Impacts on Human Health Caused by Zoonoses

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Contents

Abstract

Zoonosis is an infectious disease and a potential bioterrorism agent. Bioterrorism aimed at a society, government, and/or its citizens is meant to cause destabilization, fear, anxiety, illness, and death in people, animals, or plants using biological agents. A bioterrorism attack is the intentional release of biological agents such as viruses, bacteria, fungi, rickettsial or chlamydial organisms, toxins, or other harmful agents. This chapter focuses on the induction, monitoring, and prevention of some zoonotic diseases that have potential as

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bioterrorism agents. The etiology, clinical manifestations, transmission routes, and treatment of these zoonotic agents are briefly discussed.

Introduction

Zoonosis is an infectious disease that is transmitted between animals and humans. Zoonosis comes from the Greek words "zoon" and "osis," which represent "animal" and "ill," respectively. In a systematic review of 1,415 species of pathogens known to infect humans, 868 (61 %) were zoonotic. Unfortunately, the majority of emerging infectious diseases over the last three decades have been zoonotic (Taylor et al. 2001). Most zoonoses are often previously unrecognized diseases or have increased virulence in populations lacking immunity, such as henipavirus (Marsh and Wang 2012), severe acute respiratory syndrome (SARS), and influenza virus (swine-origin H1N1 or avian influenza H5N1) (Tseng 2007). The major factor influencing the appearance of novel zoonotic diseases in the human population is increased contact between humans and wildlife, such as (i) encroachment of human activity into wilderness areas and (ii) movement of wild animals into areas of human activity (Daszak et al. 2001).

Zoonoses are potential bioterrorism agents (Ryan 2008). Terrorist attacks using conventional weapons cause fear, havoc, illness, and death. Bioterrorism agents include bacteria, viruses, fungal, rickettsial or chlamydial organisms, and toxins, i.e., they can be transmitted between animals and humans (Spencer 2007). The potential for a bioterrorist attack is no longer a debate of "if" but "when" one will occur. It is impossible to predict when, where, or how bioterrorism will occur (Ippolito et al. 2006). Therefore, the control and prevention of these diseases in animals can also be accomplished to reduce disease transmission between humans and other animals.

This chapter documents the history, agents, routes of exposure, detection, monitoring, and prevention of zoonotic pathogens.

Zoonoses Likely to Be Used in Bioterrorism

Bioterrorism aimed at a society, government, and/or its citizens is meant to cause destabilization, fear, anxiety, illness, and death in people, animals, or plants (Balali-Mood et al. 2013). According to the US Centers for Disease Control and Prevention (CDC), a bioterrorism attack is the intentional release of biological agents such as viruses, bacteria, fungi, rickettsial or chlamydial organisms, toxins, or other harmful agents that cause illness or death in people, animals, or plants (Balali-Mood et al. 2013). These biological agents can be spread through the air, water, or food. The intended use of biological agents might target humans directly or might be used to disrupt an economy. The disease caused by anthrax was directed at animal populations as early as World War I. Glanders, a virulent disease in horses and mules, was used in the 1910s. Typhoid was reported in a water supply in the 1970s.

In September and October 2001, several cases of anthrax occurred in the United States. Letters laced with infectious anthrax were concurrently delivered to the US Congress and news media offices (Spencer 2007).

Zoonotic Pathogens

The US CDC categorizes biological toxins and bioterrorism agents as A, B, and C. Category A includes high-priority agents that pose a risk to national security because they (i) can be easily transmitted and disseminated from person to person, (ii) cause high mortality and have potentially major public health impacts, (iii) may cause public panic and social disruption, and (iv) require special action for public health preparedness. Category A agents include anthrax, plague, tularemia, botulism, filovirus, and smallpox. Category B, the second highest priority agents, includes pathogens that (i) are moderately easy to disseminate, (ii) cause moderate morbidity and low mortality rates, and (iii) require specific enhancements to the CDC's diagnostic capacity and disease surveillance ability. Category B agents include brucellosis, epsilon toxin, glanders, melioidosis, psittacosis, Q fever, ricin toxin, food safety threats, staphylococcal enterotoxin B, typhus fever, viral encephalitis, and water safety threats. Category C, the third highest priority agents, includes emerging pathogens that may be engineered for mass dissemination in the future because of (i) their availability, (ii) ease of production and dissemination, and (iii) potential for high morbidity and mortality rates and ability to cause major health effects. Category C agents include Nipah virus and hantavirus. Other zoonotic pathogens, such as rabies, West Nile virus, and *Streptococcus suis* type II, will also be discussed briefly. Table 1 summarizes the organisms and their classification by the US CDC.

Zoonotic Pathogens Listed in CDC Category A

Anthrax

Anthrax is one of the oldest known animal diseases and has been encountered since antiquity. The first documented used of anthrax as a weapon was in the 1910s during World War I. The most recent event of bioterrorism was in the United States in 2001, which resulted in five deaths (Spencer 2007). The causative pathogen, *Bacillus anthracis*, is an aerobic Gram-positive rod bacterium. It produces highly resistant spores that are stable when the vegetative form of the organism circulates in the blood during disease. Anthrax can be found naturally in soil and commonly affects wild and domesticated herbivorous animals that ingest or inhale the spores while grazing. The most common natural infection route in humans is cutaneous. However, spores may cause disease through inhalation or through the ingestion of contaminated animal products. The most common clinical manifestation is cutaneous anthrax, followed by respiratory anthrax and gastrointestinal anthrax (Balali-Mood et al. 2013; Waterer and Robertson 2009). The neurological symptoms of

Table 1 Zoonotic pathogens for potential use in bioterrorism

Disease	Pathogen	Previously used by terrorists	Clinical signs	US CDC category
Anthrax	*Bacillus anthracis*	Yes	Respiratory, gastrointestinal, or neurological symptoms	A
Plague	*Yersinia pestis*	Yes	Respiratory and gastrointestinal symptoms	A
Tularemia	*Francisella tularensis*	Yes	Respiratory symptoms	A
Viral hemorrhagic fevers	Ebola virus and Marburg virus (filovirus)	No	Neurological and respiratory symptoms	A
Brucellosis	*Brucella* spp.	No	Arthralgia, myalgia, and undulant fever	B
Salmonellosis	*Salmonella* spp.	Yes	Gastrointestinal symptoms	B
Colibacillosis	*Escherichia coli* O157:H7	No	Gastrointestinal symptoms	B
Shigellosis	*Shigella dysenteriae*	Yes	Gastrointestinal symptoms	B
Glanders	*Burkholderia mallei*	Yes	Respiratory symptoms	B
Melioidosis	*Burkholderia pseudomallei*	No	Respiratory symptoms	B
Psittacosis	*Chlamydophila psittaci*	No	Respiratory and gastrointestinal symptoms	B
Q fever	*Coxiella burnetii*	Yes	Respiratory symptoms	B
Typhus fever	*Rickettsia prowazekii*	No	Neurological and respiratory symptoms	B
Viral encephalitis	*Alphavirus*	No	Neurological symptoms	B
Cholera	*Vibrio cholerae*	Yes	Gastrointestinal symptoms	B
Cryptosporidiosis	*Cryptosporidium parvum*	No	Gastrointestinal symptoms	B
Nipah virus encephalitis	Nipah virus	No	Neurological and respiratory symptoms	C
Hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS)	Hantavirus	No	Renal and respiratory symptoms	C

(*continued*)

Table 1 (continued)

Disease	Pathogen	Previously used by terrorists	Clinical signs	US CDC category
Severe acute respiratory syndrome	SARS coronavirus	No	Respiratory and gastrointestinal symptoms	None
Influenza	Swine influenza and avian influenza virus	No	Respiratory symptoms	None
Rabies	Rabies virus	No	Neurological symptoms	None
West Nile encephalitis	West Nile virus	No	Neurological symptoms	None
Streptococcal toxic shock syndrome	*Streptococcus suis*	No	Neurological symptoms	None

anthrax infection are usually at a later stage and are part of an established systemic disease (Donaghy 2006). There are no risks of person-to-person spread. For people exposed to anthrax, 60 days of an oral antibiotic is recommended to prevent development of the disease (Waterer and Robertson 2009). Vaccination against anthrax is available and appears to be safe. However, the overall efficacy for preventing anthrax in stockpersons is 92.5 % (Inglesby et al. 2002).

Plague

Plague is an enzootic disease in rodents (Stenseth et al. 2008). The first documented use of plague as a weapon was in the fourteenth century. More recent bioterrorism using plague occurred in World War II (Spencer 2007). The causative pathogen, *Yersinia pestis*, is a Gram-negative, facultatively anaerobic, nonmotile, coccobacilli, nonspore-forming bacterium that was discovered by Yersin in 1984 to be transmitted by rat fleas (*Xenopsylla cheopis*) (Balali-Mood et al. 2013; Stenseth et al. 2008). There are three syndromes of human plague: bubonic, pneumonic, and septicemic plague. Most cases are in the bubonic form, which is a rapidly progressing, serious illness with a mortality rate of 40–70 %. *Y. pestis* is highly contagious from person to person and is transmitted by droplets of respiratory secretions. Plague is endemic in many regions such as the Americas, Asia, and Africa. Currently, more than 90 % of all plague cases are reported in Africa (Stenseth et al. 2008). Early antibiotic therapy is essential to reduce the risk of complications and death. Patients with pneumonic plague must be isolated to avoid aerosol transmission. Fortunately, unlike anthrax, *Y. pestis* does not form spores and does not survive well outside the body of the host (Waterer and Robertson 2009).

Tularemia

Francisella tularensis is a small, rod or coccoid, nonmotile, strictly aerobic Gram-negative, intracellular bacterium that causes tularemia (Waterer and Robertson 2009). Arthropod vectors transmit *F. tularensis* among animal reservoirs such as

rodents, hares, deer, beavers, and squirrels. Humans are occasionally infected via inhalation, direct contact with infected animals or their products, insect bites, or the ingestion of contaminated food or water. There are no risks of person-to-person spread. The incubation period of human tularemia is approximately 2–10 days, and it has a variety of clinical manifestations, such as asymptomatic, rapidly progressive, fulminant, and fetal disease. Antibiotics such as streptomycin and gentamicin are the drugs of choice. A live attenuated vaccine is recommended for laboratory workers who are routinely exposed to *F. tularensis* (Balali-Mood et al. 2013). There have been no confirmed cases of tularemia used in bioterrorism.

Viral Hemorrhagic Fevers

Ebola virus and Marburg virus are the causative agents of viral hemorrhagic fever (Leroy et al. 2011). Both viruses belong to the family *Filoviridae*, which causes severe disease in humans and nonhuman primates. The *Filoviridae* family is classified within the order Mononegavirales, together with the *Bornaviridae*, *Rhabdoviridae*, and *Paramyxoviridae* families. The genome of all viruses under the order Mononegavirales consists of a linear, non-segmented, single-strand RNA molecule. Filovirus hemorrhagic fevers are typical zoonotic diseases that are transmitted accidentally through direct contact with infected animals. The role of wildlife species in the human epidemiology of filovirus is only partly understood. Several Zaire Ebola virus outbreaks occurred when hunters handled the infected carcasses of nonhuman primates and duiker (Colebunders and Borchert 2000); outbreaks may also be associated with exposure to fruit bats (Calisher et al. 2006; Leroy et al. 2011). The fruit bats *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata* represent possible Ebola reservoirs in Africa (Leroy et al. 2011). A high risk of transmission to people has been reported as contact with the patient in the later disease stages. The clinical manifestations for filovirus infection are epistaxis, melena, hematemesis, petechiae, ecchymosis, and bleeding at needle puncture sites. Patients may also develop neurological symptoms such as delirium, coma, and convulsions (Colebunders and Borchert 2000). There is no specific treatment for filovirus hemorrhagic fever. Supportive care is required for the treatment. Blood transfusions from convalescent patients were reported to help in the Kikwit Ebola epidemic. Several antiviral compounds have been shown to inhibit the viral replication in vitro and prevent death in animal models (Leroy et al. 2011).

Zoonotic Pathogens Listed in CDC Category B

Brucellosis

Brucellosis is a zoonotic disease that commonly causes reproductive failure and undulant fever in domestic animals and humans, respectively (Doganay and Doganay 2013). The causative pathogen, a *Brucella* species, is a small, nonmotile, non-sporulating, Gram-negative coccobacilli bacterium. The most common transmission route of brucellosis is contact with infected animals and their products such as milk, butter, cream, cheese, ice cream, urine, blood, carcasses, and abortion

products. Brucella organisms can survive for up to 2 days, 3 weeks, and 3 months in milk (at 8 °C), frozen meat, and goat cheese, respectively. Brucellosis is rarely transmitted between humans. Aerosol transmission and dissemination is considered the most effective route of delivery in a bioterrorism scenario. The treatment of brucellosis is based on the administration of doxycycline or streptomycin (Ariza et al. 2007). Currently, there is no safe and effective human brucellosis vaccine. Only live and attenuated vaccines have been used effectively in livestock (Yumuk and O'Callaghan 2012).

Food Safety Threats

Several foodborne diseases, including *Salmonella* species, *Escherichia coli* O157: H7, and *Shigella*, should be considered (Chang et al. 2012; Franz and van Bruggen 2008; Lim et al. 2010). Salmonellosis represents a major foodborne and waterborne disease. *Salmonella* species are rod-shaped, Gram-negative, nonspore-forming, facultative anaerobic, motile enterobacteria. Salmonellosis is a zoonotic disease, and various agricultural animals, such as cattle, pigs and chickens, can form a reservoir for this bacterium. Additionally, vegetable contamination has been reported to be an important route of *Salmonella* species infection (Franz and van Bruggen 2008). The disease presents with two clinical manifestations including typhoid and typhoid-like fever and gastroenteritis. The most common infection route of salmonellosis is through the ingestion of contaminated food. Therefore, the establishment of human salmonella infection depends on the ability to survive the environment of the digestive system (such as gastric acid) and to attach and enter intestinal cells.

Escherichia coli (E. coli) is a Gram-negative, facultative anaerobic bacterium. Enterohemorrhagic *E. coli* (EHEC) is one of the main pathogroups of *E. coli* and includes a definite zoonotic pathogen. The prototype EHEC strain, *E. coli* O157: H7, was first identified in 1982 and causes bloody diarrhea and hemolytic uremic syndrome in humans (Lim et al. 2010). Cattle is considered the primary reservoir of *E. coli* O157:H7 (Etcheverria and Padola 2013), but the pathogen has been isolated from a variety of animals such as sheep, pigs, horses, chickens, and wildlife (Lim et al. 2010). The most common infection route of *E. coli* O157:H7 is contact with contaminated food, water, animal feces, or an infected animal. Several disease outbreaks have been associated with the consumption of contaminated beef (Lim et al. 2010). Shiga toxin is a potent cytotoxin and the critical virulence factor in EHEC diseases (Bergan et al. 2012).

Shigellosis is caused by *Shigella*, which is a Gram-negative, nonspore-forming, and rod-shaped bacterium. *Shigella* species are related to *E. coli* and should be classified as a distinctive species in the genus *Escherichia*. The two bacteria evolved from the same ancestor (van den Beld and Reubsaet 2012). Shigella is a human-specific causative agent of bacillary dysentery; the clinical manifestations are abdominal cramps, nausea, fever, and bloody and mucoid in diarrhea. This disease is primarily transmitted via the fecal-oral route.

To treat patients with severe diarrhea and dehydration, it is necessary to use IV fluids immediately to replace the fluids and salts that are lost. If the patients can

drink, oral rehydration therapy is satisfactory (Dekate et al. 2013). The decision to treat with antimicrobial therapy should be made on a case-by-case basis. Antimicrobials can be administered for acute diarrhea when the pathogen is known. Additionally, anti-induction strategies to prevent toxin production and the use of anti-Shiga toxin antibodies have been proposed for the treatment of *E. coli* O157: H7 (Tzipori et al. 2004).

Glanders

Burkholderia mallei is the causative agent of glanders (Whitlock et al. 2007). *B. mallei* is a Gram-negative, nonmotile, facultative intracellular bacterium. This disease primarily affects equids (such as horses, donkeys, and mules) and causes glanders and farcy (known as the cutaneous form) depending on the route of infection. The transmission route of this disease is through inhalation, percutaneous inoculation, or ingestion. Acute infection causes high fever, emaciation, and ulceration of the nasal septum with mucopurulent to hemorrhagic discharge. Glanders can cause an acute or chronic lung infection and nodules on internal organs such as the liver and spleen. *B. mallei* is highly infectious as an aerosol, and infection requires only a few bacteria. Fortunately, human glanders is rare, and human-to-human transmission is extremely rare. The clinical presentation of human glanders includes ulcerative necrosis of the upper and lower respiratory tract, extensive pneumonia, cervical or mediastinal lymphadenopathy, pustules, and abscesses. Antibiotics such as tetracycline, ceftazidime, cefotaxime, amoxicillin-clavulanate, piperacillin-tazobactam, imipenem, trimethoprim-sulfamethoxazole, and streptomycin are the drugs of choice. No vaccine is currently available (Choh et al. 2013).

Melioidosis

Melioidosis is caused by *Burkholderia pseudomallei*, a Gram-negative bacillus. This organism is most commonly found in soil and water in melioidosis-endemic areas. Transmission in humans occurs following bacterial inhalation, inoculation, and ingestion. This disease was described as a "glanders-like" disease. The development of melioidosis symptoms is related to several factors such as the bacterial strain, the host immune response, and the route of transmission. Acute infection causes severe pneumonia or rapid septicemia. Chronic stages are associated with the formation of abscesses in multiple organs or even an asymptomatic infection. Currently, prolonged antibiotic therapy is the only option for controlling the melioidosis infection. The antibiotic susceptibility pattern of *B. pseudomallei* is generally similar to that of *B. mallei*. At present, there are no effective vaccines for the prevention of melioidosis (Choh et al. 2013).

Psittacosis

Psittacosis is a zoonotic disease caused by *Chlamydophila psittaci*, which is a Gram-negative, obligate intracellular bacterium. The disease is also known as parrot fever. The clinical manifestation of human psittacosis includes flu-like syndromes such as fever, headache, exhaustion, arthralgia, and loss of appetite. Atypical pneumonia is usually detected on X-rays. In avian chlamydiosis, bird

psittacosis is characterized by clinical signs such as anorexia, depression, respiratory distress, or diarrhea. The most common transmission route for human psittacosis is via the inhalation of contaminated material such as dried feces or nasal discharge. Human psittacosis is most frequently treated with antibiotics such as doxycycline, tetracycline, or chloramphenicol. Chlamydiae can develop persistent forms, which can lead to chronic clinical courses (Magnino et al. 2009).

Q Fever

Q fever is caused by *Coxiella burnetii*, which is a Gram-negative, pleomorphic coccobacilli, and obligate intracellular bacterium. Q fever is a zoonotic disease. Sheep, cattle, goats, birds, dogs, and cats are natural reservoirs for *C. burnetii*. This rickettsia is highly sensitive to environmental stresses such as ultraviolet light, osmotic pressure, and high temperature. Disease transmission can be tick-borne between animals; infection in humans is caused by inhaling droplets containing a few *C. burnetii* bacteria. The foodborne transmission of human Q fever rarely occurs. Q fever in animals commonly causes reproductive disease, especially abortion, infertility, and retained placenta. The clinical manifestations of Q fever are chronic (such as endocarditis, chronic granulomatous hepatitis, aseptic meningitis, and encephalitis) or acutely symptomatic (pneumonia or hepatitis), while some cases are asymptomatic. Doxycycline is recommended as the first-line treatment for Q fever (Balali-Mood et al. 2013).

Typhus Fever

Typhus fever, also known as epidemic typhus, is caused by *Rickettsia prowazekii*, which is a nonmotile, Gram-negative, and obligate intracellular bacterium (Bechah et al. 2008). Four *Rickettsia* species frequently cause incapacitating and life-threatening illness. Lice are the most important reservoir of *R. prowazekii*. In the United States, flying squirrels (*Glaucomys volans volans*) have also been identified as potential reservoirs. The transmission route of epidemic typhus has been suggested to occur through the inhalation of aerosolized infected feces from lice. Disease outbreaks have generally been related to war, famine, refugee camps, cold weather, or gaps in public health management. The clinical manifestations of typhus fever include rashes, neurological syndrome, respiratory syndrome, and shock. Tetracycline and chloramphenicol have been recommended for the treatment of epidemic typhus (Badiaga and Brouqui 2012).

Viral Encephalitis

Several viral encephalitis varieties should be considered (Donaghy 2006), including eastern equine encephalitis, Venezuelan equine encephalitis, and western equine encephalitis. The pathogens are arthropod-borne RNA viruses of the genus *Alphavirus* under the family *Togaviridae* and are highly pathogenic in equines and humans. The most common transmission route of alphaviruses is thought to be an arthropod vector such as mosquitoes (Go et al. 2014). The survival of alphaviruses depends on the presence of mosquitoes and vertebrate hosts. The human infection is characterized by fever, headache, lymphopenia, myalgia, malaise, and severe

neurological signs such as fatal encephalitis. There are no effective antiviral drugs to treat the viral encephalitis. Supportive care is recommended to reduce brain swelling and seizures. Vaccines against the alphavirus are currently at various stages of development (Zacks and Paessler 2010).

Water Safety Threats

Vibrio cholerae and *Cryptosporidium parvum* should be considered water safety threats (Austin 2010; Fayer 2004) and are listed in category B by the US CDC. *V. cholerae* is a Gram-negative, rod-shaped, motile bacterium. Several cholera pandemics have been related to O1 and O139, which are structures of the O antigen in its lipopolysaccharide. The cholera toxin (CT) is the primary toxin produced by *V. cholerae* O1 and O139. CT is important for the clinical manifestations of cholera. This disease causes the patient to hypersecrete electrolytes and water, sometimes causing death. The most common clinical presentations of this disease are watery diarrhea, which may be associated with vomiting, muscle cramps, and complications related to dehydration and metabolic acidosis. There are two routes of transmission of *V. cholerae*: aquatic reservoirs in the environment (primary transmission) and already-infected individuals (secondary transmission), which initiate outbreaks and epidemics in the endemic areas, respectively. Rehydration is the first recommendation for cholera treatment, but antibiotics have also been shown to be important therapeutics in both severe cases and epidemic situations. Cholera is most frequently treated with antibiotics such as doxycycline and tetracycline. Furazolidone, erythromycin, trimethoprim-sulfamethoxazole, ampicillin, and chloramphenicol are effective against severe cholera in young children and pregnant women. For multidrug-resistant cholera, ciprofloxacin is an important substitute drug of choice. The currently available killed injectable vaccine has been shown to be less effective.

Cryptosporidiosis is the most prevalent waterborne parasitic disease caused by *C. parvum* (Fayer 2004). This medically and veterinarily important disease causes gastroenteritis in a variety of vertebrate hosts. Cryptosporidiosis is characterized by watery diarrhea; other clinical features include abdominal discomfort, nausea, vomiting, and low-grade fever. Cryptosporidium infection can also cause atypical manifestations, such as gastrointestinal, biliary, or respiratory syndromes and pancreatitis, in immunocompromised patients. Cryptosporidium transmission is waterborne and is contracted directly from infected hosts. There are no consistently effective treatments for cryptosporidiosis in animals or humans. Paromomycin provided prophylaxis in an animal model but was inconsistently efficacious in humans. No immunotherapeutics or vaccines are currently available for preventing or treating cryptosporidiosis in animals or humans.

Zoonotic Pathogens Listed in CDC Category C

Nipah Virus

Nipah virus (NiV) first emerged in the 1990s in an outbreak of neurological and respiratory disease that infected pigs and humans and caused 110 human deaths in

Malaysia and Singapore (Marsh and Wang 2012). NiV is a single-stranded negative RNA virus that, together with the Hendra virus, is a variety of *Henipavirus* under the family *Paramyxoviridae*. *Pteropus* species fruit bats were identified as natural reservoir hosts of henipavirus (Calisher et al. 2006). Several NiV outbreaks appeared after human contact with excreta such as the saliva, urine, and feces of diseased pigs or bats. Person-to-person transmission has also been reported. The treatment of human patients with NiV infection remains dependent on supportive care. Humanized monoclonal antibodies have been used successfully to treat NiV infections in animal models (Zhu et al. 2006).

Hantavirus

Hantavirus is an enveloped, single-stranded, negative-sense RNA virus. Hantaviruses cause the most widely distributed zoonotic disease (Klempa et al. 2013). There are two important syndromes: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (Macneil et al. 2011); the occurrence of these syndromes depends on the infecting virus species. HPS is also referred to as hantavirus cardiopulmonary syndrome (HCPS). The Old World hantaviruses were identified during the outbreak of HFRS in Asia and Europe. The New World hantaviruses include species that cause HPS in North and South America. The epidemiology and geographical distribution of hantaviruses are related to their rodent reservoirs. The infected rodents exhibited asymptomatic and persistent infections. Additionally, several non-rodent reservoirs, such as crocidurines, shrews, moles, and bats, have been discovered. The most common transmission route of hantaviruses is via contact with virus-contaminated rodent feces, urine, or saliva. Human-to-human transmission is minimal, with the exception of the Andes virus outbreak in Argentina. There are no effective antiviral therapeutics available for hantavirus infections. Supportive care and therapy are the best treatments to inhibit the progression toward life-threatening symptoms. The most common prevention tactic is avoiding exposure to rodent excreta (Klempa et al. 2013).

Other Zoonotic Diseases

SARS and Influenza

The outbreak of severe acute respiratory syndrome (SARS) and influenza virus (swine-origin H1N1 or avian influenza H5N1) represents the new face of pandemic disease (Tseng 2007). These pathogens share some common characteristics: they have animal origins, are highly contagious, are fatal viruses, and lack vaccines. Therefore, these zoonotic diseases are proposed as threats in a bioterrorist attack. The outbreak of SARS in 2002–2003 had approximately 8,000 probable cases in 29 countries and a fatality rate of approximately 10 %. Due to the speed and reach of international air travel, SARS spread globally within weeks; additionally, transmission was amplified within hospitals. In 2009, an outbreak of a swine-origin H1N1 demonstrated worldwide expansion. These diseases are most effectively spread as aerosols. Therefore, aerosol sprays would be the most common route in a potential bioterrorism attack (Tseng 2007).

Fig. 1 A ferret-badger suffering from rabies virus in Taiwan (From Dr. Chen-Chih Chen, National Pingtung University of Science and Technology, Taiwan)

Rabies

Rabies virus is an enveloped, single-stranded, negative-sense, bullet-shaped RNA virus that belongs to genus *Lyssavirus*, under the family *Rhabdoviridae*. Rabies virus is transmitted between mammals (Calisher et al. 2006). The most common transmission route of rabies virus is by the bite of an infected animal that has rabies virus in its saliva. More than 55,000 cases of human rabies are reported yearly in the world, most in tropical countries of Asia and Africa. Rabies in enzootic areas appears to be cyclic and spreads into unexposed and susceptible wildlife populations. These wildlife species serve as maintenance hosts for virus transmission to domestic animals. The wildlife species include foxes, raccoon dogs, jackals, mongooses, wolves, manuls, and ferret-badgers (Fig. 1).

There are two important syndromes of rabies virus infection: furious and paralytic. Not all infected animals progress through all the clinical stages. There is no effective treatment for animals and humans with this fatal encephalitis. Vaccination is recommended to control rabies in dog and cat populations. Oral ingestion of an attenuated strain of rabies virus has been used in feral and wild animals. These baited vaccines may be effective in wildlife. For preventing human rabies, three doses of an FDA-approved vaccine are recommended in preexposure. Preexposure prophylaxis is warranted in humans with a high vocational risk of encountering rabid animals, such as veterinarians, animal health technicians, animal control officers, wildlife biologists, bat handlers, laboratory workers, and spelunkers. For previously unvaccinated patients, postexposure prophylaxis is 100 % effective against rabies.

West Nile Virus

West Nile virus (WNV) is an enveloped, single-stranded, positive-sense RNA virus that, together with the Japanese encephalitis virus and dengue virus, is a variety of *Flavivirus* under the family *Flaviviridae* (Go et al. 2014). The main transmission route of flavivirus is thought to be an arthropod vector such as mosquitoes. *Culex* mosquitoes are the main vector of these viruses. WNV was first isolated in West

Fig. 2 Pig, such as the one pictured here, is affected by *Streptococcus suis*. The neurological symptoms such as meningitis, paddling, opisthotonus, convulsions, and nystagmus are the most striking feature of this disease (From Dr. Ming-Tang Chiou, National Pingtung University of Science and Technology, Taiwan)

Nile District, Uganda, in 1937. Before its appearance in New York, WNV caused sporadic outbreaks in Africa, the Middle East, Asia, and Australia. WNV has spread rapidly across the United States, Canada, and Central and South America and is currently one of the most common causes of epidemic encephalitis in the United States. The most common of the WNV infections in humans are subclinical, but some patients develop clinical signs and symptoms such as biphasic fever, malaise, headache, nausea, anorexia, vomiting, myalgia, and arthralgia. The inactivated WNV vaccine produced by Fort Dodge Animal Health received a full licensed from the US Department of Agriculture in 2003.

Streptococcus suis Type II

Streptococcus suis is a peanut-shaped, Gram-positive bacterium and an opportunistic pathogen in swine (Fig. 2). *S. suis* is also an emerging zoonotic pathogen among humans (Gottschalk et al. 2010). It is the leading cause of human acute bacterial meningitis in several countries, including Vietnam and China (Mai et al. 2008; Tang et al. 2006). The transmission route of this disease in humans is associated with direct exposure to infected pigs or infected raw or undercooked pork products. Penicillin is recommended as the first-line treatment for *S. suis* infections.

Detection and Early Identification of Zoonotic Pathogens

Syndromic Surveillance

Zoonotic pathogens, such as those in a bioterrorism event, must be recognized in a timely manner; however, this reaction time is dependent on sufficient funding, training, equipment, and personnel. An intimate understanding of the natural ecology, geographic distribution, clinical syndromes, and lesions of a given disease

is essential for early recognition and control (Bravata et al. 2004). Early diagnosis and prompt, effective control measures are critical determinants of the eventual impact of any infectious disease emergency. Syndromic surveillance is the gathering of data for public health purposes before laboratory-confirmed information is available. Nurses and veterinarians are important resources in collecting and interpreting surveillance data. Many modern diseases are zoonotic diseases; therefore, veterinarian and medical staff face an enormous challenge in the early recognition, reporting, treatment, and prevention of zoonotic diseases. After an acute outbreak event, the active surveillance of wild or domestic animal populations may help identify many ongoing exposure risks.

Molecular Approaches

Bacteria and viruses are the most problematic zoonotic pathogens. Therefore, rapidly and accurately identifying the pathogens in a disease outbreak is a key factor in any biological defense strategy. Detection and identification methods based on real-time PCR assays are currently of the greatest use for zoonotic pathogens because of their rapidity, sensitivity, and reproducibility (Ivnitski et al. 2003). Microarray-based (gene chips) technologies offer great potential for environmental monitoring; this approach includes improved accuracy, lower power and sample consumption, disposability, and automation (Ivnitski et al. 2003). Additionally, hybrid technologies represent a stand-alone system for the rapid, continuous monitoring of multiple biological agents in a given environment (Ivnitski et al. 2003). This system has several key advantages over competing technologies, including (i) the ability to detect up to 100 different agents, (ii) the flexibility and ease with which new bead-based assays can be developed and integrated into the system, (iii) low false-positive and false-negative rates, (iv) the ability to use the same basic system components for multiple deployment architectures, and (v) the relatively low cost per assay and minimal consumables. Therefore, hybridization-based approaches will be extended for detecting bioterrorism agents in the near future (Ivnitski et al. 2003).

Next-generation sequencing (NGS) can be an attractive tool for broad-based pathogen discovery. The technique, also known as massively parallel to deep sequencing, has emerged as one of the most promising strategies for discovering novel infectious agents in clinical specimens. NGS approaches have also been successful in the identification of novel animal viruses. There are two main parameters for the choice of NGS platforms for pathogen discovery: read length and rad depth. Therefore, currently available technologies such as NGS can survey the full breadth of undiscovered pathogens (Chiu 2013).

Immunological Methods

Immunoassays are regularly used to confirm a clinical diagnosis. Immunological methods include immunochromatographic lateral flow assays,

electrochemiluminescence assays, ELISA, time-resolved fluorescence assays, immunofluorescence assays, and immunohistochemistry. The primary disadvantage of polyclonal antibodies of immunoassays is the lack of the specificity required for useful detection and definitive identification, due to the cross-reactive properties of certain antigens of various pathogenic species.

Biosensors

Biosensors represent a combination of biological receptor compounds (such as enzymes, antibodies, microorganisms, and DNA) in proximity to the signal transducer that can provide a reagent-free sensing system that is specific for a target analysis (Deisingh and Thompson 2004). The first biosensor was the "enzyme electrode," which was used to describe glucose oxidase in 1962. The biosensor enables a broad spectrum of analyses in complex sample matrices (such as blood, serum, urine, or food) and the real-time monitoring of specific biological agents. Biosensors have shown great promise in areas such as clinical diagnostics, food analysis, bioprocess, and environmental monitoring (Leonard et al. 2003). However, several disadvantages of biosensors have been observed, including high costs, hazards, and disposal problems in radiolabeled probes (Ivnitski et al. 1999); a long incubation time and insufficient sensitivity in flow immunosensors (Ivnitski et al. 1999); a long incubation time in piezoelectric biosensors (Ivnitski et al. 1999); a long assay time and lack of sensitivity in bioluminescence sensors (Ivnitski et al. 1999); high cost and flow cell stability in surface plasmon resonance-based biosensors (Leonard et al. 2003); and antigen-binding sites in phage-antibody technology (Dover et al. 2009).

Prevention and Preparedness Against Zoonoses

A zoonotic outbreak has the potential for mass destruction and may cause significant economic losses. The majority of emerging infectious diseases are zoonotic in origin (Taylor et al. 2001). A zoonotic disease outbreak in human populations would likely pose a health risk to animal populations in the target area. Therefore, communication between veterinary and human public health officials is essential. There are several steps related to preparedness for zoonotic diseases: (i) Improved communication is necessary between veterinarian and human health professionals, as is surveillance of animal populations (such as wildlife and companion animals) and thus the control and prevention of zoonotic disease in animals. Domestic and wildlife animals are exposed to infectious agents and environmental contaminants in the air, soil, water, and food; therefore, animals serve as disease sentinels or an early warning system (Rabinowitz et al. 2006). (ii) There should be adequate planning, such as diagnostic tools, for the zoonotic diseases. (iii) Antibiotics should be stockpiled. (iv) Training should be provided to medical personnel and government officials. (v) Personal protective equipment (such as eye protection,

gowns, gloves, and masks) would facilitate reducing the likelihood of infection through either direct contact or respiratory droplets. (vi) Vaccinations should be planned.

Conclusion and Future Directions

The majority of emerging infectious diseases are zoonotic in origin. Medical and veterinary communities should work closely in clinical, public health, and research settings. It is impossible to predict when, where, or how zoonotic disease will occur. All countries should continue to carefully monitor the events associated with zoonotic disease and should work to develop defense strategies.

Cross-References

▶ Basic Chemistry of Botulinum Neurotoxins Relevant to Vaccines, Diagnostics, and Countermeasures
▶ Biotoxins and Food Safety
▶ Botulinum Toxin: Present Knowledge and Threats
▶ Immunosensors: Using Antibodies to Develop Biosensors for Detecting Pathogens and Their Toxins
▶ Structure, Genetics, and Mode of Disease of Cholera Toxin
▶ The Public Health Response to Potential Bioterrorism by Toxin Attack
▶ Yesterday, Today, and Tomorrow: A Selective View of Toxins in Weapons and Medicine

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