N1 has a limited capacity for cross-vertebrate

class transmission from birds to mammals, although infection is frequently fatal to humans once spillover succeeds (Guan et al. 2004; Sturm-Ramirez et al. 2004; Claas 2000; Tran et al. 2004; see the chapter by Webby et al., this volume). Monitoring avian H5N1 subtypes has been, and continues to be spotty, and largely limited to domestic poultry in which infection is often fatal to chickens and to a lesser extent ducks (Sturm-Ramirez et al. 2004). Recombination of waterfowl influenza viruses within a domestic duck H_R may have been the origin of highly pathogenic subtypes of H5N1 for chickens (Chen et al. 2004b; Tumpey et al. 2003; Guan et al. 1999, 2000), and successive isolates of H5N1 from domestic ducks over time indicate increasing virulence for mammals (Chen et al. 2004b; Guan et al. 2002a, 2002b). Domestic geese may serve a role as an independent H_R for recombinant wild waterfowl-goose influenza H5N1-subtypes and help drive the rapid evolution of highly pathogenic viruses of ducks and chickens (Webster et al. 2002; Chen et al. 2004b).

Yet the ultimate origin of H5N1 and other influenza subtypes, H7N3 and H9N2, occurring among domestic poultry and representing human threats (Campitelli et al. 2004; Choi et al. 2004), is the diverse species of waterfowl, shorebirds, and possibly other avian types in which these various influenza subtypes circulate, often with minimal morbidity (see the chapter by Webby et al., this volume). Surveillance for influenza subtypes among wild waterfowl and other migratory birds is spotty (Krauss et al. 2004; Campitelli et al. 2004; De Marco et al. 2004; Hatchette et al. 2004) and largely restricted to local or regional populations, as occurs in North America and Italy (Krauss et al. 2004; Slemons et al. 2003; Hatchette et al. 2004; Campitelli et al. 2004; De Marco et al. 2004; Ellis et al. 2004a; Stallknecht et al. 1990). The WHO has proposed establishing an Animal Influenza Network to develop and coordinate research on the ecology and molecular biology of animal influenza viruses and integrate these animal-based activities with the global surveillance program for human influenza (Stohr 2003); presumably emphasis will be placed on wild waterfowl and other migratory birds, in addition to domestic poultry and livestock.

13
Conclusions

The uneven standards of surveillance, human- or animal-based, for zoonotic diseases or pathogens maintained by wildlife H_Rs, or even domestic species (Zepeda et al. 2005), is a global problem, readily apparent even within the United States, where investment in public health, including surveillance systems, has a long and enviable history (Thacker 2000).

As of 2006, there appears to be little scientific, social, or political consensus that animal-based surveillance for zoonoses merits investment in international infrastructure. However, this trend may be changing with the recent announcement of the proposal to develop a global early warning system for certain zoonotic agents or disease to be coordinated by the WHO, FAO, and OIE.

Technologically advanced solutions to addressing vector-borne or zoonotic disease transmission, such as genetic manipulation of mosquitoes or immunocontraception aimed at target vertebrate hosts, may involve good science, but whether these approaches represent good public health is highly debatable (Scott et al. 2002; Furguson et al. 2005). Novel schemes of preventing spillover of human pathogens from animal H_Rs can only spring from improving our understanding of the ecological context and biological interactions of pathogen maintenance among H_Rs.

There are no easy solutions to preventing spillover and there is no reason to expect we will ever predict the wheres and whys of new emergences of zoonotic diseases (see the chapters by Cleaveland et al. and Daszak et al., this volume). Inevitably, the major issue arises of where surveillance and research efforts should focus, and there are many areas worthy of consideration. Where the intent exists to improve global surveillance for specific zoonoses of animals, such as influenza A, every possible effort should be made to bring in new ideas and to set a standard of excellence that will encourage additional forays into these areas. As a speculative example, the ability to genetically modify plants to produce viral antigens of potential vaccine quality (Castle and Dalgleish 2005) may provide a tool to reach wild waterfowl that gather in vast numbers in specific staging areas during migration. Could influenza A subtype H5N1 genes be introduced into corn (Tacket et al. 2004; Lamphear et al. 2004), a favorite food of virtually all waterfowl and poultry, and would such a vaccine immunize sufficient numbers of waterfowl to reduce the susceptible population if widely dispersed among migratory staging areas?

Would there be a payoff from large investments to improve surveillance and knowledge of known or potential zoonotic pathogens circulating among wildlife H_R populations? No one knows, but the alternative is to continue to rely on disease detection among sentinel humans. Our ongoing experience with HIV, the looming threat of pandemic influenza, and the myriad of other zoonotic virus emergences in the last few years inform us of the outcomes we can expect by relying on detection of post-spillover events. Efforts to create a knowledge base of the ecology of zoonotic viruses and other pathogens are not without precedent. A glimpse at the enormous achievements in the field and laboratory by scientists connected to the Rockefeller Foundation Virus Program should convince even skeptical readers of the value of an integrated research approach, without adherence to rigid disciplinary boundaries (Theiler and Downs 1973).

Public health judges its great achievements not by damage control, but permanent prevention or, ultimately, eradication of disease threats. When any zoonotic disease or agent shows up in a human, to a great degree, we have failed; in some notorious instances, such as with HIV, it will already be too late to halt a pandemic's spread. We are aware of the consequences and the difficulties in combating pandemic disease, whether it is HIV in humans or Influenza A subtype H5N1 in domestic poultry. As a conservative measure and complementary strategic approach to defensive planning for disease emergence among humans or domestic animals, more resources and research should be invested on offensive approaches whereby potentially vulnerable points in pre-spillover transmission chains involving animal and vector hosts are identified and interventions are designed and assessed.

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