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Surveillance for zoonotic diseases

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Introduction

Zoonotic infections (zoonoses) involve pathogens that are sustained in animal populations but can be transmitted to and cause disease in humans. Zoonoses encompass some of the most ancient communicable diseases, such as rabies and plague, as well as newly recognized emerging infections, such as hantavirus pulmonary syndrome (HPS) and severe acute respiratory syndrome (SARS). A recent review of agents known to infect humans identified 61% (868/1415) as zoonotic in origin; furthermore, 75% (132/175) of human diseases classified as emerging were zoonotic [1]. The global distribution, diversity, clinical severity, and potential use as bioweapons all contribute to the importance of zoonotic pathogens in public health. In this chapter, we describe key host and transmission attributes of zoonotic infections and discuss some strategies for surveillance of zoonotic pathogens. We also discuss ongoing surveillance for rabies in the United States (US) and enhanced surveillance during a monkeypox outbreak.

Overview of zoonotic diseases

Zoonoses constitute a diverse group of viral, bacterial, rickettsial, fungal, parasitic, and prion diseases with a variety of animal reservoirs, including wildlife, livestock, domestic pets, and birds (Table 8.1). Some zoonotic pathogens, such as ra-

bies virus and *Coxiella burnetii* (Q fever), can infect a broad spectrum of animal hosts that may each serve as a source of infection to humans. Other zoonotic pathogens, such as rodent-borne hantaviruses and arenaviruses, are found in a narrower range of reservoir hosts.

Transmission

Many common zoonotic pathogens are excreted in animal feces and fecal-oral transmission (ingestion) plays an important role in foodborne and waterborne infections due to enteric pathogens (e.g., *Escherichia coli*, *Salmonella*; see also Chapter 5). Other diseases caused by zoonotic pathogens are transmitted by inoculation of infected animal tissue or contaminated products (e.g., cutaneous anthrax, rabies); inhalation of small droplets or aerosols (e.g., HPS, Q fever, psittacosis); or by an arthropod vector (e.g., Lyme disease, Rocky Mountain spotted fever; see also Chapter 9). Anthrax, plague, and many other zoonoses have multiple routes of transmission.

For most zoonoses, the pathogen is maintained in one or more animal reservoirs with occasional transmission to humans but without subsequent human-to-human spread (e.g., anthrax, HPS, tularemia, Q fever). However, in some cases, initial zoonotic transmissions are responsible for significant disease epidemics that are sustained by subsequent person-to-person transmission (e.g., pandemic influenza, SARS).

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Table 8.1 Selected important zoonotic diseases.

Organism	Disease	Primary reservoir or host	Transmission to human
Bacterial			
<i>Bacillus anthracis</i>	Anthrax	Livestock	Cutaneous inoculation; ingestion; inhalation
<i>Bartonella henselae/quintana</i>	Cat scratch disease	Cats	Inoculation
<i>Brucella abortus</i> , <i>B. melitensis</i> , <i>B. canis</i> , <i>B. suis</i>	Brucellosis	Cattle, sheep, goats, dogs, swine	Ingestion; inoculation; inhalation
<i>Burkholderia mallei</i>	Glanders	Equine	Inoculation
<i>Chlamydophila psittaci</i>	Psittacosis	Birds	Inhalation
<i>Coxiella burnetii</i>	Q fever	Livestock	Inhalation; ingestion
<i>Escherichia coli</i> O157:H7	Hemolytic uremic syndrome/ <i>E. coli</i> infection	Livestock, wild ruminants	Ingestion
<i>Francisella tularensis</i> (var <i>tularensis</i> and <i>palaeartica</i>)	Tularemia	Rabbits, hares, voles, muskrat, beaver, rodents	Inoculation; inhalation; vector-borne; ingestion
<i>Leptospira interrogans</i> (multiple serovars)	Leptospirosis	Wild and domestic animals	Inoculation; ingestion
<i>Salmonella</i> spp. (multiple serovars)	Salmonellosis	Birds, mammals, reptiles, amphibians	Ingestion
<i>Yersinia pestis</i>	Plague	Rodents	Inoculation; inhalation; vector-borne
Viral			
Arenaviruses	Lymphocytic choriomeningitis virus, Bolivian (Machupo), Brazilian (Sabia), Argentine (Junin), African (Lassa) hemorrhagic fevers	Rodents	Inhalation
Filoviruses	Ebola, Marburg	Unknown (possibly bats)	Inoculation
Hantaviruses (Bunyavirus)	Hantavirus pulmonary syndrome, hemorrhagic fever with renal syndrome, hantaviral illness	Rodents	Inhalation
Influenza A	Avian influenza, swine influenza	Wild birds, swine	Inhalation
Lyssaviruses	Rabies	Dogs, wild carnivores, bats	Inoculation
Orthopoxviruses	Monkeypox, cowpox	Rodents, cattle	Direct contact
Prion			
Prion	New variant Creutzfeldt–Jakob disease in humans; Bovine Spongiform Encephalopathy (BSE, mad cow disease) in cattle	Cattle	Ingestion

Table 8.1 (Continued)

Organism	Disease	Primary reservoir or host	Transmission to human
Protozoal			
<i>Cryptosporidium parvum</i>	Cryptosporidiosis	Wild and domestic animals	Ingestion
<i>Giardia lamblia</i>	Giardiasis	Wild and domestic animals	Ingestion
<i>Toxoplasma gondii</i>	Toxoplasmosis	Felids	Ingestion
Parasitic Nematodes			
<i>Toxocara canis</i> , <i>T. cati</i> , <i>Baylisascaris procyonis</i>	Larval migrans	Dogs, cats, raccoons	Ingestion
<i>Ancylostoma</i> spp., <i>Strongyloides</i> spp.	Cutaneous larval migrans		Inoculation; direct contact
<i>Trichinella</i> spp.	Trichinosis	Swine, rodents, wild carnivores	Ingestion
Fungal			
<i>Microsporium canis</i> , Trichophyton	Dermatophytosis (ringworm)	Mammals, some birds	Direct contact

Host factors

In humans, host factors such as occupation, age, immune status, and recreational activities may facilitate exposure or susceptibility to zoonotic pathogens. For example, occupations that involve handling of animals or animal carcasses such as veterinary work, farming, aviary work, zookeeping, and slaughterhouse work may expose workers to zoonotic pathogens. Persons with immune compromising conditions such as HIV/AIDS may be more susceptible to some zoonotic pathogens [2]. Recreational and peridomestic activities that involve animals or animal product handling such as hunting, cleaning rodent infested buildings, owning exotic pets, visiting petting zoos, and ecotourism, also put people at risk for exposure to zoonotic pathogens.

Environmental factors

Zoonoses are sustained in epizootic and enzootic cycles in reservoir animals. These cycles are influenced by environmental factors such as biome, climate, land use, and the presence and behaviors of appropriate hosts. Interactions between human populations, domestic animals, and wildlife facilitate transmission of infections among these groups in what has been described as a host-pathogen

continuum (Figure 8.1) [3]. In North America, zoonoses such as rabies, plague, hantavirus, and tularemia are widespread in wildlife, posing an ongoing risk to human health. The emergence of a zoonotic disease often results from encroachment of human and domestic animal populations into wildlife habitat [3,4]. For example, recent serosurveys show evidence of novel viral infections with as yet unknown consequences in humans that hunt and trap native populations of nonhuman primates [5,6]. The global trade in wildlife shows how environmental and social factors combine to create a high risk for zoonotic disease emergence in susceptible human populations [7]. In this example, animals of unknown health status are trapped in the wild to be sold for human consumption, traditional medicine, or the commercial pet trade. Disease transmission may occur when humans have contact with infected animals. Activities involving the sale and consumption of infected wildlife in China likely resulted in the initial transmission of SARS-coronavirus to humans [8].

Prevention and control

In the US, successful surveillance and control programs have been developed for some zoonoses associated with domesticated animals. For example, a

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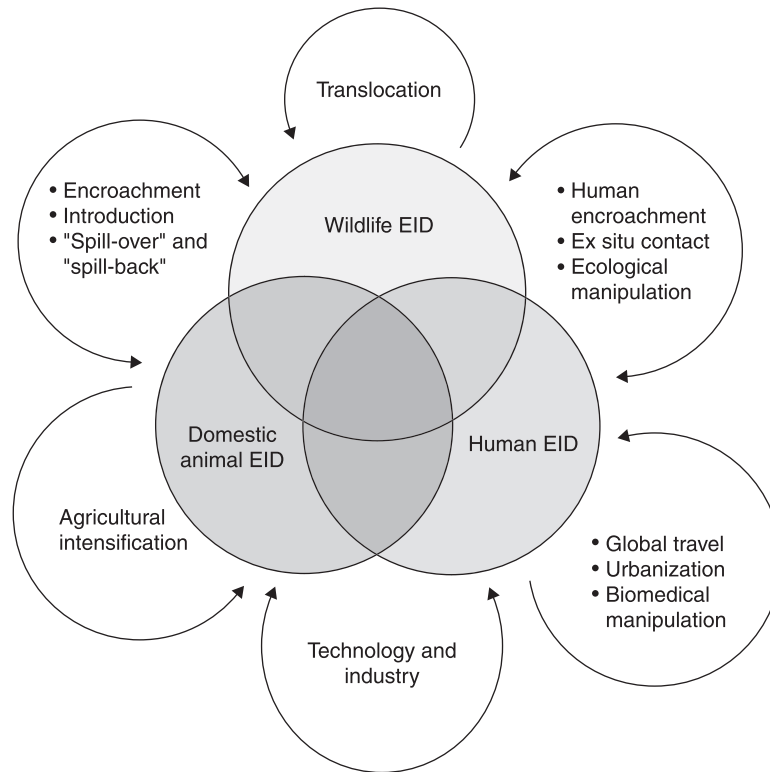


Fig 8.1 The host–pathogen ecological continuum for emerging infectious diseases (EIDs) of zoonotic origin. (Reprinted with permission from [3]. Copyright 2000 AAAS.)

national brucellosis-eradication campaign in livestock conducted by state and federal agriculture departments has included comprehensive animal testing, vaccination of breeding animals, and depopulation of affected herds. The program reduced infected herds from 124,000 in 1956 to only 5 herds nationally in 2000 [9]. Concurrently, reported brucellosis in humans plummeted from a high of approximately 6300 reported cases in 1947 to 114 cases in 2004 [10]. In the early 1900s, approximately 10,000 rabid dogs were reported annually in the US. Widespread canine rabies vaccination programs and stray animal control in the 1940s and 1950s allowed elimination of circulating canine variant of rabies virus, and in 2005 only 76 cases of rabies were reported in dogs following contact with rabid wildlife [11]. Successful programs such as these require enormous resources. As a result, there are no eradication programs for the ma-

jority of zoonotic pathogens, especially those with wildlife reservoirs.

Surveillance for zoonoses

The interconnected roles of wildlife, domestic animals, the environment, and human populations in zoonotic disease pathogenesis pose distinct challenges for surveillance. In contrast to those diseases that only affect humans, zoonotic diseases cannot be adequately studied or controlled without an understanding of the influences and dynamics of infection in animal hosts. Therefore, the approach to zoonotic disease surveillance involves flexibility, innovation, and interdisciplinary strategies. Four essential objectives of zoonotic disease surveillance include (1) designing systems for early identification of a human and animal health threat; (2) describing

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the epidemiological and ecological factors influencing zoonoses; (3) guiding and evaluating prevention, education, and control measures; and (4) describing the public health burden.

Surveillance and reporting of human infections

With the exception of rabies, zoonotic diseases are usually first recognized when human illness is reported. Surveillance depends on timely reporting of suspected and confirmed zoonotic infections by healthcare providers and laboratories to public health authorities. Depending on the pathogen and available resources, the animal source may be identified as part of the public health investigation. Linking human infection to the animal source is often more feasible with pets or livestock than with wildlife, as they may be more accessible to investigators for testing. For example, several outbreaks of human salmonellosis have been linked to contact with infected domestic and exotic pets, including cats, pet rodents, baby chicks, and reptiles [12,13]. In 2004 and 2005, three separate outbreaks identified over 170 people infected with *E. coli* O157:H7 who had visited livestock pens in petting zoos [14]. In 2005, lymphocytic choriomeningitis virus infection in four organ transplant recipients was traced to a donor who acquired infection from a pet hamster [15]. Determining whether there is ongoing risk to the public from a suspected animal source influences how much investigation is warranted.

Surveillance and reporting of animal diseases

In the US, veterinarians are required to report certain animal diseases to animal health and agriculture officials. Diseases under surveillance include diseases of livestock and poultry with serious economic implications and suspected foreign animal diseases [16]. Though many of these diseases do not infect humans, anthrax, rabies, and brucellosis are among the reportable animal diseases that also cause disease in humans (Table 8.2). Recent recognition of emerging zoonotic diseases and bioterrorism preparedness initiatives has bolstered public health's outreach to veterinarians. Some state and local public health agencies, such as those in New York City and Washington State, have developed

Table 8.2 Selected reportable zoonotic diseases in humans and animals, United States, 2006.

Disease	Reportable in humans	Reportable in animals
Anthrax	Yes	Yes
Brucellosis	Yes	Yes (cattle)
Cryptosporidiosis	Yes	No
<i>Escherichia coli</i> O157:H7; HUS	Yes	No
Hantavirus pulmonary syndrome	Yes	No
Leptospirosis	In some states	Yes
Lyme disease	Yes	No
Plague	Yes	In some western states
Prion diseases	In some states	Yes (BSE)
Psittacosis	Yes	Yes
Q fever	Yes	Yes
Rabies	Yes	Yes
Salmonellosis	Yes	In some states
Tularemia	Yes	Yes
Trichinosis	Yes	Yes

additional reporting regulations for zoonoses in animals that more commonly infect humans [17,18].

To more effectively monitor zoonotic diseases, animal and human disease data from public health and animal health agencies and laboratories should be integrated. Currently, the sharing of disease surveillance information in most states depends largely on interpersonal relationships, legal agreements such as memoranda of understanding, and agency priorities. As electronic databases become more widely utilized in public health and animal health agencies, coordination of disparate systems should be a primary goal.

Strategies for surveillance of zoonoses

Several strategies may be useful for surveillance of zoonotic pathogens in animals, including veterinary surveillance, sentinel surveillance, longitudinal surveillance, and laboratory-based surveillance.

Veterinary surveillance

As frontline healthcare providers, veterinarians assist with the recognition, diagnosis, reporting, and

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control of zoonotic disease in animals. When an unusual zoonotic disease trend or outbreak is recognized, veterinarians can assist the investigation through enhanced surveillance for animal disease. Many states, through cooperation of state veterinary medical associations, agricultural and public health agencies, have developed veterinary alert systems for rapid notification of zoonotic or animal disease outbreaks. Health alerts typically include information on veterinary occupational risks as well as symptoms, diagnosis, and reporting protocols for the disease in animals.

Sentinel surveillance

Monitoring animals for zoonotic pathogens can provide early recognition of human health risks and may allow for control efforts prior to the transmission of disease to humans. Mortality events are particularly important and some data on wildlife mortality is monitored and compiled nationally by the National Wildlife Health Center [19]. As one example, prairie dog colonies in northern Arizona experience periodic die-offs caused by enzootic cycles of plague (*Yersinia pestis*). Sentinel surveillance involves routine visual observation of prairie dog colonies to detect any increases in mortality. When plague is confirmed as the cause of a die-off, human disease prevention measures are initiated, including public education campaigns, posting of signs in the affected area, pesticide dusting of burrows to kill infected fleas, and warnings to pet owners to confine pets and use flea control.

Longitudinal surveillance

Where resources are available, meaningful surveillance to elucidate disease patterns in animal reservoirs includes ongoing systematic data collection. For example, prospective longitudinal studies at sites in Arizona, Montana, and Colorado involve serial monthly trapping of *Peromyscus* spp. of mice and serological testing for antibody to Sin Nombre virus [20,21]. Data from these studies show that the prevalence of infection in mice is influenced by local seasonal and climatic events that affect food supply and mouse population density. Trends observed assist in predicting human disease risk.

Laboratory-based surveillance

Effective surveillance for zoonotic pathogens requires diagnostic laboratory capacity for both hu-

man and animal specimens. In some states, commercial clinical laboratories are required to report positive findings for zoonotic pathogens to public health authorities. Diagnosis often requires specialized confirmatory testing that is available only in state or federal veterinary, agriculture, or public health laboratories. Advanced laboratory techniques are increasingly able to confirm genetic relationships among pathogens infecting humans and animals. This information, combined with epidemiological data, is useful for establishing zoonotic transmission events. For example, PulseNet, a national network of public health and food regulatory agency laboratories coordinated by the Center for Disease Control and Prevention (CDC), maintains a national database of molecular fingerprints of foodborne pathogens submitted from laboratories throughout the US. This system has proven very successful in detecting disease outbreaks associated with zoonotic pathogens such as *E. coli* and *Salmonella* [22]. PulseNet was used to determine that infected rodents distributed in commercial pet stores were the cause of a multistate outbreak of salmonellosis in humans [13].

Examples of zoonotic disease surveillance

The following two descriptions of zoonotic disease surveillance systems in the US illustrate some of the key ideas explained in this chapter, including the interconnected roles of human and animal disease surveillance and partnerships between human and animal health agencies. The first example describes routine disease surveillance for rabies and the second describes surveillance instituted during an outbreak of monkeypox.

Surveillance for rabies in the US

Background

Rabies is a viral disease of the central nervous system that, after the onset of clinical symptoms, is almost universally fatal—thus, rabies is a serious public health threat. Although all mammals are susceptible to rabies, the disease is efficiently maintained in enzootic cycles by specific animal reservoirs including raccoons, skunks, foxes, and several

species of insectivorous bats in North America. These wildlife reservoirs account for over 90% of confirmed rabid animals and sporadic domestic animal and human rabies cases in the US result primarily from interactions with these wildlife reservoirs [11].

Despite its high mortality rate, rabies infection can be prevented in most domestic pets and livestock with appropriate vaccination before and after exposure. Furthermore, infection in humans can be prevented after exposure through the timely administration of rabies postexposure prophylaxis (PEP) that usually consists of a series of vaccinations and administration of rabies immune globulin. Several million animal bites occur annually in the US and it is estimated that more than 35,000 people bitten by animals receive PEP every year [23]. Examples of potential human rabies exposures include bats found in houses, stray dog and feral cat bites, and wild animal bites. National guidance for human rabies exposure management is found in the Advisory Committee on Immunization Practices (ACIP) Rabies Prevention document [24].

Overview of rabies surveillance

Rabies surveillance in the US integrates human and animal zoonotic disease detection and prevention. Surveillance provides epidemiologic information to assist human PEP decisions and focus prevention and control programs. Animal bites to humans must be reported to public health authorities and each reported event is investigated. In addition, laboratory-confirmed rabies infection in both humans and animals is reportable. Because rabies poses a significant human health threat, in most areas animal rabies surveillance is primarily under the jurisdiction of local and state (human) public health agencies rather than animal health agencies. An example of a model rabies surveillance and control program is shown in Figure 8.2.

Goals and objectives of surveillance

A primary goal of rabies surveillance is to quickly evaluate and mitigate any risk of rabies; in the event of possible human exposure, this includes proper and timely administration of PEP. State and local health departments support 24/7 availability for consultation with healthcare providers and their

patients to assist in animal bite assessment, describe local and regional rabies epidemiology and risk, and facilitate correct administration of rabies PEP to prevent human rabies infection. When the biting animal is available, testing or observation periods for rabies may be initiated; however, in situations where the biting animal is not available, it is important to have robust epidemiological animal surveillance data to guide medical decisions.

Other goals of rabies surveillance include defining enzootic and epizootic status of rabies in a region, directing prevention efforts such as public education campaigns and animal control policies, detecting changes in disease patterns, and identifying unusual or novel disease events such as new modes of transmission or the evolutionary emergence of rabies virus variants. Notable recent examples in the US include the discovery of rabies transmission via organ transplantation [25] and the emergence of bat-associated rabies transmitted among skunks in an area previously free of terrestrial rabies [26].

Finally, rabies surveillance is used to evaluate the efficacy of animal vaccination in rabies control. For example, a thorough investigation of rare cases of rabies occurring in vaccinated dogs helps assess the efficacy of rabies vaccines [27]. Programs distributing oral rabies vaccine baits to control rabies in raccoons also benefit from post baiting surveillance to assess program efficacy [28].

Surveillance in animal populations

In the US, wild carnivores and bats are the most important potential source of rabies infection for humans and domestic animals. All states except Hawaii report annual cases of rabies in animals [11]. Rabies surveillance in animals includes identifying the disease in both domestic animals and wildlife. Rabies surveillance is enhanced significantly when public awareness is raised by media reports of unusual animal rabies cases, a human rabies case, or local epizootic rabies activity. The number of animals tested and those found rabid depends on the rabies reservoirs in the area, the human population base, and whether animal control, diagnostic laboratory infrastructure, and resources are available. During 2005, five states reported less than 11 rabid animals each (Alaska, Louisiana, Mississippi, New Mexico, and Oregon), and five

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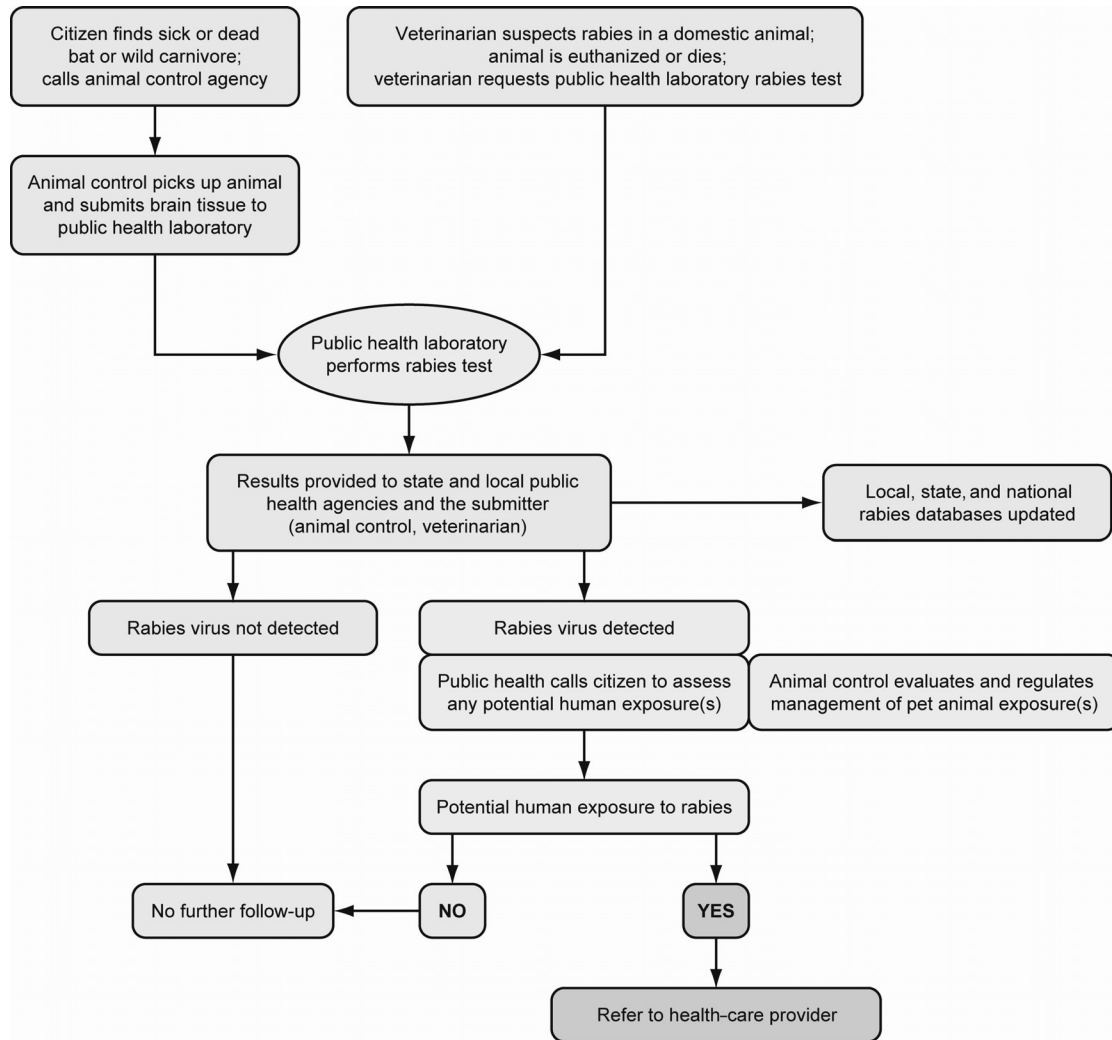


Fig 8.2 Example of a rabies surveillance and control system. Refer to national guidance for management of situations involving animal bites to human [24,30]. Designated agency

responsibilities, authorities, and systems, vary locally; State Departments of Agriculture manage rabies in livestock.

states reported over 400 animal rabies cases each (New York, North Carolina, Pennsylvania, Texas, and Virginia) [11].

Case definition of rabies in animals

Definitive diagnosis of rabies infection in animals requires laboratory testing performed on fresh brain tissue using the direct fluorescent antibody (DFA) test. Standardized protocols for performing the DFA test reduce laboratory errors and

consequently improve the accuracy of confirmed case surveillance [29]. Additional testing involving monoclonal antibody panels and nucleotide sequence analysis of rabid animal tissues can identify the specific rabies virus variant, its associated animal reservoir, and often its geographic association. Rabies virus variant typing provides important epidemiological information about rabid domestic animals and wild animals that are submitted from outside of enzootic areas.

Rabies surveillance in domestic pets and livestock Veterinarians, animal control officials, and public health agencies conduct rabies surveillance in domestic pets and livestock. Veterinarians caring for animals with severe progressive neurological signs may suspect rabies and request public health consultation and laboratory testing. Local health or animal control officials evaluate reports of animal bites and manage the biting animal to determine if there was a potential risk of rabies transmission. Public health laboratories perform the majority of animal rabies testing. National guidance for rabies vaccination, prevention, and control in animals is found in the National Association of State Public Health Veterinarian's Compendium of Animals Rabies Prevention and Control, which is updated annually [30].

Rabies surveillance in wildlife

Conducting surveillance for rabies in wildlife is challenging because of the difficulty in effectively observing and monitoring illness and death in wild animals. Successful wildlife rabies surveillance programs promote and encourage citizen reporting and laboratory testing of all sick and dead wild carnivores that do not have obvious evidence of trauma, even in situations without human or pet exposure. In situations requiring enhanced surveillance, programs may include collection and testing of road-killed animals. In some states, limited resources preclude this type of surveillance and rabies testing of wildlife is consequently performed only after bites are inflicted on people or pets. To facilitate wildlife surveillance, a direct rapid immunohistochemical test that can be performed by trained wildlife biologists on animals in the field has recently been developed. Field testing reduces the need for refrigeration of the brain and transport to public health laboratories [31].

Rabies surveillance in humans

Health departments receive and investigate reports of human illnesses and death due to unexplained viral encephalitis with characteristics resembling rabies. However, the disease is so uncommon in North America (less than 10 cases annually) that it is often clinically unrecognized by physicians unfamiliar with its presentation. A history of an an-

imal bite may be absent in some patients, particularly because of the long incubation period (usually 3–16 wk; range 2 wk to several years), the inability of encephalitic patients to recall exposures, and the minor injury related to exposures from bats. Bat-associated rabies viruses cause the majority of North American human rabies cases; 85% of the 24 indigenously acquired human rabies cases reported in the US between 1997 and 2004 were caused by bat-associated rabies virus variants [11,32]. In rare events, donors infected with rabies have been the source of human to human transmitted infection via corneal and organ transplantation [25].

Case definition of rabies in humans Diagnosis of human rabies is based on laboratory testing. Clinical rabies rapidly progresses to death and most cases of human rabies in the US are diagnosed postmortem during laboratory examination of brain tissue collected at autopsy. Antemortem tests for human rabies, performed primarily at CDC, may provide a diagnosis of rabies before death; however, negative antemortem test results are not definitive and must be confirmed by brain tissue examination postmortem [33].

Molecular laboratory tests are used to identify the rabies virus variant causing infection in human patients. This information has established that most human rabies cases acquired in the US are attributable to variants of rabies virus found in insectivorous bats [11,30]. Knowledge that contact with bats poses an important public health risk to humans has improved PEP recommendations and educational and prevention efforts.

Data collection, analysis, feedback

Confirmed animal rabies cases are reported regularly from state public health laboratories to their epidemiology programs, local health agencies, the submitter (animal control, veterinarians, wildlife biologists, etc.), and to national databases. National rabies data are summarized and published annually, including changes in trends and distribution of reported animal cases [11]. State and local health departments compile and disseminate current local epidemiological rabies information on Web sites, in health alerts, and in media releases. A geographic information system (GIS) with

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an Internet-accessible centralized database called RabID is being developed to map, compile, and disseminate rabies data in real time [34]. Surveillance using GIS is described in Chapter 31.

Partners

Surveillance for rabies relies on an extensive network of partnerships, including healthcare providers, veterinarians, animal control officers, public health officials (local, state, and federal), agriculture and wildlife officials, laboratories, wildlife rehabilitators, humane organizations, pharmaceutical companies, and the general public. This framework can also be adapted and used to address other zoonoses. In many areas, interagency advisory committees and task force groups are organized to coordinate rabies issues. Risk communication skills and public information officers are essential to public health messaging about rabies. Rapid surveillance efforts are often assisted by the media especially during attempts to identify people who may not be aware that they were potentially exposed to rabies, for example, by contact with a rabid animal in a petting zoo, campground, or pet store.

Strengths and weaknesses

Several limitations affect the efficacy of rabies surveillance. Clinical rabies infection in both humans and domestic animals may be underrecognized since it resembles several other encephalitic diseases. Many fatal cases of unexplained viral encephalitis in humans do not undergo postmortem autopsy. Antemortem rabies tests for animals are not available and definitive diagnosis requires public health resources for specialized laboratory testing of fresh brain tissues. Where resources are limited, rabies testing is often offered only for animals that have potentially exposed pets or people. Thus, the data generated are incomplete and biased by the degree of human and pet interaction with a particular species. The number of confirmed cases of animal rabies does not approximate the true incidence of disease, since many infected wild, stray, and feral animals are not observed or submitted for testing.

A primary strength of the system is that the results of surveillance (animal test results) are used to guide human treatment options and prevent hu-

man infection and death. As a result, very few human cases are reported each year in the US with many potential cases avoided through appropriate and timely administration of PEP.

Surveillance for monkeypox during an outbreak

Background

In 2003, an outbreak of monkeypox occurred in the US, representing the first time this disease had been recognized in humans outside of Africa where the disease is endemic [35]. Monkeypox is in the orthopoxvirus group of viruses (as is smallpox) and is capable of causing severe or fatal illness in humans. Some strains of monkeypox may be transmissible between humans and associated with higher mortality. Fortunately, the virus associated with the 2003 outbreak in the US was a less virulent West African strain of virus.

During the US outbreak, disease transmission was linked to contact with infected prairie dogs distributed in the commercial pet trade through an Illinois animal dealer. Over 70 persons in several Midwestern states were infected [36]. Extensive investigations of the implicated prairie dogs revealed that the Illinois dealer also bought and sold African rodents and epidemiologic evidence suggested that the prairie dogs were infected at this location. Traceback investigations of the African rodents linked them to a shipment from Ghana that contained over 800 small mammals [36]. Laboratory testing showed that several of the imported African rodent species were infected with monkeypox virus. The investigation was complicated by inadequate record keeping and widespread dissemination of the imported animals.

In the following section we will describe the enhanced surveillance for monkeypox virus infection in humans and animals that enabled characterization of the outbreak and guided containment of disease. Early identification of cases offered the possibility of reducing the clinical impact. Additionally, rapid control of the outbreak was needed to prevent the establishment of an enzootic cycle of monkeypox in native US wildlife. Federal emergency orders restricting the movement, trade, and importation of implicated species of animals contributed to control of the outbreak [37].

Goals of surveillance

A primary goal of surveillance was to define the extent and magnitude of the outbreak in humans and animals. The number of infected animals and their distribution was unknown initially, as was the clinical spectrum of illness in prairie dogs. Therefore, surveillance to detect human infection was the most effective way to define the extent and magnitude of the outbreak initially. Effective control of the outbreak required identification of close contacts to infected humans to monitor for and prevent human-to-human transmission of virus. An important objective of surveillance in animals was to identify infected and exposed animals so they could be removed from situations where they could transmit the infection to humans or other animals. Surveillance in animals also facilitated traceback investigations to identify the source of infection and to determine how many animals were potentially involved. Surveillance in native and captive wild rodents and other mammals was initiated to determine whether monkeypox had been introduced to, and spread among, native US wildlife species.

Surveillance in humans

Because human monkeypox had never been previously reported outside of continental Africa and it was considered implausible that the virus could affect the US, it was not a reportable disease at the time of the outbreak. However, its public health significance, clinical resemblance to smallpox, and the fact that it was not an endemic disease, allowed surveillance and reporting to be implemented under state regulations that address public health emergencies due to bioterrorism or novel agents. Retrospective surveillance included contacting and interviewing people who had handled potentially infected animals and reviewing patients with recent clinically compatible illnesses in outbreak-affected areas. Prospective surveillance involved identifying suspected cases meeting the clinical and epidemiologic case definition through reports from healthcare providers. Surveillance was facilitated by dissemination of outbreak updates and reporting guidelines through Internet-based systems (e.g., Health Alert Network, Epidemic Information Exchange (Epi-X) and *Morbidity and Mortality Weekly Report* (MMWR) [36,38–40].

Human cases identified during the investigation were classified as either suspect, probable, or confirmed monkeypox infections depending on the clinical presentation (presence of rash, fever, and lymphadenopathy) and epidemiological information available [37]. Confirmed cases required laboratory demonstration of the presence of virus through culture, electron microscopy, or nucleic acid detection techniques in the absence of another potential poxvirus [37]. Because laboratory testing for monkeypox is highly specialized, it was initially primarily conducted at CDC. However, through the healthcare worker smallpox vaccination program preparations, the Laboratory Response Network (LRN) laboratories had the capacity to screen clinical rash-derived samples for orthopoxvirus nucleic acid signatures; these facilities were used to aid in the triage and initial testing of samples, largely derived from the Midwestern states.

The investigations and case follow-up required extensive local, state, and federal resources and personnel and in many cases these resources were diverted from other important public health issues to accommodate outbreak needs. Coordination among affected states, confirmatory testing, and communication was facilitated by the CDC with daily national conference calls. This ensured consistency of case investigations and reporting, appropriate laboratory submissions, and rapid dissemination of current information and case numbers.

Surveillance in animals

In 2003, although many studies of experimental infection of animals existed, scientific information about the natural history of monkeypox in animals was sparse. Unknown factors included the range of susceptible animal species, the spectrum of clinical syndromes, and the possibility of viral shedding from asymptomatic animals. Therefore, surveillance focused on identifying animals with potential exposure to infected or exposed animals. The histories of infected animals were meticulously investigated, including their points of sale and shipments to identify additional exposed animals, and to reveal the source of infection for the animals. Clinical presentations were compiled to generate an animal case definition [37]. The investigation involved site visits to animal dealers and traders, pet shops, pet owners' homes, and the examination of

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written records or verbal interviews. Known clinical symptoms such as lethargy, cough, conjunctivitis, and skin lesions were useful in identifying potentially infected animals [37]. Because CDC and LRN laboratory testing was prioritized for human illness, there were inadequate laboratory resources for processing and testing animal specimens. Additionally, tests had not been fully evaluated with any of the animal specimen types submitted for analysis. Viral and serologic testing at CDC was conducted to confirm the initial infections in prairie dogs, to investigate possible infections in African rodents from the implicated shipment, and to investigate reports of diseased/suspect case animals in new locations.

A coalition of federal and state agriculture officials, state and local public health officials, and practicing veterinarians conducted the animal surveillance and investigations. Involved federal agencies included CDC, the Food and Drug Administration (FDA), and the United States Department of Agriculture (USDA)/Animal and Plant Health Inspection Service (APHIS). Animal breeders licensed by the USDA were visited and provided information about the outbreak. Educational materials were developed and disseminated to pet stores and veterinarians. National conference calls were held several times a week between federal and state agency personnel to coordinate activities.

Surveillance to determine whether monkeypox had exposed native wild rodents was coordinated by USDA-APHIS Wildlife Services. Traps were set on and near premises holding infected prairie dogs or African rodents. Blood collected on trapped wildlife was tested for antibodies to assess whether infection had been transmitted to native species. This surveillance found no evidence of infection in native rodents.

Strengths and weaknesses

A weakness of human and animal surveillance associated with this outbreak is that the systems were necessarily largely reactive and were implemented during the height of the outbreak. Because the initial infections in prairie dogs were not recognized as significant and reported to authorities, recognition of the outbreak was delayed until the first human cases were diagnosed. Thus, health authorities missed an early opportunity to control the out-

break. Educating animal dealers and veterinarians to quickly report unusual or suspicious illnesses in animals to authorities, and ensuring that state agriculture, wildlife, and human health agencies have the capacity to respond could facilitate a more rapid response in the future.

A primary strength of the surveillance system is the collaborative efforts that evolved between state and federal partners for human health and animal health. Although this emerged out of necessity during the emergency response, the relationships that were forged proved to be effective and have continued during subsequent zoonotic disease outbreaks and preparedness activities. Bioterrorism preparedness initiatives related to the detection and diagnosis of orthopoxviruses (due to smallpox concerns) greatly assisted in the response to this outbreak at both CDC and affiliated LRN laboratories. Additional benefits of the investigation include an enhanced understanding of the natural history of monkeypox virus and the development of testing strategies that may be used to identify monkeypox in various animal species.

Discussion

Surveillance for zoonotic diseases involves many challenges and offers opportunities for early detection of disease threats, improved assessment of risks posed by enzootic pathogens, and targeting effective prevention and control measures (see Chapter 10). In addition to providing direction for immediate public health actions, surveillance systems for zoonoses can provide vital insight into the factors influencing disease emergence, persistence, and spread. The importance of good communication and multidisciplinary participation in monitoring zoonoses is highlighted by the examples of rabies and monkeypox surveillance, and also through programs such as ProMED-mail, an Internet-based reporting system dedicated to rapid global dissemination of information on outbreaks of infectious diseases in humans, animals, and plants (available at: www.promedmail.org). ProMED-mail, a program of the International Society of Infectious Diseases, is widely used by public health agencies, animal health agencies, scientists, and medical and veterinary providers to provide early warnings of

zoonotic disease issues that might benefit from enhanced surveillance efforts [41].

The close association of humans and animals in modern society, including the globalization of agriculture, the pet trade, tourism and recreation, combined with ecologic pressures such as habitat transformation, climate change, and human overpopulation, will continue to facilitate unpredictable zoonotic disease threats [42]. Whether dealing with the persistence of ancient zoonoses, or the mysteries of newly recognized diseases, astute, innovative, and vigilant disease surveillance is imperative to reduce morbidity and mortality among humans and animals.

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References

- 1 Taylor LH, Latham SM, Woolhouse MEJ. Risk factors for human disease emergence. *Philos Trans R Soc Lond B* 2001;356:983–9.
- 2 Glaser CA, Angulo FJ, Rooney J. Animal associated opportunistic infections in HIV-infected persons. *Clin Infect Dis* 1994;18:14–24.
- 3 Daszak P, Cunningham AA, Hyatt AD. Emerging infectious diseases of wildlife—threats to biodiversity and human health. *Science* 2000;287:443–9.
- 4 Blancou J, Chomel BB, Belotto A, Meslin FX. Emerging or re-emerging bacterial zoonoses: factors of emergence, surveillance and control. *Vet Res* 2005;36(3):507–22.
- 5 Wolfe ND, Heneine W, Carr JK, *et al.* Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. *Proc Natl Acad Sci U S A* May 31,2005;102(22):7994–9.
- 6 Peeters M, Courgnaud V, Abela B, *et al.* Risk to human health from a plethora of simian immunodeficiency viruses in primate bushmeat. *Emerg Infect Dis* 2002;8(5):451–7.
- 7 Karesh WB, Cook RA, Bennett EL, Newcomb J. Wildlife trade and global disease emergence. *Emerg Infect Dis* 2005;11:1000–2.
- 8 Song HD, Tu CC, Zhang GW, *et al.* Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. *Proc Natl Acad Sci U S A* 2005;102:2430–5.
- 9 United States Department of Agriculture, Animal and Plant Health Inspection Services, Veterinary Services. Facts about Brucellosis. Available from: <http://www.aphis.usda.gov/vs/naahps/brucellosis/>. Accessed November 21, 2006.
- 10 Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2004. *MMWR Morb Mortal Wkly Rep* 2006;53:1–79.
- 11 Blanton JD, Krebs JW, Hanlon CA, Rupprecht CE. Rabies surveillance in the United States during 2005. *J Am Vet Med Assoc* 2006;229:1897–911.
- 12 National Association of State Public Health Veterinarians. Compendium of measures to prevent disease associated with animals in public settings, 2006. Available from: <http://www.nasphv.org/documents/Compendia.html>. Accessed October 30, 2006.
- 13 Centers for Disease Control and Prevention. Outbreak of multidrug resistant *Salmonella* Typhimurium associated with rodents purchased at pet stores—United States—December 2003–October 2004. *MMWR Morb Mortal Wkly Rep* 2005;54:429–33.
- 14 Centers for Disease Control and Prevention. Outbreaks of *Escherichia coli* O157:H7 associated with petting zoos—North Carolina, Florida, and Arizona, 2004 and 2005. *MMWR Morb Mortal Wkly Rep* 2005;54:1277–80.
- 15 Centers for Disease Control and Prevention. Lymphocytic choriomeningitis virus infection in organ transplant recipients—Massachusetts, Rhode Island. *MMWR Morb Mortal Wkly Rep* 2005;54(21):537–9.
- 16 List of Animal Diseases Notifiable to USDA and OIE. Available from: http://www.oie.int/eng/maladies/en_classification.htm. Accessed October 17, 2006.
- 17 New York City Department of Health and Hygiene: Reporting Zoonoses in animals. Available from: <http://home2.nyc.gov/html/doh/html/zoo/zoo-reporting.shtml>. Accessed October 17, 2006.
- 18 Washington Department of Health. Notifiable condition for the veterinarian. Available from: <http://apps.leg.wa.gov/WAC/default.aspx?cite=246-101-405>. Accessed January 10, 2007.
- 19 United States Geological Survey, National Wildlife Health Center Disease Information. Mortality events in wildlife. Available from: http://www.nwhc.usgs.gov/disease/information/mortality_events/index.jsp. Accessed November 2, 2006.
- 20 Abbott K, Ksiazek T, Mills JN. Long-term hantavirus persistence in rodent populations in Central Arizona. *Emerg Infect Dis* 1999;5:102–12.

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- 21 Calisher CH, Root JJ, Mills JN, *et al.* Epizootiology of Sin Nombre and El Moro Canyon viruses, southeastern Colorado 1995–2000. *J Wildl Dis* 2005;41(1):1–11.
- 22 Swaminathan B, Barrett TJ, Fields P. Surveillance for human *Salmonella* infections in the United States. *J AOAC Int* 2006;89:553–9.
- 23 Krebs JW, Long-Marin SC, Childs JE. Causes, costs, and estimates of rabies postexposure prophylaxis treatment in the United States. *J Public Health Manag Pract* 1998;4:56–62.
- 24 Human Rabies Prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Available from: <http://www.cdc.gov/MMWR/preview/mmwrhtml/00056176.htm>. Accessed October 30, 2006.
- 25 Srinivasan A, Burton EC, Kuehnert MJ, *et al.* Rabies in Transplant Recipients Investigation Team. Transmission of rabies virus from an organ donor to four transplant recipients. *N Engl J Med* 2005;352(11):1103–11.
- 26 Leslie MJ, Messenger S, Rohde RE, *et al.* Bat-associated rabies virus in skunks. *Emerg Infect Dis* 2006;12:1274–7.
- 27 McQuiston JH, Yager PA, Smith JS, Rupprecht CE. Epidemiologic characteristics of rabies virus variants in dogs and cats in the United States, 1999. *J Am Vet Med Assoc* 2001;218(12):1939–42.
- 28 Slate D, Rupprecht CE, Rooney JA, Donovan D, Lein DH, Chipman RB. Status of oral rabies vaccination in wild carnivores in the United States. *Virus Res* 2005;111:68–76.
- 29 Centers for Disease Control and Prevention. Rabies diagnosis. Available from: <http://www.cdc.gov/ncidod/dvrd/rabies/Diagnosis/diagnosi.htm>. Accessed November 15, 2006.
- 30 National Association of State Public Health Veterinarians. Compendium of animal rabies prevention and control, 2006. *J Am Vet Med Assoc* 2006;228(6):858–64.
- 31 Lembo T, Niezgoda M, Velasco-Villa A, Cleaveland S, Ernset E, Rupprecht CE. Evaluation of a direct rapid immunohistochemical test for rabies diagnosis. *Emerg Infect Dis* 2006;12(2):310–3.
- 32 Chapman AS, Hanlon CA, McQuiston J, *et al.* Epidemiology of human rabies in the United States, 1997 to 2004. Abstract #337, presented at *International Conference on Emerging Infectious Diseases*. Atlanta, GA, March 19–22, 2006.
- 33 Noah DL, Drenzek CL, Smith JS, *et al.* Epidemiology of human rabies in the United States, 1980–1996. *Ann Intern Med* 1998;126(11):922–30.
- 34 Blanton JD, Managan A, Managan J, Hanlon CA, Slate D, Rupprecht CE. Development of a GIS based, real-time Internet mapping tool for rabies surveillance. *Int J Health Geogr* 2006;5:47.
- 35 Reed KD, Melski JW, Graham MB, *et al.* The detection of monkeypox in humans in the Western hemisphere. *N Engl J Med* 2004;350:342–50.
- 36 Centers for Disease Control and Prevention. Update: multistate outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin. *MMWR Morb Mortal Wkly Rep* 2003;52:642–6.
- 37 Centers for Disease Control and Prevention. Monkeypox website <http://www.cdc.gov/ncidod/monkeypox/index.htm>. Accessed October 30, 2006; Human Case definition: <http://www.cdc.gov/ncidod/monkeypox/casedefinition.htm>; Animal Case definition: <http://www.cdc.gov/ncidod/monkeypox/animalcasedefinition.htm>.
- 38 Centers for Disease Control and Prevention. Health Alert Network. Available from: <http://www2a.cdc.gov/HAN/Index.asp>. Accessed November 1, 2006.
- 39 Centers for Disease Control and Prevention. Epi-X <http://www.cdc.gov/epix/>. Accessed November 1, 2006.
- 40 Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR). Available from: <http://www.cdc.gov/mmwr/>. Accessed January 9, 2007.
- 41 Cowen P, Garland T, Hugh-Jones ME, *et al.* Evaluation of ProMED-mail as an electronic early warning system for emerging animal diseases: 1996 to 2004. *J Am Vet Med Assoc* 2006;229:1090–9.
- 42 Gibbs EPJ. Emerging zoonotic epidemics in the interconnected global community. *Vet Rec* 2005;157:673–9.

Additional resources

- Centers for Disease Control and Prevention—Healthy Pets/Healthy People: <http://www.cdc.gov/healthypets/>
- Rabies Professional Resources: <http://www.cdc.gov/ncidod/dvrd/rabies/Professional/professi.htm>
- Health Topics Alphabetical List: <http://www.cdc.gov/az.do>
- Emerging Infectious Disease Journal: <http://www.cdc.gov/ncidod/EID/>
- National Association of State Public Health Veterinarians Documents: <http://www.nasphv.org/documents/Compendia.html>
- United States Department of Agriculture, Animal Plant and Health Inspection Service—National Animal Health Surveillance System: <http://www.aphis.usda.gov/vs/nahss/>
- National Annual Animal Disease Summary report: <http://www.aphis.usda.gov/vs/ceah/ncahs/index.htm>
- ProMED-mail: <http://www.promedmail.org/>
- Hugh-Jones ME, Hubbert WMT, Hagstad HV. *Zoonoses Recognition, Control, and Prevention*. Iowa: Iowa State University Press; 1995.