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CHAPTER

28

Selected Zoonoses

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OUTLINE

I. INTRODUCTION

Human risks of acquiring a zoonotic disease from animals used in biomedical research have declined over the past decade because higher quality research animals have defined microbiologic profiles. Even with diminished risks, the potential for exposure to infectious agents still exists, especially from larger species such as nonhuman primates, which may be obtained from the wild, and from livestock, dogs, ferrets, and

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cats, which are generally not raised in barrier facilities and are not subject to the intensive health monitoring performed routinely on laboratory rodents and rabbits. Additionally, when laboratory animals are used as models for infectious disease studies, exposure to microbial pathogens presents a threat to human health. Also, with the recognition of emerging diseases, some of which are zoonotic, constant vigilance and surveillance of laboratory animals for zoonotic diseases are still required.

Transmission of zoonotic agents between animals and personnel is either by direct contact with the infected animal or by indirect contact by exposure to contaminated equipment or supplies. Many activities performed in laboratories and animal facilities result in the formation of small particles or droplets that are suspended and transferred in air currents, and this aerosolization of infectious material is a principal means of disease transmission. However, direct inoculation through bites and scratches, skin or mucous membrane exposure to contaminated surfaces, and accidental ingestion can also result in agent transmission.

As in a microbiologic laboratory or an infectious disease ward of a hospital, safety procedures can minimize potential zoonotic disease transmission to associated personnel in the biomedical laboratory. Some examples of sound procedures to follow in the control of exposure to zoonotic pathogens are (1) purchase of pathogen-free animals; (2) quarantine of incoming animals to detect any zoonotic pathogens; (3) appropriate treatment of infected animals or their removal from the facility; (4) vaccination of animal carriers and high-risk contacts if/when vaccines are available; (5) use of specialized containment caging or facilities and protective clothing; and (6) regular surveillance.

It is not within the scope of this chapter to discuss these issues in detail. A number of sources are available that offer additional information. In particular, the Centers for Disease Control and Prevention (CDCP) in conjunction with the National Institutes of Health (NIH) has published a monograph, *Biosafety in Microbiological and Biomedical Laboratories* (CDCP-NIH, 2009). The National Academy of Sciences (NAS) has published *Occupational Health and Safety in the Care and Use of Research Animals* (National Research Council, 1997). *Occupational Medicine: State of the Art Reviews*, dealing with animal handlers (Langley, 1999), is also available. All of these are important resources available for use in designing protective programs for personnel involved in biomedical research using animals.

The discussion that follows is a brief overview of select viral, rickettsial, chlamydial, bacterial, fungal, protozoal, and parasitic diseases shared by humans and the animals that are commonly used in biomedical laboratories.

II. VIRAL DISEASES

A. Poxviruses

Numerous poxviruses are capable of zoonotic transmission from laboratory animals to humans. While many poxviruses are predominantly of historical interest, some may be encountered in the research setting and are of increasing concern in the United States (Reid and Dagleish, 2011). The poxviruses associated with zoonosis are classified within three genera, *Orthopoxvirus*, *Parapoxvirus*, and *Yatapoxvirus*, with the nonhuman primate serving as host for the majority of the potentially zoonotic poxviruses species. In humans, these infections are usually characterized by the development of proliferative cutaneous or subcutaneous self-limiting lesions and, in a laboratory animal setting, most frequently result from a nonhuman primate or small ruminant exposure. Fomite transmission is also of concern as most poxviruses can persist for prolonged periods in the environment and sloughed scab material.

1. Nonhuman Primate Poxvirus Infections

The zoonotic poxviruses most likely to infect nonhuman primates bred or captured for use in research include monkeypox virus, Yaba-like disease virus, and Yaba virus, although the incidence of infection is low.

a. Monkeypox

Reservoir and Incidence Monkeypox is an *Orthopoxvirus* causing sporadic cases of human disease in Africa. Natural outbreaks of monkeypox have been recorded in nonhuman primates in the wild and in laboratory settings (CDCP-NIH, 2009; Essbauer *et al.*, 2010). Two clades of the virus are recognized: the Congo Basin clade and the West African clade. Disease severity in both humans and nonhuman primates differs with the West African clade causing a milder disease with lower mortality and rare person-to-person transmission (Wachtman and Mansfield, 2012).

The virus is naturally occurring in animals only on the continent of Africa where infection has been documented in at least 10 nonhuman primate species and four squirrel species. Squirrels are believed to be the major disease reservoir in Africa (Reid and Dagleish, 2011). The virus has a broad host range of Asian, African, and South American nonhuman primates including select apes, and New and Old World monkeys (Wachtman and Mansfield, 2012). Most of the infections of captive nonhuman primates have involved Asian macaques (Fenner, 1990).

Mode of Transmission Within susceptible nonhuman primate populations, the disease spreads rapidly with high morbidity and variable mortality. Suspected modes of transmission between nonhuman primates include aerosol, direct contact, and biting insects (Wachtman and

Mansfield, 2012). Transmission of monkeypox from captive nonhuman primate populations to humans has not been recorded. The first reported case of human monkeypox outside of Africa occurred in the Midwestern United States in June 2003 following the importation of 800 West African small rodents for the pet trade, six of which (two rope squirrels (*Funisciurus* spp.), one Gambian giant rat (*Cricetomys* spp.), and three dormice (*Graphiurus*)) were later shown to be infected with the West African clade of monkeypox virus (CDC, 2003; Guarner *et al*., 2004). The infected rodents were co-housed with black-tailed prairie dogs (*Cynomys ludovicianus*) who contracted the disease and then served as the source of a human monkeypox disease outbreak with 87 reported (37 laboratory-confirmed) human cases (CDC, 2003; Parker *et al*., 2007). Infection was also identified in hamsters (*Cricetus* spp.), gerbils (*Gerbillus* spp.), and chinchillas (*Chinchilla* spp.) cohoused with the infected animals (Parker *et al*., 2007). As a result of this outbreak, U.S. importation of African rodents and interstate transportation of prairie dogs and select African rodents was banned. Human-to-human and zoonotic transmission of this agent is low and has occurred presumably through close contact with active lesions, recently contaminated fomites, or respiratory secretions (CDC, 1997; Damon, 2011; Ligon, 2004).

Clinical Signs Clinical signs in the nonhuman primate host include fever followed in 4–7 days by cutaneous eruptions, usually on the limbs and face and less frequently on the trunk. The disease may be fatal in nonhuman primates although subclinical infections are common in endemically infected populations. Fatal infections do occur in humans, predominantly in children, the malnourished, or immunocompromised individuals.

Monkeypox in humans is primarily of interest and importance because it produces a disease similar to smallpox (variola virus). Following a 7- to 19-day incubation period, monkeypox infection of humans is characterized by fever, malaise, headache, severe backache, prostration, and occasional abdominal pain (Damon, 2011; Sejvar *et al*., 2004). Subsequent signs include lymphadenopathy of the neck, inguinal, and axillary region (a condition not normally observed with smallpox (Parker *et al*., 2007)), as well as a maculopustular skin rash characterized by papules, vesicles, peduncles, scabs, and desquamation (Fig. 28.1). Encephalitis rarely develops. A severe fulminating disease with an approximate 10% fatality rate is observed in individuals infected with the Congo Basin clade and not vaccinated against smallpox (Reid and Dagleish, 2011).

Control and Prevention As is characteristic of *Orthopoxviruses*, monkeypox infection does not normally produce a carrier state or latent infection. Unlike most other poxviruses, monkeypox has a wide host range. It is endemic in some wild populations whose geographic ranges increasingly overlap with encroaching human populations, many of which have increasingly high numbers of immunocompromised individuals. These factors increase the potential for human transmission (Parker *et al*., 2007). Within human populations, infections occur in small clusters, not larger outbreaks as is typical with smallpox (Reid and Dagleish, 2011). Smallpox vaccination provides partial and limited-term protection against the development and severity of monkeypox disease in both humans and nonhuman primates (Reynolds *et al*., 2012).

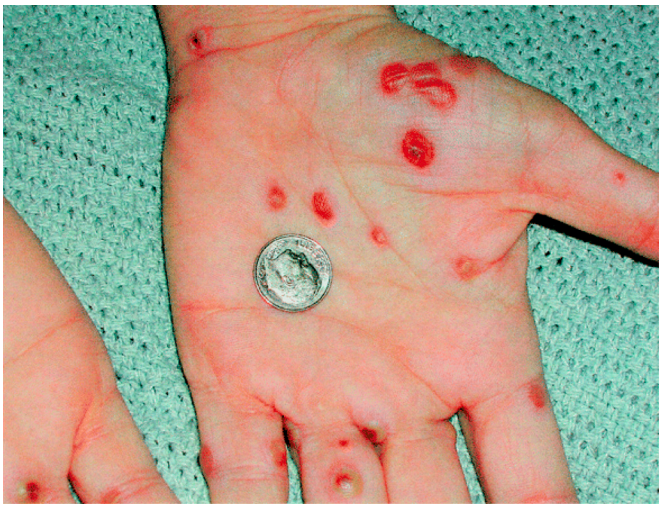

FIGURE 28.1 Photograph of skin lesions on patient A. Hemorrhagic-appearing palmar lesions are depicted. *JID, 2004: Human Monkeypox Infection: A Family Cluster in the Midwestern United States.*

Aside from the direct health impact of human infection, the monkeypox virus holds significant public health importance given its clinical similarity to smallpox in both human and animal populations. While smallpox, a zoonotic *Orthopoxvirus*, was once a significant cause of human morbidity and mortality throughout the world, the virus was declared eradicated in 1980 by the World Health Organization. Nonhuman primates are susceptible to experimental smallpox virus infection and have been shown to contract the virus from infected humans. It is considered unlikely that nonhuman primates in the wild could serve as a natural reservoir of the disease. Current concern regarding smallpox relates to its potential use as a bioterrorism agent given the public panic and high human mortality rate likely to occur in an outbreak.

Monkeypox virus (excluding the West African clade) is classified as a 'Select Agent' in the United States. Although human and animal clinical smallpox disease does not occur, an awareness of the clinical disease and diagnostic methods to rule out its presence is still relevant.

b. Yaba-Like Disease Virus

Yaba like disease virus (YLDV), previously known as benign epidermal monkeypox (BEMP) and OrTeCa poxvirus, is a *Yatapoxvirus* that has been zoonotic in the

laboratory environment on numerous occasions. YLDV was once believed to be identical to tanapox. Subsequent genetic analysis has shown YLDV and tanapox to be two strains of the same virus with YLDV causing disease predominantly in nonhuman primates and tanapox causing disease (a benign cutaneous infection) in humans in East Africa (Wachtman and Mansfield, 2012).

Reservoir and Incidence Natural infections with YLDV have been documented in African but not New World primates. In 1967, an outbreak of YLDV occurred in macaque colonies of three U.S. primate facilities during which human handlers were also affected. The source of this outbreak was never identified.

Mode of Transmission The rapid spread of YLDV among nonhuman primates housed in gang cages suggests direct viral transmission. Infections in animal handlers were attributed to viral contamination of skin abrasions.

Clinical Signs YLDV infection of nonhuman primates is characterized by the development of circumscribed, oval-to-circular, elevated red lesions usually on the eyelids, face, body, or genitalia that regress spontaneously in 3–4 weeks. The localization of YLDV lesions in the epidermis and adnexal structures differentiates them histologically from Yaba lesions, but similar to Yaba, eosinophilic intracytoplasmic inclusion bodies are present (Kupper *et al*., 1970). Clinical disease in humans is characterized by a short febrile illness and lymphadenopathy followed by the development of pock lesions (Wachtman and Mansfield, 2012).

Control and Prevention Appropriate personal protective equipment employed (PPE) while working with nonhuman primates is believed sufficient to prevent the zoonotic transmission of this agent.

c. Yaba

Yaba monkey tumor virus is an oncogenic member of the genus *Yatapoxvirus* that was reported initially in a colony of rhesus macaques (*Macaca mulatta*) housed outdoors in Yaba, Nigeria (Bearcroft and Jamieson, 1958). There have been subsequent outbreaks and experimental studies of the agent, as well as sporadic incidental cases of the disease in laboratory-housed nonhuman primates.

Reservoir and Transmission Natural cases of the disease have been reported in the rhesus macaque and the baboon (*Papio* spp.) while experimental studies have expanded the host range to include pigtail macaques (*Macaca nemestrina*), stumptail macaques (*Macaca arctoides*), cynomolgus (*Macaca fascicularis*), African green (*Chlorocebus aethiops*), sooty mangabey (*Cercocebus atys*), and patas monkeys (*Erythrocebus patas*) (Ambrus and Strandstrom, 1966; Ambrus *et al*., 1969). Many African monkeys apparently originate from areas with endemic infection and are immune to the agent, and New World nonhuman primate species are resistant to infection (Ambrus and Strandstrom, 1966). The route(s) of transmission are not yet known; arthropod vectors, tattoo needles, and trauma are suspected (Wachtman and Mansfield, 2012). Experimental studies in macaques have demonstrated aerosol transmission of the agent. Thus, aerosolized Yaba virus must be considered a potential hazard to humans.

Clinical Signs Infected animals consistently develop subcutaneous masses 5–7 days after viral exposure that reach a maximum size of approximately 2–5 cm in 3 weeks with spontaneous regression by 6–8 weeks postexposure. Mass development may not be synchronous and may occur over several months, so masses at varying stages of development may be observed (Blanchard and Russell-Lodrigue, 2012). Larger masses may ulcerate (Wachtman and Mansfield, 2012). Natural mass regression confers immunity to reinfection (Niven *et al*., 1961), and the surgical removal of a Yaba mass in a baboon prior to natural regression was associated with subsequent susceptibility and reinfection with Yaba virus.

Six human volunteers have been inoculated experimentally with Yaba virus and developed similar, but smaller masses than those seen in monkeys; mass regression was also earlier. Yaba mass induction has been recorded as a result of accidental self-inoculation (needlestick) in a laboratory worker using the virally infected cells. Complete mass resection was curative.

2. *Orf Virus (Contagious Ecthyma)*

Orf virus is a *Parapoxvirus* disease of sheep, goats, and wild ungulates characterized by epithelial proliferation and necrosis of the skin and mucous membranes of the urogenital and gastrointestinal tracts.

Reservoir and Incidence Orf virus disease is an endemic infection in many sheep flocks and goat herds throughout the United States and worldwide. The disease affects all age groups although young or immunocompromised animals are most frequently and most severely affected. Mortality may be high in lambs (10%) and kids (93%) often partially due to anorexia resulting from severe oral lesions or secondary infections (Hosamani *et al*., 2009). In sheep, orf virus infection does not reliably confer protection against reinfection with different strains of virus, aiding in viral persistence within a population (Haig *et al*., 1997). Recently, orf virus infections have been reported in multiple other ungulate species (Hosamani *et al*., 2009).

Mode of Transmission Orf virus is transmitted to humans by direct contact with scabs and exudates from viral-laden lesions. Scabs may remain infectious in the environment for years. External lesions are not always readily apparent. Transmission of this agent by fomites or other animals contaminated with the virus is also possible due to the extended environmental persistence of the virus. Although the virus requires a break in the

skin for entry, rare cases of person-to-person transmission have been recorded (Chin, 2000).

Clinical Signs Orf virus produces proliferative, pustular encrustations on the lips, nostrils, and mucous membranes of the oral cavity and urogenital orifices of infected animals. Internal organs may also be affected.

The disease in humans is usually characterized by a 3- to 7-day incubation period followed by the development of a solitary lesion on the hands, arms, or face (Fig. 28.2). Initially, the lesion is maculopapular or pustular but then progresses to a weeping proliferative nodule with central umbilication. Occasionally, several nodules are present, each measuring up to 3 cm in diameter and persisting for 3–6 weeks, followed by spontaneous regression with minimal residual scarring. Regional adenitis is uncommon, and progression to generalized disease is considered a rare event although severe disease may develop in immunocompromised individuals. Previous infection does not confer protection as reinfection can occur in both humans and animals (Chin, 2000; Reid and Dagleish, 2011).

Control and Prevention Personnel should wear gloves and hand wash, as well as launder clothing and disinfect boots, after contact with sheep and goats. Current herd management practices in endemic areas can involve the use of live attenuated orf virus vaccines that provide only short-term (approximately 6 months), partial protection and contribute to the perpetuation of environmental contamination. The vaccines also pose some risk to the individuals handling the vaccine product, and there is currently no effective human vaccine. Next generation approaches, such as the development of recombinant subunit vaccines or the use of DNA vaccines, may be able to improve this situation in the future (Hosamani *et al*., 2009; Mercer *et al*., 1997; Zhao, *et al*., 2011).

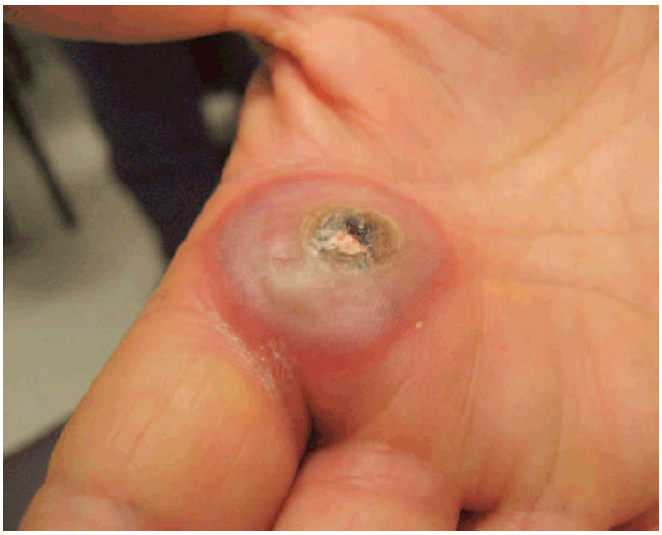

FIGURE 28.2 Bulla caused by orf virus infection after puncture by a bone of a recently slaughtered goat – Pennsylvania, 2009. *MMWR – Human Orf Virus Infection from Household Exposures – United States, 2009–2011.*

B. Hemorrhagic Fevers

The hemorrhagic fever viruses constitute a group of RNA viruses that produce a clinical syndrome in humans characterized by high fever, epistaxis, ecchymosis, diffuse hemorrhage in the gastrointestinal tract and other organs, hypotension, and shock. These diseases often are spread to humans by mosquitoes, ticks, or other arthropod vectors; by direct contact with the excreta of infected rodents; or by the contaminated blood and bodily fluids of other infected animals. These viral agents have taken on increased importance in recent years and are receiving considerable attention within the context of emerging infections potentially impacting the United States and other regions of the globe. Contemporary society has catalyzed the process of emerging infections by introducing ecological disturbances affecting host and vector availability and distribution, by developing rapid means of international transportation, and through the increased proportion of immunocompromised individuals within many populations (e.g., secondary to endemic human immunodeficiency virus (HIV) infections), thereby enhancing the potential dissemination and dispersion of these agents (Bengis *et al*., 2004; Jones *et al*., 2013).

Nonhuman primates serve as reservoirs of and are susceptible to numerous zoonotic viral hemorrhagic diseases (e.g., yellow fever, dengue, Marburg virus disease, and Ebola) as well as to viral hemorrhagic diseases that are not considered zoonotic (e.g., simian hemorrhagic fever). The zoonotic viral hemorrhagic diseases are not likely to be encountered in programs that follow an appropriate quarantine/importation process and are involved in the conventional care of nonhuman primates in indoor facilities. The salient features of natural and experimental infections by these agents in nonhuman primates have been reviewed in detail (Blanchard and Russell-Lodrigue, 2012; Wachtman and Mansfield, 2012) but will be discussed only briefly in this section. Rodent hantavirus infections have resulted in serious and fatal human infection in association with laboratory animal studies and field studies involving wild animals and are covered in more detail.

1. *Flaviviruses – Yellow Fever and Dengue*

Reservoir, Incidence, and Transmission Yellow fever, caused by an RNA flavivirus, is endemic in the tropical regions of the Americas and Africa where the mosquito serves as the reservoir host. The virus is not naturally transmitted directly between humans or between nonhuman primates. Although multiple genuses of mosquitos can be infected and transmit the disease, the *Aedes* spp. (*Stegomyia* spp.) mosquito is of primary importance due to its feeding habits and the ability of the virus to persist in the insect over the dry season by transovarian transmission (Wachtman and Mansfield, 2012).

Two forms of the disease are recognized based on the cyclic transmission between vertebrate hosts and mosquito vectors. In the jungle (sylvatic) form, disease transmission occurs most commonly between tree-hole breeding mosquitoes (e.g., *A. africanus* in Africa, *Haemagogus* spp. in Central and South America) and nonhuman primates residing in the forest canopy. Virus transmission to humans occurs where the human and mosquito ranges overlap such as during forestry activities that disrupt mosquito feeding preferences. Once introduced into a human population, the urban (rural) form of disease transmission may develop in which the virus is transmitted between individuals by peridomestic mosquitoes (predominantly *Aedes aegypti)* which breed well in urban settings and feed on humans (Blanchard and Russell-Lodrigue, 2012; Monath and Staples, 2011).

There are four serotypes of dengue virus, any of which can cause dengue hemorrhagic fever in humans. Dengue is endemic in tropical and subtropical Asia, Africa, Oceania, Australia, and the Americas, and is widespread in the Caribbean basin. Dengue is regarded as one of the most significant emerging diseases in the United States. The virus persists in nonhuman primate–mosquito and human–mosquito cycles involving *A. aegypti* and *A. albopictus.* While *A. aegypti* have been present in the southern United States for many years, the more aggressive *A. albopictus* was only introduced into the United States in 1985 but has quickly expanded its range to at least 18 states (Blanchard and Russell-Lodrigue, 2012). Dengue virus is passed transovarially in the mosquito vector (Chin, 2000).

Clinical Signs Most nonhuman primates are susceptible to yellow fever although disease severity varies significantly across species, with some species exhibiting no clinical signs despite an active infection. African monkeys apparently acquire yellow fever infection as young animals and develop a mild and brief form of the disease with subsequent immunity and induced antibody titers. The disease in both New World nonhuman primates and humans is most frequently fulminating and severe, characterized by fever, vomiting, anorexia, yellow to green urine, icterus, and albuminuria. In humans, a hepatic-induced coagulopathy may develop with gingival hemorrhage, epistaxis, petechiae, hematemesis, melena, or blood oozing from the skin. At necropsy, the internal organs are hemorrhagic, necrotic, and bile-stained. The classic lesion is massive, midzonal necrotizing hepatitis with necrotic hepatocytes containing characteristic eosinophilic, intracytoplasmic inclusion bodies, or 'Councilman bodies' (Gardner and Ryman, 2010; Monath and Staples, 2011).

Immune response to the dengue virus has been demonstrated in a wide range of free roaming nonhuman primate species, indicating that they can be naturally infected with the virus. However, the significance of infection in nonhuman primates is unknown (Wachtman and Mansfield, 2012). Experimental infection of nonhuman primates can induce mild to severe clinical signs. Human dengue infection is characterized by the abrupt onset of fever, intense headache, myalgia, arthralgia, retro-orbital pain, anorexia, gastrointestinal disturbances, and rash. In some, the disease progresses to include a generalized hemorrhagic syndrome with increased vascular permeability, thrombocytopenia, unusual bleeding manifestations, and death.

Diagnosis and Control Yellow fever is diagnosed by identification of the virus in the blood, a specific antibody response, or histopathology. The variable expression of yellow fever in African *versus* New World nonhuman primates decreases the reliability of clinical signs as indicators of active infection. Consequently, imported monkeys should have a certificate that they have originated from a yellow fever-free area; have been maintained in double-screened, mosquito-proof enclosures; or have been vaccinated for yellow fever. The same general principles apply to the prevention of introduction of dengue virus in newly imported nonhuman primates.

The Centers for Disease Control and Prevention (CDC), which regulates nonhuman primate importation facilities, stipulates specific record-keeping procedures, and requires the prompt (within 24 h) reporting of any disease in a nonhuman primate suspected of being infected with yellow fever, Marburg, monkeypox, or Ebola disease (filovirus). This reporting requirement also applies to any illness among staff members that may have been acquired from nonhuman primates. Nonhuman primates that die during primary import quarantine must be necropsied and evaluated for characteristic lesions of yellow fever or other zoonotic diseases (42 CFR 71.53).

Control of human yellow fever is centered on eradication of the *A. aegypti* mosquito as well as human vaccination with the live-attenuated 17D vaccine strain (Gardner and Ryman, 2010). Dengue disease prevention also emphasizes control of the mosquito vector. Human vaccines are being developed.

2. *Marburg Virus Disease*

Marburg virus is a single-stranded RNA virus (genus *Marburgvirus,* family Filoviridae) that is the etiologic agent of Marburg hemorrhagic fever in humans and nonhuman primates (Mehedi *et al.*, 2011). The first outbreak occurred simultaneously in 1967 in Marburg, Frankfurt, and Belgrade with 31 human cases, 7 of which were fatal. The outbreak was traced to one shipment of African green monkeys originating from Uganda, held in an airport exotic animal quarantine facility in London and then shipped to Marburg, Frankfurt, and Belgrade for use in vaccine production. Primary infections were traced to humans exposed to tissues, blood, or primary

cell cultures derived from infected African green monkeys or infected humans. Secondary infection occurred in additional persons in contact with one or more primary cases. No animal handlers were infected. Although African green monkeys are not now believed to serve as a reservoir of the virus, Marburg virus disease is often referred to as African green monkey disease or vervet monkey disease due to the initial association between this nonhuman primate species and virus.

Reservoir and Incidence Between the initial 1967 outbreak and 2013, there have been 10 recognized outbreaks of human Marburg virus infection. In these, the number of identified cases ranged from 1 to 252 cases with the case fatality rate in the four larger outbreaks ranging from 22% to 90%. While most cases are confined to Africa, human cases have been diagnosed in Europe, the Netherlands, and the U.S. Each has been linked to travel in or animal importation from Africa (Centers for Disease Control and Prevention, n.d.-a, n.d.-b).

The natural reservoir for the Marburg disease agent has not been definitively identified, although African fruit bats (*Rousettus aegyptiacus*) are considered highly likely (Towner *et al.*, 2007). Experimental studies in nonhuman primates and other laboratory animals have shown that the virus produces a 100% fatal infection in African green monkeys, rhesus monkeys, squirrel monkeys, guinea pigs, and hamsters. Although African green monkeys were clearly incriminated in the original outbreak, the high fatality rate observed following the experimental infection of African green monkeys and other nonhuman primate species suggests that nonhuman primates are not a likely natural reservoir of the disease (Mehedi *et al.*, 2011).

Mode of Transmission In humans, disease transmission is most commonly traced to mucous membrane or skin exposure to tissues or bodily fluids during the clinical care of infected patients or in handling of their bodies for burial. Parental transmission has occurred and sexual transmission has been suspected in at least one case. Studies in nonhuman primates have demonstrated lethal infections following experimental aerosol exposure. Although human epidemiologic data does not suggest a high risk of aerosol transmission during the clinical care of infected individuals, respiratory transmission has been suspected from inhalation of infected bat excreta. Significant concern exists regarding the potential use of Marburg virus as a bioterrorism agent (Lloyd, 2011; Mehedi *et al.*, 2011). As such, Marburg virus as been classified as a Tier 1 Select Agent (CDC, n.d.-c).

Clinical Signs The incubation period for Marburg disease is 2–21 days in humans and 4–20 days in nonhuman primates (Lloyd, 2011). The disease in humans includes systemic viral replication, immunosuppression, and abnormal inflammatory response, and is manifested by the abrupt onset of fever, chills, myalgia, headache, anorexia, and conjunctival suffusion. In fatal cases, progressive involvement of the gastrointestinal tract with severe pain and gastrointestinal bleeding, maculopapular rash, severe coagulation abnormalities with uncontrolled hemorrhage, renal dysfunction, multiorgan failure, and shock often occurs (Mehedi *et al.*, 2011). The clinical course is very similar in nonhuman primates (Schou and Hansen, 2000) although severity varies across species. Treatment of Marburg virus disease consists of intensive supportive therapy and pain management.

Diagnosis and Prevention Disease diagnosis is possible through virological, serological, and molecular methods, with polymerase chain reaction (PCR) and antigen detection enzyme-linked immunosorbent assay (ELISAs) most commonly employed (Mehedi *et al.*, 2011). Biosafety level 4 (BSL4) containment is required for any procedures involving potentially contaminated substances (e.g., blood, saliva, urine, breast milk). Irradiation and heat can be used to inactivate the virus in some samples to allow their safe handling at lower containment levels. In a recent study, a live, attenuated recombinant vaccine was shown to protect rhesus macaques from development of Marburg virus infection when administered soon after experimental challenge. It is hoped that a similar treatment could be developed for use in humans (Geisbert *et al.*, 2010). No Marburg virus disease vaccines are currently approved for human use.

3. *Ebola Hemorrhagic Fever*

Reservoir and Incidence Ebola and Marburg viruses share many similarities. Morphologically identical but antigenically distinct, they are members of the family Filoviridae. Human cases of Ebola are rare and have been confined to the continent of Africa. Ebola was first detected in Sudan and the Democratic Republic of Congo in 1976. Since that time, multiple virus subtypes have been identified. All induce clinical, often fatal disease in humans with the exception of Ebola-Reston. Hospital case fatality rates range from 42% to 88% (Gire *et al.*, 2012). The subtypes are, in approximate decreasing degree of human disease severity (based on case fatality rates), Zaire, Sudan, Bundibugyo, Ivory Coast, and Reston.

Ebola-Reston is unique as it is the only subtype of Asian (not African) origin and is not known to induce human disease, although human infection can occur. Ebola-Reston was first identified in 1989 in cynomolgus macaques soon after their importation into the United States from an export facility in the Philippines. The infected monkeys died of an acute hemorrhagic disease. It is unknown what influence their coinfection with the immunosuppressive simian hemorrhagic fever virus played in the animals' deaths. Clinical disease was not recognized in animal technicians who handled the

infected animals and who developed filovirus-specific serum antibodies (CDC, 1990;- Dalgard *et al.*, 1992). Nevertheless, the disease outbreak in this nonhuman primate colony within the United States garnered significant public health concerns, ultimately resulting in the development and ongoing enforcement of nonhuman primate importation and handling guidelines (42 CFR Part 71.53). Since the 1989 nonhuman primate outbreak, Ebola-Reston has been identified in additional cynomolgus monkeys associated with the same Philippine export facility as well as on a pig farm in the Philippines where viral transmission, but not disease, occurred in humans (CDC, n.d.-c).

The natural reservoir(s) for the Ebola virus is still debated. Nonhuman primates are not likely natural disease reservoirs (Dalgard *et al.*, 1992). African fruit bats are the leading reservoir candidate of Ebola subtypes of African origin (Leroy *et al.*, 2005). The reservoir for Ebola-Reston is suspected to be a mammal native to Asia.

Mode of Transmission As with Marburg virus, transmission appears in most cases to be from direct contact with infected tissues or close contact with humans or animals shedding the organism. Oral and conjunctival transmission of Ebola-Zaire in macaques has also been confirmed experimentally (Jaax *et al.*, 1996). However, in the natural outbreak of Ebola-Reston infection in a laboratory colony of nonhuman primates, transmission occurred among animals without apparent direct intimate contact, suggesting the possibility of airborne or aerosol transmission. Three of six animal technicians working with these animals developed antibody response to Ebola-Reston virus, but the details of transmission were not determined in all cases. One of these individuals was infected during *postmortem* examination of an infected monkey (Ksiazek *et al.*, 1999). Epidemiologic findings in animal caretakers working in the Philippine-source colony for Ebola-Reston-infected nonhuman primates suggest that the transmission of Ebola-Reston to humans is rare (Miranda *et al.*, 1999).

Clinical Signs In experimental nonhuman primate infections with Ebola-Zaire or Sudan, animals rapidly develop a febrile, debilitating illness characterized by high-titer viremia; virus dissemination and replication in multiple organs producing tissue necrosis, effusions, coagulopathy, and hemorrhage; and death. Although less virulent than the Sudan or Zaire strains of Ebola virus in nonhuman primates, Ebola-Reston produces a hemorrhagic disease in macaques involving multiple organ systems, resulting in death in 8–14 days. Clinical signs in humans vary somewhat by infecting Ebola subtype. With the exception of Ebola-Reston, humans develop a pattern of infection similar to that of nonhuman primates manifested by acute illness, fever, chills, headache, myalgia, and anorexia with progressive deterioration to vomiting, abdominal pain, and sore throat with or without obvious bleeding abnormalities (Feldmann and Geisbert, 2011).

Diagnosis and Prevention The gross and histopathologic findings of Ebola infection have been reported in numerous nonhuman primate species including chimpanzees (Wyers *et al.*, 1999), baboons, African green monkeys (Ryabchikova *et al.*, 1999), and macaques (Dalgard *et al.*, 1992). In macaques, intracytoplasmic inclusion bodies associated with hepatocellular necrosis, adrenal necrosis, and patchy pulmonary interstitial infiltrates were noted in cases of Ebola-Reston infection and considered useful for the differentiation of this disease from simian hemorrhagic fever (Dalgard *et al.*, 1992).

Diagnostic tests commonly used for human infection include reverse transcriptase PCR (RT-PCR), antigen capture ELISA testing, ELISAs for IgM and IgG antibody levels, and virus isolation. A human vaccine is not yet available. Most current vaccine candidates are based on recombinant technologies.

Due to effective importation procedures mandated by the CDC (CDC, 1990), only those personnel employed in nonhuman primate facilities involved in animal importation should have the potential for Ebola virus exposure. These personnel should become familiar with the equipment and procedures used to minimize the potential for Ebola virus transmission in the event of an outbreak. Neither vaccination nor antiviral pharmaceuticals are available for the treatment of Ebola virus infection. Experimental drugs are being tested in an attempt to curb the African Ebola outbreak in 2014. Recently, 16/16 macaques experimentally infected with Marburg virus, a close filovirus relative of Ebola virus, have been protected by administering a small interfering RNA molecule, encapsulated in a lip nanoparticle (Tekmira drug — TKM-Marburg) on day 3 postinfection, when clinical signs begin to manifest. Infected monkeys not receiving the drug died between days 7 and 9 (Thi *et al.*, 2014). It is recommended that BSL 4 containment be employed with Ebola virus (CDCP-NIH, 2009).

4. Hantaviruses (Hemorrhagic Fever with Renal Syndrome; Hantavirus Pulmonary Syndrome)

Reservoir and Incidence Within the family Bunyaviridae, the genus *Hantavirus* is composed of at least 20 viruses known to naturally infect a wide range of mammalian species including numerous wild rodents that serve as disease reservoirs. Unlike other members of the Bunyaviridae family, hantaviruses are maintained in vertebrate–vertebrate cycles without arthropod vectors (Maclachlan *et al.*, 2011a). Antibodies against hantaviruses have been detected in multiple species including domestic and wild cats, dogs, pigs, cattle, deer, and nonhuman primates. Evidence exists that cats and pigs may

serve as a reservoir of infection for humans for at least one hantavirus (Zeier *et al*., 2005). Other animal species may also serve as disease reservoirs for human infection. In the United States, serological surveys have detected evidence of hantavirus infection in urban and rural areas involving *Rattus norvegicus*, *Peromyscus maniculatus*, *P. leucopus, Microtus pennsylvanicus*, *Tamias* spp., *Sigmodon hispidus*, *Reithrodontomys megalotis*, *Oryzomys palustris*, and *Neotoma* spp. (CDCP-NIH, 2009; Schmaljohn and Hjelle, 1997; Tsai *et al*., 1985).

In humans, hantaviruses are responsible for two recognized disease syndromes, hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). The severity of the disease produced depends on the specific virus involved (LeDuc, 1987; Maclachlan *et al*., 2011a; Schmaljohn and Hjelle, 1997). Old World (Asia and Europe) hantaviruses are responsible for HFRS, whereas New World (the Americas) hantaviruses are responsible for HPS. Rodent reservoir species typically remain asymptomatic despite persistent infection and viral shedding in the saliva, urine, and feces (Maclachlan *et al*., 2011a).

Over 200,000 human cases of HFRS are reported yearly throughout the world with most cases in China, Russia, and Korea (Maclachlan *et al*., 2011a). At least four hantaviruses are involved (Hantaan, Seoul, Puumala, and Dobrava), each with a specific reservoir rodent host.

Multiple hantaviruses can induce HPS. In 1993, the first cases of HPS were diagnosed in the Four Corners area of the United States with an over 50% case fatality rate (CDC, n.d.-f; Schmaljohn and Hjelle, 1997). The genetically distinct hantavirus responsible for this outbreak was subsequently named Sin Nombre virus (Zeier *et al*., 2005). Since the initial outbreak, cases of HPS have been reported in 34 U.S. states (36% case fatality rate) and Central and South America including a 2012 outbreak in Yosemite National Park. About three-quarters of identified cases have been from rural areas and half have been from areas outside of the Four Corners area (CDC, n.d.-f). Hantavirus pulmonary syndrome has been reported in the United States in persons associated with outdoor activities and occupations that place them in close proximity to infected wild rodents and their excrement (Hjelle *et al*., 1996; Jay *et al*., 1996; Schmaljohn and Hjelle, 1997). Cases of clinical disease and/or seroconversion has been recognized in individuals involved in field research studies (Torres-Perez *et al*., 2010), but whether this is directly attributable to wild animal handling or could be associated with contamination of the living quarters associated with fieldwork is not always clear (Kelt *et al*., 2007).

Numerous cases of hantavirus infection have occurred among laboratory animal facility personnel following exposure to infected rats (*Rattus*), including outbreaks in Korea, Japan, Belgium, France, and England (LeDuc, 1987). Infected individuals exhibited clinical signs consistent with HFRS.

Mode of Transmission The transmission of hantavirus infection is through the inhalation of infectious aerosols; brief exposure times (5 min) have resulted in human infection. Rodents shed the virus in their respiratory secretions, saliva, urine, and feces for many months (Tsai, 1987). Transmission of the infection can also occur through an animal bite or from disturbing dried materials contaminated with rodent excreta, allowing wound contamination, conjunctival exposure, or ingestion to occur (CDCP-NIH, 2009). Infection of animal caretakers and research personnel has resulted from the introduction of infected wild rodents into the laboratory animal facility environment as well as biologics derived or contaminated by them. Person-to-person transmission is rare, but has been documented with select hantaviruses (Schmaljohn and Hjelle, 1997).

Clinical Signs Clinical signs are related to the hantavirus species involved and are largely a result of the target cell of infection, endothelial cells (Zeier *et al*., 2005). The classical pattern of HFRS is characterized by fever, headache, myalgia, and hemorrhagic manifestations including petechiae, anemia, gastrointestinal bleeding, oliguria, hematuria, severe electrolyte abnormalities, and shock (Lee and Johnson, 1982). Common clinical signs and laboratory abnormalities of HPS include a febrile prodrome, headache, thrombocytopenia (usually without overt hemorrhage), and leukocytosis. In addition, patients may develop a non-productive cough and shortness of breath that can rapidly proceed to respiratory failure due to capillary leakage into the lungs, followed by shock and cardiac complications (CDCP-NIH, 2009; Schmaljohn and Hjelle, 1997).

Diagnosis and Prevention Both antigenic and genetic methods have been used for the characterization of the hantaviruses. RT-PCR, antigen capture ELISA, and immunohistochemistry are most commonly used (Maclachlan *et al*., 2011a). Additional information about hantavirus serological testing is available through the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention. Treatment is based on provision of supportive care. Administration of the antiviral drug ribavirin can be beneficial in the treatment of HFRS, but not HPS (Bi *et al*., 2008). No vaccine is currently available.

Hantavirus infections should be prevented through the detection of infection in rodents and rodent tissues prior to their introduction into resident laboratory animal populations and facilities (Maclachlan *et al*., 2011a). Rodent tumors and cell lines can be tested for hantavirus contamination with PCR and immunofluorescence assays. Also, wild rodent intrusions into animal facilities must be prevented. Animal BSL 4 (ABSL4) guidelines are recommended for

animal studies involving hantavirus infections in permissive hosts such as *P. maniculatus*. Wild-caught rodents brought into the laboratory that are susceptible to hantaviruses producing HPS or HFRS should also be handled according to these guidelines (CDCP-NIH, 2009).

C. Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus (LCMV) infections in rodents (e.g., mice, hamsters) are of particular interest and concern as the virus can be transmitted from asymptomatic, infected animals to humans with relative ease. While some estimate that up to 5% of the U.S. population has been infected with LCMV, seriously debilitating and fatal human infections are uncommon (case fatality rate <1%), but do occur (Childs *et al*., 1997; Fischer *et al*., 2006; Morita *et al*., 1996; Smith *et al*., 1993; Stephensen *et al*., 1992). In parallel with the persistent and emerging importance of arenaviruses for humans with wild rodent contact, LCMV has remained an important natural infection of laboratory animals (Bowen *et al*., 1975; Dykewicz *et al*., 1992; Jahrling and Peters, 1992; Rousseau *et al*., 1997).

Reservoir and Incidence LCMV is a member of the family Arenaviridae, which are single-stranded RNA viruses with a predilection for rodent reservoirs. Other members of the family are important zoonoses that produce a hemorrhagic fever syndrome, including Lassa fever (in Africa) and Argentine and Bolivian hemorrhagic fevers (in South America).

The house mouse, *Mus musculus*, is the recognized natural reservoir host of LCMV with infected wild mouse populations present throughout most of the world. LCMV infections have also been noted in multiple common laboratory animal species including rats, hamsters, guinea pigs, rabbits, swine, dogs, and nonhuman primates. LCMV is especially well adapted to the mouse, living in a symbiotic relationship characterized by asymptomatic infection with lifelong virus shedding. The mouse, and in certain well-defined outbreaks, the hamster, has remained the species of primary concern as zoonotic reservoirs in the laboratory as evidenced by a recent outbreak of LCMV in humans (Dykewicz *et al*., 1992). Athymic and other immunodeficient mouse strains may pose a special risk by harboring silent, chronic infections (CDCP-NIH, 2009; Dykewicz *et al*., 1992).

An LCMV variant has been identified as the etiologic agent of the disease marmoset (callitrichid) hepatitis (Stephensen *et al*., 1995). First reported in the 1980s at 11 North American zoos, epizootics of the disease have occurred in zoological parks in both the United States and England, often with high case fatality rates in marmosets and tamarins (Montali *et al*., 1989, 1995). Rodent infestations are common in zoos and mice, as known carriers of LCMV are the probable source of infection in these outbreaks. Some outbreaks have been traced to the feeding of neonatal mice ('pinkies') from enzootically infected mouse populations to callitrichids (Montali *et al*., 1993). Interestingly, two veterinarians involved in the care of infected callitrichids seroconverted to the agent but did not develop clinical signs of disease (Blanchard and Russell-Lodrigue, 2012). The pathologic lesions observed in LCMV-infected callitrichids share many similarities with those of humans infected with another *Arenavirus* in sub-Saharan Africa, Lassa hemorrhagic fever virus. As a result, callitrichids have been proposed as an animal model of human Lassa disease.

Mode of Transmission The course of LCMV infection of the laboratory mouse is influenced by host factors and the organotrophism of the LCMV strain (Baker, 1998). Under some circumstances, LCMV produces a pantropic infection and may be copiously present in the blood, cerebrospinal fluid, urine, nasopharyngeal secretions, feces, and tissues of natural hosts and possibly humans. In endemically infected mouse and hamster colonies, the infection is transmitted *in utero* or early in the neonatal period, producing a tolerant infection characterized by chronic viremia and viruria without significant clinical disease. Thus, bedding material and other fomites contaminated by LCMV-infected animals can be important sources of infection for humans, as demonstrated in numerous outbreaks among laboratory animal technicians (Dykewicz *et al*., 1992; Newcomer and Fox, 2007; CDC, 2012b). Exposure of adult, immunocompetent mice most frequently results in a transient infection with seroconversion although persistent infection with wasting may develop following immune exhaustion (Maclachlan *et al*., 2011b). This differs from the hamster that may remain persistently infected regardless of the age at exposure.

The experimental passage of tumors and cell lines appears to pose one of the biggest threats for the introduction of LCMV into animal facilities at the present time. Spread of LCMV among animals by contaminated tumors and cell lines has been widely recognized (Bhatt *et al*., 1986; Dykewicz *et al*., 1992; Nicklas *et al*., 1993). Transmission by infected, bloodsucking ectoparasites has been demonstrated experimentally, and LCMV has been recovered from cockroaches. However, these sources for LCMV infection have not been shown to play a significant role in any of the LCMV infections (human or animal) in laboratory animal facilities to date.

Infection in humans may be by parental inoculation, inhalation, or contamination of mucous membranes or broken skin with infectious tissues or fluids from infected animals as may occur with bites. Airborne transmission is well documented. In human LCMV infections associated with infected pet hamsters, the infection rate correlated with cage type and cage location in the household. Open wire cages were correlated with the highest rate

of infection, whereas deep boxes and aquariums were associated with a lower human infection rate. Similarly, cage placement in an area of high human activity was associated with infection, but cages located away from areas of frequent human activity (e.g., the basement) did not result in infection of occupants (Biggar *et al.*, 1975). Also, infections are known to occur in individuals who have not had direct physical contact with infected hamsters but who had simply entered the room housing the animals (Hinman *et al.*, 1975). These findings suggest that airborne transmission plays an important role in human infection. Human-to-human transmission has been documented through maternal–fetal transmission and solid organ transplantation (CDC, 2008; Fischer *et al.*, 2006; Macneil *et al.*, 2012).

Clinical Signs LCMV was so named due to the lymphocytic choriomeningitis induced in multiple species following experimental intracerebral inoculation. Clinical signs are not usually evident in immunocompetent mice naturally infected as fetuses or neonates, although signs (e.g., body condition wasting, weakness, tremors) may develop if immunotolerance wanes ('late-onset disease') or if mice are infected a few days after birth. Hamsters infected as adults typically remain asymptomatic, while hamsters infected early in life may fail to thrive and display growth retardation, weakness, conjunctivitis, dehydration, and/or tremors (Maclachlan *et al.*, 2011b).

Humans usually develop a transient flu-like illness characterized by fever, myalgia, headache, and malaise following an incubation period of 1–3 weeks (Table 28.1). However, more serious disease manifestations may develop in patients including photophobia, vomiting, nuchal rigidity, central nervous system disease (e.g., septic meningitis, meningoencephalitis), and rarely pneumonitis, myocarditis, orchitis, dermatitis, and pharyngitis (Bonthius, 2012; Maclachlan *et al.*, 2011b). Fatal human cases have been characterized by severe pharyngitis, fever, bleeding abnormalities, pneumonia, and hepatic triaditis. In the last decade, at least five clusters of deaths in human transplant recipients have resulted from the implantation of solid organs from donors later known or presumed to be infected with LCVM (Macneil *et al.*, 2012; Schafer *et al.*, 2014). A hemorrhagic fever-like disease was noted in some of these individuals (CDC, 2008). It is postulated that the severity of disease in transplant recipients is largely influenced by their induced immunosuppression (Fischer *et al.*, 2006). Intrauterine infection has resulted in fetal and neonatal death, hydrocephalus, and chorioretinitis (Maclachlan *et al.*, 2011b).

Diagnosis and Prevention ELISAs and immunofluorescence assays are most commonly employed to screen mice that may have been exposed to the virus after the neonatal period. These assays are not useful to diagnose persistently infected, immune tolerant mice, as circulating antibodies may not be present at detectable levels. RT-PCR should be used in these circumstances and to screen biologic materials (e.g., cell lines, tumors, serum). The virus does grow easily in many cell types but produces minimal cytopathic effects. Therefore, cell cultures must be assayed for antigen detection (Charrel and de Lamballerie, 2010; Maclachlan *et al.*, 2011b). Depopulation of infected colonies is highly recommended. Prevention of this disease in animal facilities is achieved through the periodic serological surveillance of both new animals with inadequate disease profiles and resident animal colonies at risk. Screening all biologics intended for animal passage for the presence of LCMV is another crucial element in the program to prevent the introduction of LCMV into established animal colonies. The exclusion of wild rodent vermin and the elimination of ectoparasites and insect vectors from animal facilities are part of the overall scheme for LCMV disease prevention and are expected of modern laboratory animal facilities.

Human infection is most frequently diagnosed through a combination of serologic testing, virus isolation from the blood or cerebrospinal fluid, PCR testing, and immunohistochemistry. Treatment consists of supportive care as no specific antiviral medications are recommended.

TABLE 28.1 Symptoms of Persons with Positive Titers for Lymphocytic Choriomeningitis

	Number of cases	
Symptom	**49[a]**	**11[b]**
None recognized	3	1
Fever	44	9
Headache	42	7
Myalgia	39	8
Pain on moving eyes	29	7
Nausea	26	9
Vomiting	17	9
Biphasic illness	12	NR[c]
Sore throat	12	NR
Photophobia	12	7
Cough	9	1
Swollen glands	8	NR
Diarrhea	8	1
Rash	6	1
Upper respiratory tract symptoms	6	NR
Orchitis	1	NR

[a]*From Biggar et al. (1975).*
[b]*From Maetz et al. (1976).*
[c]*NR, None recognized.*

D. B Virus Infection (*Macacine herpesvirus* 1)

Many animal species commonly maintained in a research setting are susceptible to natural infections with herpesviruses (e.g., saimiriine herpesvirus 1 and 2, suid herpesvirus 1, porcine lymphotrophic herpesvirus 1). While few animal herpesviruses are proven zoonotic agents, there is great concern that at least some may crossover to the human population, especially into immunocompromised individuals or in association with xenotransplantation. However, macacine herpesvirus 1 (formerly *Cercopithecine herpesvirus 1* and *herpesvirus simiae* and often referred to as herpes B, monkey B virus, and herpesvirus B) stands alone as a documented hazard with devastating potential for humans working with select nonhuman primate species.

Reservoir and Incidence First described by Gay and Holden following a cluster of human cases in 1932, B virus produces a life-threatening disease of humans that has resulted in approximately 40 reported human cases with a greater than 70% case fatality rate (CDC, 1987, 1989a,c, 1998; Huff and Barry, 2003). Only macaque monkeys (e.g., rhesus, cynomolgus, and pig-tailed macaques) are known to naturally harbor B virus (Cohen *et al.*, 2002). The virus has been detected in the saliva, urine, feces, and nervous tissue of infected macaques as well as cell cultures derived from their tissues. The virus persists latently in the trigeminal and lumbosacral ganglia of the macaque with occasional reactivation of viral shedding from peripheral sites in asymptomatic animals in response to physical or psychological stressors or during periods of immunosuppression (Estep *et al.*, 2010; Simmons, 2010). The infection is transmitted between macaques by virus-laden secretions through close contact involving primarily the oral, conjunctival, and genital mucous membranes (Weigler *et al.*, 1995). Infection of other nonhuman primate species can be fatal although select Old World monkey species have been shown to be seropositive to B virus, indicating that they may also be potential disease reservoirs (Kalter *et al.*, 1997).

In an endemically infected domestic macaque production colony, the incidence of B virus infection was shown to increase with animal age, approaching 100% by the end of their first breeding season (Weigler *et al.*, 1993). Wild-caught rhesus macaques have also exhibited a high (near 100%) seroconversion rate following their capture. Consequently, B virus should be considered endemic among Asian monkeys of the genus *Macaca*.

Three genotypes of B virus have been identified through molecular and phylogenetic analysis with each genotype represented by isolates from the presumed macaque species of origin: rhesus and Japanese macaques, cynomolgus macaques, and pigtail macaques (Smith *et al.*, 1998). Nearly all humans diagnosed with B virus infection have had known contact with rhesus macaques in a research setting and all recovered human isolates have been of the rhesus viral genotype (Smith *et al.*, 1998; Weigler, 1992). As a result, the strain common in rhesus macaques is suspected to be more pathogenic for humans (Huff and Barry, 2003).

Mode of Transmission The transmission of B virus to humans primarily occurs through exposure to contaminated saliva through bites and scratches. Exposure by the airborne route may have played a role in several human cases (Palmer, 1987), and exposure of ocular mucous membranes to biological material, possibly fecal, has been confirmed in one human fatality (CDC, 1998). Other confirmed routes of B virus transmission to humans include needle stick injury (Benson *et al.*, 1989) and exposure to infected nonhuman primate tissues (Wells *et al.*, 1989). The possibility of fomite transmission through an injury obtained in handling contaminated caging warrants consideration in an institution's hazard assessment and risk analysis. One case of human-to-human transmission has been documented (CDC, 1987). In this case, the spouse of an infected animal handler contracted B virus infection after applying ointment to herpetic skin lesions on her husband and then to an area of dermatitis on her own hand (Cohen *et al.*, 2002).

Clinical Signs In macaques, the natural disease reservoir, infection is asymptomatic or results in only a mild clinical disease similar to human herpes simplex virus infection. During primary infection, macaques develop vesicles or ulcers on the mucous membranes or skin that generally heal within a 1- to 2-week period; keratoconjunctivitis or corneal ulcer may also be noted. Recovery is usually uneventful.

In humans, the period between initial exposure and onset of clinical signs ranges from 2 days to, more frequently, 2–5 weeks. However, in one case, an individual developed severe clinical disease from B virus 10 years after his last known exposure to the agent. Researchers in the field have also suggested that asymptomatic human B virus infection may occur (Benson *et al.*, 1989), but it is not known whether viral reactivation resulting in severe clinical disease can occur later.

Disease progression is influenced by the number of inoculated infectious viral particles as well as the anatomic site of exposure. In most cases, following exposure by bite, scratch, or other local trauma, humans may develop a herpetiform vesicle at the site of inoculation. In the B virus fatality resulting from ocular exposure, the patient did not develop a dendritic corneal lesion typical of ocular herpes infections; rather, she developed a swollen, painful orbit with conjunctivitis (CDC, 1998). As the clinical signs in this patient progressed, she developed retro-orbital pain, photophobia, anorexia, nausea, and abdominal pain. Other early clinical signs of B virus include myalgia, fever, headache, and fatigue followed by progressive neurological disease characterized by

numbness, hyperesthesia, paresthesia, diplopia, ataxia, confusion, urinary retention, convulsions, dysphagia, and an ascending flaccid paralysis resulting in respiratory failure. Central nervous system involvement signals a grave prognosis even with aggressive treatment (Huff and Barry, 2003).

Diagnosis and Prevention Direct virus isolation is the 'gold standard' in B virus disease diagnosis, although it cannot detect latent infections *pre-mortem*. Serologic assays are often used to detect an immunological response to infection. However, immunologic response is delayed for some period of time after infection. Both virus isolation and the conduct of select serologic assays require BSL4 containment as they involve manipulation of live, infectious virus. More recently, PCR methods and serologic assays with recombinant technology have been developed that do not require BSL4 containment, thus simplifying disease diagnosis (Huff and Barry, 2003; Katz *et al*., 2012).

A key provision to prevent B virus exposures within an institution's animal care and use program concerns the utilization of macaques as research subjects. Macaques should be used only when there are no suitable alternative animal models. Efforts to acquire and maintain macaques free of B virus infection should be pursued whenever feasible. Efforts have been made to produce macaque colonies free of B virus (Weir *et al*., 1993). While the incidence of disease in these colonies is significantly lower than in conventional colonies, all macaques must be considered potentially infected with B virus and handled accordingly.

Following a 1987 outbreak of B virus infection in monkey handlers, guidelines were developed to prevent B virus infection in humans (CDC, 1987). Additional provisions for protection against B virus exposure via ocular splash were adopted following the death of a young woman exposed by this route (CDC, 1998). Readers should refer to these sources or other detailed reviews before engaging in studies involving macaques or developing institutional programs for the prevention and control of B virus among monkey handlers (Blanchard and Russell-Lodrigue, 2012; Cohen *et al*., 2002). Briefly, these recommendations emphasize the need for nonhuman primate handlers to conform fully with a written comprehensive PPE program based on a thorough hazard assessment of all work procedures, potential routes of exposure, and potential adverse health outcomes (CDC, 1998).

Approaches to hazard assessment and the development of occupational health and safety programs for research animal facilities have been reviewed extensively in other sources (ILAR, 1997). Use of protective clothing, including protective gloves or long-sleeved garments and barriers to mucous membrane exposure (e.g., goggles, mask), is essential to prevent exposure to infectious secretions. The use of a face shield is insufficient as the sole method for protection against ocular exposure because droplet splashes to the head may drain into the eyes and infectious materials may enter via the gap along the margins of the shield. The use of examination gloves alone for hand protection should be reserved for the handling of monkeys under full chemical restraint. Chemical restraint or specialized restraining devices should be used whenever possible to reduce personnel injuries.

The outcome of a human exposure is heavily influenced by the time until treatment initiation. Patients should have direct and immediate access to local medical consultants knowledgeable about B virus and versed in current B virus treatment recommendations as prescribed by the Centers for Disease Control and Prevention and the B Virus Working Group (Cohen *et al*., 2002). Prompt and thorough cleaning of the exposure site is vital after which serum samples and cultures should be obtained for serology and viral isolation from both the patient and the macaque. Antiviral therapy (e.g., valacylovir or acyclovir) may also be warranted based on the nature of the exposure (e.g., deep puncture bite, mucosal exposure), the interval between exposure and cleaning of the exposure site, and a positive culture of B virus from the patient or nonhuman primate (Cohen *et al*., 2002). However, antiviral therapy is not without risk to the patient and may complicate diagnostic testing. The administration of antiviral therapy in patients diagnosed with B virus infection is controversial because increasing antibody titer has been demonstrated in a patient following its discontinuation (Cohen *et al*., 2002). The determination of the most efficacious antiviral(s) for use is ongoing (Krug *et al*., 2010). Physicians should consult the National Center for Immunization and Respiratory Disease, Division of Viral Diseases, Centers for Disease Control and Prevention, for assistance in case management. Additional information about B virus diagnostic resources is available through the National B Virus Resource Center, Georgia State University, Atlanta, Georgia.

E. Rabies

Rabies is an acute, almost invariably fatal disease caused by a virus in the genus *Lyssavirus* of the family *Rhabdoviridae* (Banyard and Fooks, 2011).

Reservoir and Incidence Rabies occurs worldwide with the exception of a few countries, generally island nations and other regions that have excluded the disease through animal importation and control programs with the aid of geographic barriers. Bats and terrestrial carnivores are the natural hosts of the rabies virus; however, most mammals are susceptible to infection (CDCP-NIH, 2009). Historically, most human rabies cases resulted from contact with infected domestic animals including pets and agricultural species. This has slowly changed

such that now most human cases result from contact with infected wildlife.

The grand majority of confirmed animal rabies cases in the United States are reported in wildlife species with raccoons, bats, skunks, and foxes predominating (Dyer *et al.*, 2013). Only two laboratory-acquired human rabies cases have been documented in the United States, neither involving direct animal exposure (CDC, 1977; Winkler *et al.*, 1973). Among the rodent and lagomorph species maintained in the laboratory, the wild-caught groundhog and rabbit appear to represent a risk of transmitting rabies (Childs *et al.*, 1997; Karp *et al.*, 1999). In addition, other rabies-susceptible wildlife species studied in the field or introduced into the laboratory have the potential to harbor rabies virus (Fitzpatrick *et al.*, 2014). Because the incidence of rabies in wildlife in the United States is high and continues to increase, the possibility of rabies transmission to dogs, cats, or other species with uncertain vaccination histories and originating from an uncontrolled environment must be considered.

Mode of Transmission Rabies virus is transmitted by the bite of a rabid animal or by the introduction of virus-laden saliva into a fresh skin wound or intact mucous membrane. Transmission through urine and feces exposure is technically possible, but considered to be of low risk (Banyard and Fooks, 2011). Of particular concern is the risk of aerosol transmission of the rabies virus, although the true risk of this means of transmission has been questioned (Gibbons, 2002). Most human cases are associated with bat variant rabies virus infection contracted either during an unrecognized exposure incident or following an exposure incident for which the individual did not seek prompt medical care (Dyer *et al.*, 2013). The virus has also been transmitted through corneal and organ transplants from individuals with undiagnosed central nervous system disease.

Clinical Signs While there are no pathognomonic signs of animal rabies cases, most infected animals will develop either the 'furious' or 'dumb' form of the disease. The furious form is characterized by progressive neurologic signs often including hyperexcitability, parasthesia occasionally with self-mutilation, and death secondary to respiratory arrest and organ failure. In contrast, the dumb form is characterized by lethargy, incoordination, and ascending paralysis (Banyard and Fooks, 2011).

In humans, the timing until disease onset as well as the speed of disease progression is influenced by many variables including the anatomic site of exposure, the quantity of virus inoculated, virus strain, and host age and immune status (Banyard and Fooks, 2011). The disease course proceeds through several phases: incubation, prodrome state, acute neurologic period, coma, and death (CDC, 2010a). The incubation period in humans is ordinarily 1–3 months but may vary from 9 days to over 8 months. During the 2- to 4-day prodromal stage, patients experience a period of apprehension and develop headache, malaise, and fever. An abnormal, indefinite sensation at the exposure site is the first specific symptom. Patients may also develop intermittent periods of excitation, nervousness, or anxiety interspersed with quiet periods when the mental state appears normal. Further progression of the disease is marked by paresis or paralysis, inability to swallow, hydrophobia, delirium, convulsions, and coma. Few individuals recover from rabies infection; once clinical signs develop, the disease is almost invariably fatal from an acute viral encephalomyelitis followed by respiratory paralysis (Banyard and Fooks, 2011; Hemachudha *et al.*, 2013).

Diagnosis and Prevention Rabies should be considered as a differential diagnosis in any wild-caught or random-source laboratory animal of unknown vaccination history exhibiting encephalitic signs. Any wild animal that has bitten a human should be submitted for rabies examination in a manner that permits definitive identification of the species for epidemiologic purposes if the species is not already known.

No reliable *pre-mortem* diagnostic test is available for use in animals. In human patients, multiple methods are most frequently used in combination to diagnose the disease. These include virus isolation, molecular techniques (e.g., RT-PCR), and antibody or antigen detection techniques.

The definitive diagnosis of rabies requires identification of the virus in any part of the brain via the direct fluorescent antibody (DFA) test and therefore is conducted *postmortem*. Most commonly, at least two brain regions are examined with the brain stem and cerebellum preferred. In the absence of the DFA test, histologic examination of brain tissue or molecular evaluation of other tissues or fluids can be useful but must be interpreted with caution and have not been widely adopted for use by diagnostic laboratories.

Preventing or minimizing disease development following a potential rabies virus exposure is heavily influenced by a person's pre-exposure rabies vaccination status as well as the speed at which the exposure site is thoroughly cleaned and additional postexposure prophylaxis (PEP) is provided. Rabies vaccines, administered in a series of injections as a component of pre-exposure prophylaxis, are highly efficacious and should be available to personnel at high risk for encountering the virus including veterinarians, personnel involved in the care of high-risk or inadequately characterized animals, field biologists working in rabies-endemic areas, and scientists working directly with the virus. The need for periodic booster vaccinations is determined by an individual's subsequently measured rabies serum antibody titer (Banyard and Fooks, 2011).

General guidelines for PEP administration are published and periodically updated by the CDC's Advisory

Committee on Immunization Practices. In addition to prompt cleaning and wound care, the guidelines call for application of human rabies immune globulin at and around the exposure site of individuals without prior vaccination as well as multiple parental administrations of rabies vaccine. The number of recommended vaccine doses, administered at a defined interval, varies based on the individual's pre-exposure vaccination status and presumed general immunocompetence (CDC, 2010a).

Whenever possible, animals brought into the laboratory should have histories that preclude their exposure to rabies or assure that they have been previously vaccinated for this disease. Serologic assays have been developed to help identify vaccinated animals. Vaccine titers should not be used to determine the timing of booster vaccinations (Banyard and Fooks, 2011; Brown *et al.*, 2011).

F. Viral Hepatitis Infections

Many of the nonhuman primate zoonoses causing systemic infections in humans include hepatitis as one component of the disease. However, of the viral infections that target the liver as the primary site of involvement, only hepatitis A virus (HAV) has proven to be a significant zoonotic pathogen in the laboratory animal facility environment. Nonhuman primates are important experimental hosts in viral hepatitis research and have been used to study hepatitis A, B, C, D, and E infections (Vitral *et al.*, 1998). Other viruses known to induce hepatitis in naturally acquired infections of laboratory animal species include the coronavirus, mouse hepatitis virus; the adenovirus, infectious canine hepatitis virus; and the hepadnavirus, woodchuck hepatitis virus. None of these are recognized zoonotic agents.

1. Hepatitis A

Reservoir and Incidence HAV is a human enterovirus belonging to the family Picornaviridae. The primary reservoirs for HAV infection are humans, with nonhuman primate infections resulting from contact with infected humans or other infected nonhuman primates. However, more than 100 cases of HAV infection in humans have been associated with newly imported chimpanzees (Dienstag *et al.*, 1976; Hinthorn *et al.*, 1974). There are also many other nonhuman primate species naturally susceptible to HAV, including tamarins, owl monkeys (*Aotus trivirgatus*), African green monkeys, cynomolgus (*M. fascicularis*) and rhesus macaques, and that could serve as sources for human HAV infection (Burgos-Rodriguez, 2011; Lemon *et al.*, 1990; Shevtsova *et al.*, 1988; Wachtman and Mansfield, 2012).

Mode of Transmission HAV can be isolated from the blood and is shed in the feces during the prodromal phase of the disease. It is transmitted by the fecal–oral route, most commonly via contaminated food or water. Aerosol transmission is not suspected (CDCP-NIH, 2009).

Clinical Signs The disease in nonhuman primates is much less severe than in humans and is frequently subclinical. Clinical disease develops in the chimpanzee, owl monkey, and several marmoset species, and is characterized by malaise, vomiting, jaundice, and elevated serum levels of hepatic enzymes.

The disease in humans varies from a mild illness lasting less than 2 months to a severely debilitating illness lasting up to 6 months. Following an incubation period of approximately 1 month, patients experience an abrupt onset of fever, malaise, anorexia, nausea, joint pain, and abdominal discomfort followed within a few days by jaundice (Fig. 28.3). Children often have mild disease without jaundice, whereas HAV infections in older patients may be fulminant and protracted with prolonged convalescence. However, protracted HAV infection is considered an acute infection that is ultimately resolved by the patient; a chronic hepatitis A carrier state has never been shown to exist. Infection confers lifelong immunity (ACIP, 2006).

Diagnosis and Prevention Infection is diagnosed by demonstration of elevated IgM-specific anti-HAV or total combined IgM and IgG anti-HAV antibodies in the serum or plasma. Alternatively, detection of HAV RNA in the blood or feces is considered diagnostic of active infections. The presence of IgG anti-HAV antibodies is useful in detecting previous infection (ACIP, 2006).

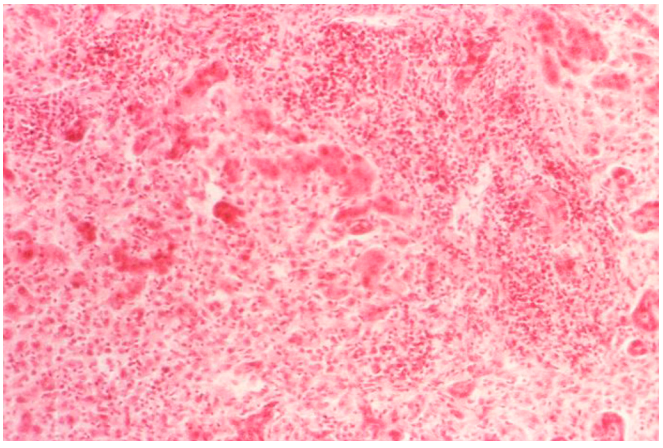

FIGURE 28.3 Under a magnification of 100×, this hematoxylin and eosin photomicrograph depicts the cytoarchitectural changes found in a liver tissue specimen extracted from a hepatitis A patient. In this particular view, note that there are several layers of hepatic parenchyma, which are still recognizable in the midst of massive necrosis. There is no fatty change, but there is an extensive inflammatory infiltrate. *Source: PHIL Library ID# 13020.*

A safe, effective multidose hepatitis A vaccine is available in the United States and is recommended for individuals at high risk for exposure to HAV infection, such as persons involved with the care of nonhuman primates used in experimental HAV infection studies. Passive protection of such persons can also be undertaken through the intramuscular administration of specific immune serum globulin (ISG). Passive protection should be given before experimental animal HAV infection studies begin because infected animals start shedding HAV at 7–11 days postinoculation and continue shedding for several weeks. Two different dosages of ISG are recommended, each providing differing durations of passive protection (1–2 months *versus* 3–5 months) (ACIP, 2006). PEP can be administered following suspected virus exposure. PEP recommendations varies with the age and prior vaccination history of the exposed individual and may include administration of a single-antigen hepatitis A vaccine and/or ISG within 2 weeks of exposure (ACIP, 2007). The use of protective clothing, personal hygiene, and appropriate sanitation practices for equipment and facilities will also minimize the potential for zoonotic transmission.

2. *Hepatitis E Virus*

Hepatitis E virus (HEV) is unique among the major hepatitis viruses (A, B, C, and D) in that animals serve as natural reservoirs of the virus (Pavio *et al.*, 2010). HEV is classified in the genus *Hepevirus* and is currently subdivided into at least four major genotypes, although additional genotypes are proposed (Maclachlan *et al.*, 2011c). Genotypes 1 and 2 infect only humans; genotypes 3 and 4 can infect both humans and a range of other species involved in zoonotic transmission of the virus. HEV infects people worldwide, causing a sometimes fatal viral hepatitis (Lhomme *et al.*, 2013). Its detection in animal populations has steadily risen in the recent past, thereby prompting increased concern of its zoonotic potential.

Reservoir and Incidence In humans, a large proportion of the enterically transmitted acute viral hepatitis cases in developing countries in Asia, Africa, and Mexico are due to HEV infections. In industrialized countries, serologic evidence of HEV exposure is high and widespread, although clinical HEV infection is only sporadically diagnosed. Hepatitis E may be disproportionally fatal in pregnant women, with over a 25% case fatality rate as compared to 1% in the general population (Meng, 2005). However, it is unclear what role other underlying health factors may have played in this increased fatality rate (Meng, 2010a). In industrialized countries, identified cases usually occur sporadically, presumably due to zoonotic transmission from one or more animal reservoirs or following consumption of contaminated meat or shellfish (Lhomme *et al.*, 2013; Meng, 2010a). In contrast, outbreaks most commonly occur in developing countries secondary to fecal contamination of food or water (Maclachlan *et al.*, 2011c; Meng, 2005). Direct human-to-human transmission is rare (Pavio *et al.*, 2010).

Domestic pigs can be naturally infected with HEV and shed large quantities of virus in their feces. Under experimental conditions, swine HEV strains are infectious for nonhuman primates and the human strains of HEV are infectious to pigs. In addition, pig handlers (e.g., swine veterinarians, swine farmers) have a significantly higher rate of seroconversion to HEV than does the general population (Huang *et al.*, 2002). Swine infection is widespread and worldwide. In the United States, the seroprevalence rate of swine HEV infection ranges between 50 and 100% in some herds (Lhomme *et al.*, 2013). Infection occurs in farmed pigs between 2 and 4 months of age, presumably by fecal–oral transmission, with a transient viremia followed by fecal shedding (Huang *et al.*, 2002; Meng, 2011). Given this, domestic pigs are recognized as likely reservoirs of HEV for the human population.

An avian strain of HEV exists with a high incidence of seroconversion in farmed chickens. The virus is now believed to be the etiologic agent of big liver and spleen disease (hepatitis-splenomegaly syndrome) of chickens. However, disease has not resulted following experimental transmission of the avian virus to other species including nonhuman primates, suggesting that the avian strain does not present a significant zoonotic threat. Other animals including farmed rabbits, wild rats, wild boar, bats, mongeese, and deer are susceptible to HEV infection and are being evaluated as potential sources of human disease (Cossaboom *et al.*, 2011; Lhomme *et al.*, 2013; Meng, 2011). Of these, rabbit HEV is of greatest concern as antibody titers, suggestive of infection, have been detected in rabbit farms in the United States and China, and experimental infection of pigs has been demonstrated (Cossaboom *et al.*, 2012). Some species (e.g., tamarins, owls monkeys, and cynomolgus monkeys) are susceptible to experimental infection and antibody response to HEV has been detected in wild-caught macaques. Nonhuman primates are not considered likely disease reservoirs although disease transmission from nonhuman primates to humans should not be discounted (Wachtman and Mansfield, 2012).

Mode of Transmission In human populations, hepatitis E was originally believed to result most commonly from human fecal contamination of drinking water in areas endemic for the disease. Recent research has focused on the role that many animal species may play in zoonotic disease transmission from the feces of infected animals and the consumption of undercooked, contaminated animal tissues (meat and liver) (Lhomme *et al.*, 2013). Aerosol transmission is not suspected. Given the suspected routes of virus transmission to humans,

the risk within an animal facility should be minimal. Nevertheless, personnel are advised to observe proper PPE practices to prevent possible HEV exposure.

Clinical Signs Disease is frequently self-limiting and asymptomatic, although an acute hepatitis can develop with classical signs of liver involvement including jaundice, anorexia, and hepatomegaly. A fulminant, fatal hepatitis of pregnant women has been attributed to HEV infection, although this disease course has not been observed in naturally or experimentally infected pigs or experimentally infected rhesus macaques (Lhomme *et al.*, 2013; Meng, 2010b). Chronic disease may develop in the immunocompromised including transplant recipients (Zhou *et al.*, 2013). Infected pigs most frequently appear clinically normal despite microscopic lesions of hepatitis (Meng *et al.*, 1997).

Diagnosis and Prevention Propagation of HEV in cell culture has been problematic, hindering its evaluation and development of diagnostic tests. Disease diagnosis in both humans and pigs is based on the detection of anti-HEV antibodies or the presence of HEV RNA in serum or feces (Pavio *et al.*, 2010). Treatment is limited to provision of supportive care.

A hepatitis E vaccine is not currently available.

3. Other Viral Hepatitis Agents

Humans are considered natural hosts for viral hepatitis types B, C, and D, all of which are transmitted parenterally by exposure to blood or other bodily fluids. Hepatitis B virus (HBV), caused by a human hepadnavirus, has been widely studied experimentally in the chimpanzee although the gibbon, orangutan, and wooly monkey are known to be susceptible (MacDonald *et al.*, 2000). Natural HBV infection was first noted by demonstration of HBV surface antigen in cynomologus in 1985 (Kornegay *et al.*, 1985). Recently, wild-living cynomolgus macaques from Mauritius Island were diagnosed with natural, chronic infection of a genotype of HBV distinct from the human genotype. The disease appears relatively benign in the infected animals. The zoonotic risk of the cynomolgus genotype is yet unknown (Dupinay *et al.*, 2013). It is postulated that infected cynomolgus monkeys may serve as a useful animal model of the disease. Other natural hepadnavirus infections of animals (woodchuck, ground squirrel, and duck) are used as animal models of HBV infection, but none are transmissible to humans (Blanchard and Russell-Lodrigue, 2012). The chimpanzee has been used as an experimental model for the study of hepatitis C and D viruses. Thus, the concern for hepatitis B, C, and D as zoonoses is minimal in the laboratory animal facility environment except where these agents are used in experimental animal studies. In these cases, personnel should adhere to appropriate precautions when handling nonhuman primates.

G. Retroviruses

In the wake of the human acquired immunodeficiency syndrome (AIDS) epidemic, there has been an intense, multifaceted interest in the study of human and comparative retrovirology. The zoonotic potential for animal retroviruses has been clearly identified. Retroviruses are RNA viruses with a high mutation rate, facilitating the virus' adaptation to novel hosts. It is currently postulated that all human retroviral pathogens have evolved from simian retroviral precursors (Huang *et al.*, 2012). HIV-1 and HIV-2 evolved from simian immunodeficiency virus (SIV) strains originating in the chimpanzee (*Pan troglodytes troglodytes*) and sooty mangabey (*Cercocebus atys*), respectively (Chen *et al.*, 1996; Gao *et al.*, 1999). In addition, human T-cell lymphotropic virus type 1 (HTLV-1) appears to have evolved in humans following interspecies transmission of an earlier form of the virus (simian Tcell leukemia virus) from nonhuman primates (Gessain *et al.*, 2013). These findings have heightened the concerns of zoonotic retroviral transmission, particularly in connection with the use of nonhuman primates as potential xenograft donors to humans requiring organ transplantation. Similar concerns have been raised about the pig as a donor for xenotransplants to humans because the porcine endogenous retrovirus has been demonstrated to grow in human cells *in vitro* (Wilson *et al.*, 1998). However, although there are numerous retrovirus infections of wild, laboratory, and domestic animal species, the transmission of these agents from their natural host to humans under laboratory conditions has been infrequent but consistently involves nonhuman primates as source species. Four simian retroviruses have crossed species to infect humans: SIV, simian retrovirus, simian T-cell leukemia virus, and simian foamy virus (SFV). Each is detailed below although it must be noted that there is concern that additional simian retroviruses may adapt and become zoonotic agents.

When working with any nonhuman primates or associated tissues or fluids, personnel should be instructed to observe applicable PPE requirements, operational procedures, and safe syringe/needle-handling practices. Potential virus exposure sites should be immediately cleansed and/or disinfected and medical attention sought. Follow-up medical evaluations with periodic monitoring for infection may be warranted. Supervisory personnel should be informed of the incident. Written institutional policies should be in place to address confidentiality, counseling, and other issues related to potential retrovirus exposure. Those with evidence of retroviral infection should not donate blood or tissues.

1. Simian Immunodeficiency Virus

Reservoir and Incidence SIV is a lentivirus known to infect over 45 species of nonhuman primates in Africa

in which it is endemic in many nonhuman primate populations. Seroprevalence rates increase with animal age and may be as high as 76% (Murphy *et al.*, 2006) in naturally infected, wild populations. A unique species-specific SIV strain has been identified in 33 infected nonhuman primate species (Kalish *et al.*, 2005), although cross-species transmission does occur. To date, infection has not been detected in Asian or South American nonhuman primates in the wild (Hayami *et al.*, 1994; Locatelli and Peeters, 2012).

Most SIV strains can grow in human cells *in vitro*. Seroconversion to the virus has been detected in multiple individuals with occupational exposure to nonhuman primates or their tissues. Occupational exposures have included an individual with active dermatitis of the hands who handled SIV-infected primate samples and cultures while not wearing gloves. SIV was successfully isolated from this individual. Seroconversion has also been documented in two other individuals, each of which suffered accidental needlesticks while working with samples from SIV-infected macaques. One individual remained seropositive for only a short time, whereas the second individual remained seropositive for 11 years. SIV was not isolated from either individual (Khabbaz *et al.*, 1994; Murphy *et al.*, 2006).

Mode of Transmission The blood, cerebrospinal fluid, secretions (e.g., semen, saliva, urine, milk), and tissues of SIV-infected monkeys should be presumed to be infectious. Both horizontal (via sexual contact and fight wounds) and vertical virus transmission occurs between nonhuman primates (Locatelli and Peeters, 2012). Aerosol transmission is not suspected.

Clinical Signs Initially, it was presumed that SIV infections were nonpathogenic in natural hosts despite their persistent, lifelong infection. However, an acquired immunodeficiency disease with chronic wasting has rarely developed in some naturally infected animals after prolonged infection. Disease does develop in nonhuman primate species that are not natural hosts of the virus following natural or experimental infection. In these animals, an acute infection or a chronic, latent infection may occur. Asian nonhuman primates, including rhesus macaques, may develop an especially severe form of the disease that closely resembles human AIDS including immunosuppression and increased susceptibility to opportunistic infections. Clinical signs have not been recorded in any cases of human SIV infection.

Diagnosis and Prevention A combination of serologic (e.g., ELISA, Western blot) and molecular assays (PCR) as well as virus isolation are employed to detect infection in both humans and nonhuman primates. Testing samples can include blood, urine, feces, and tissues. However, the selection and interpretation of specific diagnostic assays must be made with consideration of the numerous, genetically diverse strains of SIV identified and the knowledge that cross-species transmission may occur (Murphy *et al.*, 2006). African species may not develop antibody titers despite infection. To prevent inadvertent disease transmission, Asian macaques should not be allowed direct contact with African species.

2. *Simian Retrovirus*

Reservoir and Incidence Simian retrovirus (SRV) was first identified in the 1980s soon after which it was detected in nonhuman primate colonies in several U.S. regional primate research centers. SRV, an oncogenic betaretrovirus and formally designated the Mason-Pfizer monkey virus, is now known to exist in at least seven serotypes. Some serotypes have been confirmed to be endogenous retroviruses, resulting in germline transmission with no easily detectable, induced serologic immune response. Up to 90% of some wild and captive nonhuman primate populations are infected. Serologic evidence of human infection exists in West African populations as well as those with occupational exposure to nonhuman primates. In addition, the virus has been isolated from one patient with AIDS and lymphoma but with no known nonhuman primate contact (Murphy *et al.*, 2006; Wachtman and Mansfield, 2012). Overall, the degree of the risk for zoonotic transmission of SRV remains unclear.

Mode of Transmission Blood, urine, and bodily fluids can be infectious, and both horizontal (via bite wounds and sexual contact) and vertical transmission occurs in nonhuman primates (Burgos-Rodriguez, 2011). Human infection may result from contact with infectious substances such as through wound contamination, mucous membrane exposure, and needlestick injuries. Aerosol transmission is not suspected at this time.

Clinical Signs New World primates appear resistant to SRV infection, whereas other species (e.g., macaques) may develop immunodeficiency with chronic wasting, increased susceptibility to opportunistic infections, necrotizing gingivitis, retroperitoneal fibromatosis, persistent diarrhea, hematologic abnormalities, and sudden death (Burgos-Rodriguez, 2011; Murphy *et al.*, 2006; Wachtman and Mansfield, 2012). No clinical signs have been noted in humans with serologic evidence of infection.

Diagnosis and Prevention In nonhuman primates, severe disease may exist in the absence of a serologic antibody response, whereas an antibody response may be detectable in the absence of clinical signs. Therefore, attempts at virus isolation, molecular assays (e.g., PCR), and direct visualization of the virus in fixed tissue are necessary to help rule out infection. Chronic wasting and/or clinical signs related to a specific opportunistic infection may be the first indication of SRV infection (Wachtman and Mansfield, 2012). Prevention of disease transmission in an occupational setting is based on strict

observance of practices and procedures designed to limit human exposure to infected nonhuman primates and their tissues.

3. Simian T-Cell Leukemia Virus

Reservoir and Incidence Human T-cell leukemia virus subtypes 1–3 (HTLV-1, HTLV-2, and HTLV-3) are believed to have developed following multiple instances of transmission of the oncogenic *Deltaretrovirus* primate T-lymphotropic virus subtypes 1–3 (PTLV-1, PTLV-2, and PTLV-3) from African nonhuman primates to humans. A simian analog of HTLV-4 has not yet been identified, nor has a human analog been identified for the recently discovered PTLV-5 of macaques. HTLV is a significant disease of humans, infecting approximately 10–20 million people worldwide. PTLV infections have been documented in over 33 species of Old World monkeys and apes in Africa and Asia, with seroprevalence increasing with age. Some subtypes have species specificity in natural infections of wild populations with PTLV-2 currently found only in bonobos (*Pan paniscus*) and PTLV-3 found only in African nonhuman primates. Infection with multiple PTLV subtypes does occur (Locatelli and Peeters, 2012). Some New World primates are susceptible to experimental infection, but natural infection has not been identified in their wild populations (Murphy *et al.*, 2006).

Mode of Transmission Within nonhuman primate species, PTLV disease transmission occurs through sexual contact and fight wounds, and possibly through the nursing of young. Human infection with PTLV has occurred in Africa in individuals exposed to blood, bodily fluids, or tissues of infected nonhuman primates. Infection of persons with occupational exposure to nonhuman primates or their fluids has not been documented.

Clinical Signs Nonhuman primates infected with PTLV-1 infrequently develop a lymphoproliferative disease with persistent lymphocytosis and T-cell abnormalities; lymphoma and leukemia with accompanying skin lesions; hepatosplenomegaly; or, in gorillas only, chronic wasting (Murphy *et al.*, 2006). Clinical signs are not observed in nonhuman primates infected with PTLV-2 or PTLV-3 (Burgos-Rodriguez, 2011).

Diagnosis and Prevention Infection is diagnosed through serologic assays employing ELISA, IFA, Western blot, and PCR assays. Subtype differentiation requires sequence analysis (Murphy *et al.*, 2006; Wachtman and Mansfield, 2012).

4. SFV Infection

Natural infections of foamy viruses have been identified in many species including nonhuman primates, cats, cows, and horses. *In vitro*, foamy viruses cause cytopathic effects in many cell types, yet in their natural host, foamy viruses do not induce pathologies and remain lifelong persistent infections (Murray and Linial, 2006).

Reservoir, Incidence, Transmission, and Clinical Signs The SFVs are complex retroviruses (genus *Spumavirus*) that have been isolated from a number of New and Old World nonhuman primates (Wachtman and Mansfield, 2012). Infection rates in many wild and captive nonhuman primate colonies approach 100% with transmission suspected to occur through exposure to saliva (e.g., contamination of deep fight wounds) and possibly blood. A wide range of animal species have been experimentally infected with SFV. No evidence of pathogenicity has been detected in these species or the natural nonhuman primate hosts although lifelong, stable virus persistence is suspected (Khan, 2009). Human infection with SFV has been documented with no apparent ill effects. The virus has recently been detected in the saliva of infected humans (Huang *et al.*, 2012). Human-to-human transmission has not been detected, suggesting that humans may serve as dead-end hosts. In Africa and Asia, human infection is believed to result from contact with infected wild nonhuman primates, especially during their hunting, butchering, or consumption (Khan, 2009). It is debatable if a human foamy virus variant exists. However, foamy virus infections have been confirmed on multiple occasions. The first was reported in 1971 from the cell culture of an East African patient with nasopharyngeal carcinoma. The isolated foamy virus was, based on immunologic and sequence data, judged to be closely related to a chimpanzee foamy virus (Heneine *et al.*, 1998; Schweizer *et al.*, 1997). The second case involved an animal handler employed at a research institute for over 20 years and who had suffered multiple bite wounds from African green monkeys. The worker became seropositive for foamy virus within 6 years of employment. African green monkey foamy virus DNA was later detected in his peripheral blood mononuclear cells, indicating persistent yet asymptomatic infection (Schweizer *et al.*, 1997). A subsequent survey of U.S. and Canadian workers with occupational exposure to nonhuman primates revealed evidence of SFV infection via serology, proviral DNA detection, and/or virus isolation in 4 of the 231 individuals tested. Each of the four was employed at different institutions. Three individuals were infected with SFV of baboon origin, one with SFV of African green monkey origin. Infection was asymptomatic in all four individuals and evidence of infection was not found among their close contacts, including the three spouses tested (Heneine *et al.*, 1998). From these and other confirmed cases of human infection (Gessain *et al.*, 2013; Switzer *et al.*, 2004), it is now assumed that human infections with SFV result in a latent, asymptomatic infection with minimal risk for human-to-human transmission.

Prevention Those with occupational exposure to nonhuman primates are at a significantly increased risk of SFV infection. The risk that SFV may have yet unseen, long-term effects or could mutate into a human-adapted, pathologic form should not be dismissed. Infected humans are advised to not donate blood or other tissues (Boneva *et al*., 2002; Heneine *et al*., 1998; Khan and Kumar, 2006). The use of PPE as described in connection with the prevention of SIV transmission to humans should be applied when handling SFV-infected nonhuman primates.

H. Measles Virus (Rubeola)

Reservoir and Incidence Measles virus, a paramyxovirus (genus *Morbillivirus*), infects millions of people worldwide and can have devastating effects on nonhuman primate colonies. In the United States, approximately 60 human measles cases are reported each year although that number has been significantly higher in the most recent past (CDC, 2013). A small number of human measles infections are postulated to have resulted from contact with infected macaques during one large-scale measles outbreak at a U.S. primate center (Roberts *et al*., 1988). The virus can infect both Old World and New World monkeys and apes although it is not naturally found in wild populations removed from human contact. Humans are the natural disease reservoir and serve as the reservoir for nonhuman primates (Wachtman and Mansfield, 2012).

Measles outbreaks within U.S. and European domestically born nonhuman primate colonies are infrequent, but do occur (Willy *et al*., 1999). In these domestic colonies, the source of the virus is infected humans or the importation of infected animals. Outbreaks frequently occur in geographic regions where naïve nonhuman primate populations may come into close association with endemically infected human populations. Within these nonhuman primate populations, the seroprevalence of infection may, depending on animal species, approach 100%. With the current emphasis on and success of domestic nonhuman primate production, it has become more likely that institutions will develop large populations of susceptible nonhuman primates that could contract measles and then transmit the disease to susceptible humans.

Mode of Transmission Measles is a highly communicable disease that is transmitted by infectious aerosols, contact with nasal or throat secretions, or contact with fomites freshly contaminated with infectious secretions. Viral shedding can occur prior to clinical signs and continues until after rash onset. (CDC, 2012a).

Clinical Signs The clinical course of the disease differs significantly between nonhuman primate species. Macaques and other species of Old World primates commonly develop a mild upper respiratory infection although asymptomatic infections occur. Clinical signs most frequently seen in Old World monkeys include nasal and ocular discharge, conjunctivitis, facial edema, blepharitis, and a maculopapular skin rash. The rash first develops on the ventral body surface then becomes generalized before ultimately progressing to a dry and scaly desquamative dermatitis. Immunosuppression is common. Occasionally, measles infection progresses to depression, anorexia, coughing, and dyspnea in conjunction with giant cell pneumonia. Abortions and neurologic signs have also been reported. Koplik's spots inconsistently appear on the buccal mucosa (Wachtman and Mansfield, 2012). Morbidity is high and mortality, caused by secondary bacterial infections, is low in Old World monkeys. The disease is much more severe in marmosets, owl monkeys, and colobines in which hemorrhagic gastroenteritis and immunosuppression predominate and respiratory tract lesions and the skin rash are absent or less significant. To mitigate the possibility of introducing the virus into a susceptible monkey population, personnel working with these primates should have a measles virus antibody titer to assess their immunity to the virus.

The clinical signs observed in humans (CDC, 2012a) closely resembles those seen in macaques.

Diagnosis and Prevention Characteristic clinical signs can be highly suggestive of the disease. Diagnostics include serology to detect virus-specific antibodies, virus isolation, and molecular assays. Treatment of animals at high risk for virus exposure with human gamma globulin may be useful in controlling disease during epizootics (Roberts *et al*., 1988). A monovalent human measles vaccine is effective in protecting both Old World and New World monkeys from the disease. A less expensive monovalent vaccine designed for use in dogs has been shown to be equally effective. However, production of this vaccine has been suspended and an alternate monovalent vaccine has not yet been validated for use in nonhuman primates. Polyvalent vaccines may be shown to be efficacious in measles prevention; however, they may produce an immune response that interferes with select research.

A current measles vaccination or evidence of immunity should be assured for all handlers of nonhuman primates.

I. Newcastle Disease Virus

Reservoir and Incidence Newcastle disease is caused by a paramyxovirus that can infect possibly all bird species and results in a wide range of disease outcomes ranging from unapparent infection to 100% mortality (CDCP-NIH, 2009). Virus strains are classified into five pathotypes based upon the clinical signs

they induce in chickens. The five pathotypes are as follows: viscerotropic velogenic, neurotropic velogenic, mesogenic, lentogenic, and asymptomatic (OIE, n.d.). The zoonotic potential of this agent in the laboratory environment has been realized on numerous occasions (Barkley and Richardson, 1984).

Mode of Transmission The virus is shed in the respiratory secretions and feces of infected birds. Disease transmission between birds occurs via aerosol exposure or ingestion of contaminated food or water. Transmission to humans occurs via aerosols (usually in a laboratory setting) or by direct or indirect inoculation of the eyes as may occur during handling of infected animals, their tissues, or contaminated fomites during necropsy or at poultry processing plants. Human-to-human transmission is not suspected although human-to-bird transmission is possible (Maclachlan *et al.*, 2011d; Swayne and King, 2003).

Clinical Signs The severity of the disease in birds depends on the pathogenicity of the infecting strain. Highly pathogenic strains have largely been excluded from flocks within the United States. Moderately pathogenic strains produce anorexia and respiratory disease in adult birds and neurologic signs in young birds. In humans, the disease is characterized by a mild-to-moderate self-limiting conjunctivitis with orbital pain without corneal involvement that resolves without complications and without therapy. Mild fever and respiratory involvement may rarely develop in humans, most frequently following aerosol exposure (Swayne and King, 2003) although some question the true frequency of this occurrence (Goebel *et al.*, 2007). One fatal case has been documented in a severely immunosuppressed individual (Goebel *et al.*, 2007).

Diagnosis and Prevention Virus isolation and characterization from avian tracheal, oropharyngeal, or cloacal samples is the preferred diagnostic method although molecular assays and serologic tests (e.g., hemagglutination, hemagglutination inhibition, and ELISA) are also frequently utilized (OIE, n.d.). This disease can be prevented in the laboratory environment by immunizing birds susceptible for this disease or obtaining birds from flocks known to be free of this agent. Live, inactivated, and recombinant vaccine strains are used. Personal hygiene practices should also be in place to prevent zoonotic transmission. Select virulent strains of Newcastle disease virus are designated as Select Agents (CDC, n.d.-c) due to their potential use as an agribioterrorism agent.

J. Influenza Virus

Influenza viruses are RNA orthomyxoviruses that are categorized into three types (A, B, and C) based upon antigenic variation, host specificity, and pathogenicity. Type A influenza naturally infects humans as well as a wide range of avian and mammalian species including swine, horses, ferrets, dogs, large felids, domestic cats, mink, and seals, and is further subclassified into subtypes based upon two viral surface glycoproteins: hemagglutinin and neuraminidase. Type B and C influenza viruses infect only humans (Harder and Vahlenkamp, 2010; Mak *et al.*, 2012).

Reservoir and Incidence Humans are considered the reservoir for human influenza virus infections. Animals, however, are thought to play a significant role in the emergence of new human strains of influenza virus and may serve as disease reservoirs. Animals can be infected with influenza strains that then undergo mutational and reassortment events resulting in the emergence of a novel, pathogenic virus transmissible to humans. Pigs are well-known examples and are believed to serve as 'mixing vessels' during the adaptation of avian influenza viruses to human hosts, although their full role in this capacity is still unknown (De Vleeschauwer *et al.*, 2009; Mak *et al.*, 2012; Webster, 1997). In the laboratory, ferrets are highly susceptible to human influenza and often are used as experimental models of influenza infection (Belser *et al.*, 2011). Recently, concern of avian-to-mammalian transmission has intensified, as such transmissions are presumed to have occurred resulting in human fatalities such as in the 1997 H5N1 influenza outbreak in Hong Kong. In addition, the human influenza viruses from the 1918, 1957, and 1968 pandemics are believed to have originated in avian species (CDCP-NIH, 2009).

Mode of Transmission Transmission occurs by airborne spread of the virus and by direct contact through droplet spread or contact with infectious tissues, feces (in select avian species), or secretions. The transmission of animal influenza strains from animals to humans is an uncommon occurrence, but one of increasing concerns due to perceived significant public health implications. Pigs experimentally infected with influenza virus in the laboratory have been shown to directly and readily spread the virus to persons working with these animals (Wentworth *et al.*, 1997). Ferrets housed in the laboratory will develop epizootic infection concomitant with human outbreaks of the disease. Ferret-to-human transmission of the virus has been documented (Marini *et al.*, 1989).

Clinical Signs In humans, influenza is an acute disease of the respiratory tract characterized by fever, headache, myalgia, prostration, coryza, sore throat, and cough. Viral pneumonia and gastrointestinal involvement manifested by nausea, vomiting, and diarrhea may also develop, especially in children.

Diagnosis and Prevention Poultry may remain asymptomatic or only mildly affected with reduced weight gain or egg production although some will develop neurologic symptoms (e.g., ataxia, torticollis,

and seizures). In contrast, waterfowl infected with highly pathogenic avian influenza may exhibit sudden death or develop lethargy; diarrhea; and edema and cyanosis of the comb, wattles, and legs with near 100% mortality (Kalthoff *et al.*, 2010).

Diagnostic tests include virus isolation, rapid antigen tests, and molecular assays (Mak *et al.*, 2012). Personnel should wear proper protective clothing including respiratory protection and practice appropriate personal hygiene measures when contacting experimentally infected animals or with animals suspected of having natural influenza infection (e.g., ferrets, pigs, birds). Vaccination of personnel may be indicated.

Select influenza strains (e.g., reconstructed replication competent forms of the 1918 pandemic influenza virus and highly virulent avian influenza virus) are classified as Select Agents due to their potential use as a bioterrorism or agribioterrorism agent.

III. RICKETTSIAL DISEASES

A. Murine Typhus (Endemic Typhus)

Murine typhus is caused by *Rickettsia typhi.* Although this flea-borne disease has been recognized for centuries, it was not until the 1920s that it was distinguished from louse-borne or epidemic typhus. The absence of louse infestation in humans, seasonal occurrence, and sporadic nature help differentiate murine typhus from epidemic typhus, which is caused by *R. prowazekii* and is seen only in the eastern United States in association with flying squirrels (Reynolds *et al.*, 2003).

Reservoir and Incidence Murine typhus is worldwide, and in the United States, it is usually diagnosed in southeastern or Gulf Coast states and in areas along the northern portion of the Mississippi River and southern California. It is also associated with human populations subjected to areas of high-density wild rat colonies, such as ports, granaries, farms, or rat-infested buildings in inner cities. Laboratory personnel have been infected with this agent when inoculating rodents and handling infected animals.

Since the 1970s, there has been a shift in the distribution of human cases of murine typhus to more rural locales in southern California and central and south Texas (Adams *et al.*, 1970). Southern California was considered an unusual locale because the area was considered a wealthy region where rat infestation and the associated flea (*Xenopsylla cheopis*) were uncommon. Epidemiologic studies indicated that opossums had a high seropositivity to murine typhus, and some of the cat fleas (*Ctenocephalides felis*) infesting the opossums were infected with a newly recognized rickettsia eventually named *R. felis* (Adams *et al.*, 1990; Williams *et al.*, 1992). Follow-up studies have confirmed the presence of both *R. typhi* and *R. felis* in California, Texas, and other southern locales, helping explain the spread of flea-borne murine rickettsia into rural areas in the United States (Boostrom *et al.*, 2002; Eremeeva *et al.*, 2012). Human cases of disease caused by *R. felis* have been identified throught the world, establishing the zoonotic potential of this organism that is grouped with the spotted fever group of Rickettsia based on genetic analysis (Perez-Osorio *et al.*, 2008).

Mode of Transmission Murine typhus is primarily a disease of rats, with its principal vectors being the oriental rat flea, *X. cheopis*, and the flea *Nasopsyllus fasciatus.* These fleas will also naturally colonize the mouse *M. musculus.* The cat flea, *Ctenocephalides felis*, (as well as seven other species of fleas) has also been implicated in the spread of the disease. Rickettsiae are ingested by a blood meal of the flea, where they multiply in the gut, and are subsequently passed out in the dejecta of the flea. Infection in the rat and the human is the result of contamination of the puncture wound by flea feces (Farhang-Azad *et al.*, 1985). Experimental evidence indicates that a flea bite can also directly transmit the infection (Farhang-Azad *et al.*, 1985). *R. typhi* are resistant to drying and remain infectious for up to 100 days in rat feces.

Clinical Signs After infection with rickettsia, the incubation period is 7–14 days. Because murine typhus is difficult to differentiate either clinically or anatomically from other rickettsial diseases, specific serological tests or PCR-based assays are extremely important in making the correct diagnosis (Farhang-Azad *et al.*, 1985). The acute febrile disease is usually characterized by general malaise, headache, rash, and chills, with signs ranging from mild to severe. An encephalitic syndrome can also occur (Mushatt and Hyslop, 1991). In one report, 25% of 180 patients with the disease had delirium, stupor, or coma. Fortunately, these findings resolve with lowering of the febrile response. Fatality rate for all ages is about 2% but increases with age. Proper antibiotic therapy is the most effective measure to prevent morbidity or mortality due to rickettsial infections and has been shown to be effective in hastening recovery and preventing neurologic sequelae, such as deafness due to eighth cranial nerve involvement (Mushatt and Hyslop, 1991). Doxycycline, tetracycline, and chloramphenicol are considered agents of choice.

Diagnosis and Control Recovery of rickettsial organisms or antigens from biological specimens is inconsistent and is not routinely done except in labs equipped to process and identify these samples. It must be stressed that manipulation of rickettsia in the laboratory is hazardous and has accounted for numerous infections of laboratory personnel. Serological diagnosis via the IFA technique has been considered to be the standard reference test, but the classical assay is not species-specific and does not distinguish epidemic from

endemic typhus. Differentiation between IgM and IgG antibodies or evidence of a rising titer on serial samples can be used to confirm recent, active infections. Species-specific ELISA and PCR tests are becoming available and can be used to differentiate between the rickettsia.

Fleas can be controlled by applying insecticides as residual powders or sprays in areas where rats nest or traverse. It is imperative that insecticides be applied prior to using rodenticides; this will prevent fleas from leaving the dead rodents and feeding on human hosts (Beaver and Jung, 1985). This disease should not be encountered in rat colonies in well-maintained research vivaria. However, with the cat flea being a newly recognized vector of rickettsial disease, its presence on random-source dogs, cats, and opossums raises the risk of transmission to personnel working with these flea-infested animals.

B. Rickettsial Pox

A variety of rodents are infected with other rickettsial diseases. *M. musculus* is the natural host for the causative agent of rickettsial pox, *Rickettsia akari*, a member of the spotted fever group of rickettsia (Chin, 2000). This organism is also isolated from *Rattus rattus* and *R. norvegicus*, and the rat under certain circumstances may transmit the disease to humans. The disease is transmitted by the mite *Liponyssoides* (*Allodermanyssus*) *sanguineus* and has been diagnosed in New York City and other eastern cities, as well as in Russia, Egypt, and South Africa (Chin, 2000). The incubation period is approximately 10–24 days, and the clinical disease is similar to that noted in murine typhus. The rash of rickettsial pox commences as a discrete maculopapular rash, which then becomes vesicular. The palms and soles are usually not involved. About 90% of affected persons develop an eschar, with a shallow ulcer covered by a brown scab (Farhang-Azad *et al.*, 1985; Chin, 2000) (Fig. 28.4). Although headaches are common and may be accompanied by stiff necks, lumbar cerebrospinal fluid samples are normal. Pulmonary and gastrointestinal involvement also are almost never encountered. Diagnosis, treatment, and control are similar to those described for murine typhus and *Yersinia pestis.*

As discussed above with the emerging pathogen *R. felis*, the recognized geographical and host ranges of rickettsia are likely to continue to grow. Serological evidence of exposure to *R. akari* or an antigenically related rickettsia has been found in humans in southern California, and associated animal screening identified serological evidence of prior exposure in rodents of the genera *Mus, Rattus, Peromyscus, and Neotoma* (Bennett *et al.*, 2007).

C. *Coxiella burnetii* Infection (Q Fever)

Reservoir and Incidence *Coxiella burnetii*, the causative agent of Q fever, has a worldwide distribution perpetuated in two intersecting cycles of infection composed of domestic or wild animals and their associated ticks (Babudieri, 1959; Marrie, 1990). The domestic animal cycle involves mainly sheep, goats, and cattle. The prevalence of the infection among sheep is high throughout the United States, and sheep have been the primary species associated with disease outbreaks associated with research animal facilities (Anderson *et al.*, 2013). However, human cases of the disease have also been associated with nonruminants, such as pregnant cats (Langley *et al.*, 1988; Kopecny *et al.*, 2013) and wild rabbits (Marrie *et al.*, 1986). Thus, a broad range of domestic and wild animal species, including birds, should be given consideration as potential sources for Q fever infection in animal care and use activities (To *et al.*, 1998). A survey of other domestic animals performed as part of the investigation into a major goat-related outbreak in the Netherlands found evidence of the agent in dog and horse placentas (Roest *et al.*, 2013).

Mode of Transmission *C. burnetii* are shed in the urine, feces, milk, and especially placental tissues of domestic ungulates that generally are asymptomatic. The organism is highly infectious with possibly as few as 10 organisms inducing infection, which is significant considering that the placenta of infected ewes can contain up to 10^9 organisms per gram of tissue, and milk may contain 10^5 organisms per gram (Chosewood and Wilson, 2009). The primary method of transmission is through infectious aerosols. The organism produces a spore-like form that is resistant to desiccation and persists in the environment for long periods of time, contributing to the widespread dissemination of infectious aerosols and resulting in infections miles from the original organism source (Franz *et al.*, 1997; Tissot-Dupont *et al.*, 1999). The importance of these factors was

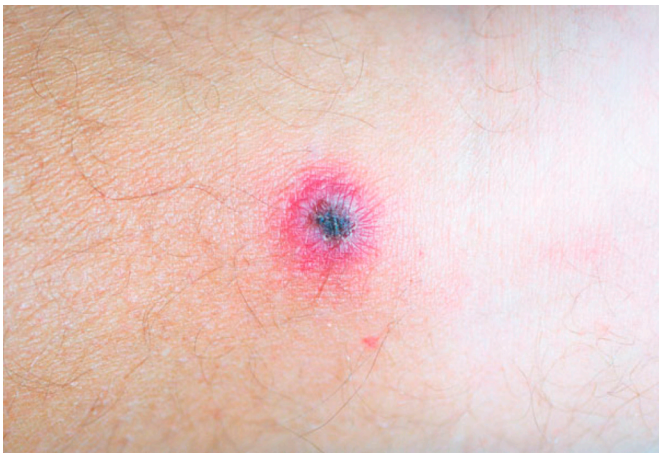

FIGURE 28.4 Eschar on posterior right calf of patient with rickettsial pox. *Source: Emerg Infect Dis – "Rickettsial pox in North Carolina: A Case Report."*

illustrated in outbreaks of the disease associated with the use of pregnant sheep in research facilities in the United States (Bernard *et al.*, 1982). In these outbreaks, personnel who did not have direct contact with infected sheep but who worked along the transport routes for these animals became serologically positive for Q fever (Bernard *et al.*, 1982; Reimer, 1993). Also, five of nine laundry workers without direct sheep contact but who processed linens soiled during sheep surgery developed serological evidence of infection.

Clinical Signs, Susceptibility, and Resistance in Humans Q fever in humans varies in duration and severity, and asymptomatic infection may occur. The disease often presents as an acute flu-like illness with fever, frontal headache with retro-orbital pain, and chest pain with a nonproductive cough and pneumonia, resolving within 2 weeks of infection. However, serious extrapulmonary complications, such as acute or chronic hepatitis, nephritis, epicarditis, and endocarditis, may also occur. Individuals with valvular heart disease should not work with *C. burnetii* due to the prospect of serious, chronic, relapsing infection (Asher, 1989; Chosewood and Wilson, 2009). A linkage between Q fever and a chronic fatigue syndrome is also suspected (Ayres *et al.*, 1998).

Diagnosis, Prevention, and Control Whenever possible, male or nonpregnant sheep should be used in research programs; however, many research applications specifically call for the use of pregnant animals. Multiple commercial vendors now supply sheep from closed, SPF flocks that have been serologically negative for an extended period. Although serological status is not a reliable indicator of organism shedding in an individual sheep, many institutions have elected to use these animals, reasoning that cumulative and consistent negative Q fever serology on a herd basis provides a reasonably strong assurance of Q fever-free status. Advances in PCR methods have improved the sensitivity of *C. burnetii* detection over that of the antigen capture ELISA, as well as improved the speed, safety, and convenience of the assay. The PCR method allows for the assessment of organism shedding, which may provide an option to minimize the potential risk of Q fever outbreaks in animal facilities (Lorenz *et al.*, 1998; Yanase *et al.*, 1998). However, shedding can be sporadic, and diagnostic samples such as amniotic fluid and placenta are not readily available *antemortem*. A combination of colony health components such as acquisition from a 'clean' flock, serological testing of incoming animals with follow-up *postmortem* PCR screening can be combined for a comprehensive program to minimize Q fever risks.

Sheep and other animals known to harbor Q fever infections (e.g., experimentally infected animals) should be maintained under ABSL3 conditions to prevent the transmission of the organism in the research animal facility environment (Chosewood and Wilson, 2009). Additional detailed recommendations have been published concerning sheep handling in biomedical research programs (Bernard *et al.*, 1982; Anderson *et al.*, 2013). In many institutions, ABSL3 compliant physical containment for sheep may prove to be unachievable as a preventative measure for sheep held under agricultural conditions for food and fiber production or utilized for instructional exercises. The use of enhanced personal protective equipment such as N95-type respirators and protective face shields should be considered in those settings, especially if pregnant ruminants are involved. The extracellular form of the organism is very resistant to inactivation and nearly sporicidal treatments are required for decontamination.

An effective Q fever vaccine is licensed in Australia (Q-Vax), but the only vaccines that have been utilized in the United States are experimental and have seen very limited distribution.

IV. CHLAMYDIAL INFECTIONS

A. Chlamydiosis (Psittacosis, Ornithosis, or Parrot Fever)

Reservoir and Incidence The taxonomy for the order Chlamydiales has been extensively revised and re-revised in the past two decades based upon evolving genotopic and phenotypic information. A proposal to split a number of species into the new genus *Chlamydophila* has been published (Everett *et al.*, 1999), but it has not been uniformly adopted by the scientific community and the latest edition of Bergey's Manual retains the designation of these species as *Chlamydia* spp. (Kuo *et al.*, 2010). Chlamydial species are widely distributed among birds and mammals worldwide and occur naturally among many laboratory animal species, including birds, mice, guinea pigs, hamsters, rabbits, ruminants, swine, cats, ferrets, muskrats, and frogs (Storz, 1971; Newcomer *et al.*, 1982). Of these host species, birds with *Chlamydia psittaci* infection, particularly psittacines, have proven to be the most frequent sources of virulent human infection (CDCP, 1997); however, infections with *C. abortus* in ruminants (Hyde and Benirschke, 1997; Jorgesen, 1997) and *C. felis* in cats (Cotton and Partridge, 1998) also have the potential to cause human disease. The most common human chlamydial infection, *C. trachomatis*, is not naturally transmissible to animals but is used to produce experimental infections in nonhuman primates. *C. muridarium* occurring in the mouse and *C. suis* occurring in the pig are closely related to *C. trachomatis* but are not infectious for humans. *C. caviae* has been isolated from the guinea pig. *C. pecorum* produces intestinal

infection in ruminants and other animals but not in humans. *C. pneumoniae* produces respiratory infections in humans and related biovars have been isolated from the koala, horse, frog, and reptiles (Bodetti, *et al.*, 2002). Zoonotic infections from animal-related biovars of *Chlamydia pneumoniae* have not been recorded, but genomic studies suggest that one or more animal-to-human transmission events led to the establishment of the human *C. pneumonia* biovar (Roulis *et al.*, 2013).

Mode of Transmission The organism is spread to humans from infectious material present in exudates, secretions, or desiccated fecal material by direct contact or the aerosol route. Latent infection is an important feature of epizootology of the *C. psittaci* infection in birds; stress can reactivate enteric shedding of the organism and clinical signs (Storz, 1971).

Clinical Signs, Susceptibility, and Resistance in Humans Chlamydiae produce a diverse spectrum of animal disease, including conjunctivitis, pneumonitis, air sacculitis, pericarditis, hepatitis, enteritis, arthritis, meningoencephalitis, urethritis, endometritis, and abortion. Zoonotic infections in humans are characterized mainly by upper and lower respiratory tract complaints; however, conjunctivitis, thrombophlebitis, myocarditis, hepatitis, and encephalitis have also been reported (Smith, 1989; Leitman *et al.*, 1998). Although *C. psittaci* is considered to be more pathogenic for humans than are the mammalian species, as mentioned above the occurrence of ovine strain-related (*C. abortus*) human gestational infections and feline pneumonitis strain-related (*C. felis*) conjunctivitis, pneumonia, and extrapulmonary infection (Cotton and Partridge, 1998) emphasizes the zoonotic potential of a variety of reservoir hosts.

Diagnosis and Control The diagnosis of *C. psittaci* in birds can be made by the identification of inclusions in tissue specimens or impression smears, by actual isolation of the organism, or by using ELISA-based fecal antigen tests. PCR can also detect the organism in blood, cloacal or throat swabs, and environmental samples. A variety of serological tests are available, but differentiation between active infection and previous exposure can be difficult. Whenever possible, birds used in research animal facilities should be acquired from flocks free from *C. psittaci* infection. Prophylactic antibiotic treatment should be considered for wild-caught birds or birds of unknown disease status, and therapeutic antibiotics may be useful when treating mammals or amphibians diagnosed with chlamydial infection. Personnel protection adhering to ABSL-2 procedures along with respiratory protection is generally adequate when dealing with known infections, but ABSL-3 procedures are warranted for research activities with the high potential for droplet or infectious aerosol production, such as necropsy of known-infected birds (Chosewood and Wilson, 2009).

V. BACTERIAL DISEASES

A. Trauma-Associated Bacterial Diseases

1. Bites and Scratches

Several million Americans, with up to 2% of the population, annually suffer animal bites, which continues to be a major health problem in the United States and accounts for approximately 1% of emergency room visits. Dogs and cats are responsible for 90% of the recorded bites (Weber and Hansen, 1991; Talan *et al.*, 1999). The majority of these bites are due to dog bites, with up to 4.7 million sustaining injury and approximately 800,000 requiring some form of medical care annually (CDC, n.d-g). Each year dog attacks account for 10–20 deaths in the United States (Sacks *et al.*, 2000). It is estimated that 400,000 persons in the United States are bitten or scratched by cats annually. According to one report, approximately 40,000 rat bites are recorded annually (Committee on Urban Pest Management, 1980). As with bites from dogs and cats, the majority of rat bites occur in children. It is estimated that 2% of rat bites become infected (Ordog, 1985). The hand is the most likely anatomic site to develop infection and long-term disability (Thomas and Brook, 2011). One report notes that up to 40% of hand bites become infected (Oehler *et al.*, 2009).

Veterinarians, animal control officers, and presumably animal care personnel in research facilities as well as in municipal pounds are at higher risk of bites than the general population. Although rabies is the most serious public health threat from bites and scratches, the risk of bacterial infection from dog bites is lower (approximately 3–18%) than that from cat bites, which is reported to be approximately 28–80% (Weber and Hansen, 1991).

Animals in general have a complex oral microflora consisting of numerous bacterial species; both aerobic and anaerobic bacteria are therefore routinely isolated from traumatic bite wounds inflicted by domestic and wild animals. Common organisms isolated from dog bites include *Staphylococcus* species, *Streptococcus* species, including *S. canis* and a variety of anaerobes, and *Pasteurella multocida* (Takeda *et al.*, 2001; Bert and Lambert-Zechovsky, 1997). Also, a case of zoonotic transmission of *S. equi* subsp. *zooepidemicus* from a dog to its handler, via wound infection or aerosols, has been recently reported (Abbott *et al.*, 2010). In a comprehensive multicenter study, 60% of dog bite wounds were punctures, 10% were lacerations, and 30% were a combination of both. This compared to 85% of cat bite wounds being punctures, 3% lacerations, and 12% a combination of both. In this study, 39% of 57 patients with cat bites presented as purulent wounds, whereas abscesses were present in 19% of the cases reviewed (Talan *et al.*, 1999). Of the 50 patients with dog bites, 58% had purulent wounds, 30% were nonpurulent, and 12% were noted to

have abscesses. Dog and cat bites had a mean of five bacterial species per wound; 63% of the cat bites analyzed compared to 48% of dog bites had a mixed anaerobic and aerobic population (Talan *et al*., 1999). Only aerobes grew in 36% of the cases (42% of dog bites and 32% cat bites), whereas anaerobes were the only species grown in 1% of the cases. *Capnocytophaga canimorsus*, an invasive organism, was recovered from 4.7% of the wounds. It should be noted that if fever occurs in immunocompromised patients (including asplenic individuals) after a bite wound, this organism should be considered in the differential diagnosis. *Erysipelothrix rhusiopathiae* was isolated from two cat bite wounds, whereas *Pasteurella* spp. were present in the wounds 75% of the time in cats and 50% in dogs. Geographic locale is also important in defining bacterial flora of bites and scratches. In a study conducted in the southwestern and central United States, 17 of 1041 (1.6%) of the cases of tularemia in humans diagnosed from 1981 to 1987 were associated with cat scratches or bites (Taylor *et al*., 1991).

Several bacterial pathogens have been isolated from rat bites, including *Leptospira interrogans*, *P. multocida*, and *Staphylococcus* species; however, the most commonly isolated pathogens are *Streptobacillus moniliformis* and *Spirillum minus* (Fox, 2009). Bite wounds from primates and ferrets (and other laboratory animals) can also result in bacterial infection. For example, a chronic *Mycobacterium bovis* infection on the hand of a human resulted from a ferret bite that had occurred 22 years previously (Jones *et al*., 1993). The greatest concern from macaque bites still remains the threat of B virus infection.

Thorough cleaning and debridement (if necessary) is required for all bite wounds. Determination of tetanus vaccination and radiologic assessment are critically important in bite wound management. Amoxicillin/Clavulanate is considered the standard oral antibiotic therapy to empirically treat mammalian bite wound infections (Thomas and Brook, 2011).

2. Atypical Mycobacteriosis

Reservoir and Incidence The rapidly growing mycobacteria (RGM) *Mycobacterium fortuitum*, *M. chelonae*, and *M. abscessus* are ubiquitous, being found in soil throughout the world. *M. chelonae* was first isolated from sea turtles; *M. fortuitum* from frogs (originally called *ranae*); and *M. abscessus*, as the name implies, from soft tissue abscesses of a patient. Of the nontuberculosis mycobacterium belonging to Runyon group I, *M. marinum* is by far the most common. The organism was first isolated from cutaneous lesions in 1826 and was responsible for the death of saltwater fish in a Philadelphia aquarium 100 years later; the authors named the mycobacterium *M. marinum.*

Mode of Transmission The RGM most commonly are associated with a traumatic injury with potential soil contamination and result in skin, soft tissue, or bone disease. *M. marinum* is pathogenic only on abraded skin; a disruption of the epidermis must be present for development of disease. Because this organism is recognized as a pathogen in zebrafish, it can be a source of infection in personnel working with this species in a research environment.

Clinical Signs *M. marinum* is a free-living mycobacterium that causes disease in fresh-water and saltwater fish and occasionally in humans. Initially called swimming pool granuloma, it is now commonly named fish tank granuloma because of the association with this environmental exposures and human infections. Importantly, *M. marinum*, because of its optimum growth at 30–32°C, is primarily localized to skin infections. However, it can extend to deeper tissues, including joints and tendons. For individuals exposed to diseased fish and/or their environment, the lesions are in general located on the backs of hands or fingers or forearms (Baiano and Barnes, 2009). Infections have also resulted from the bite of a dolphin (Flowers, 1970).

Diagnosis and Control Identification for the common RGM and *M. marinum* has been given low priority and is only performed routinely in reference laboratories. Fortunately, however, PCR-based assays have become available for rapid diagnosis of atypical mycobacteria.

3. Rat-Bite Fever

Rat-bite fever (RBF) can be caused by either of two microorganisms: *Streptobacillus moniliformis* or *Spirillum minus. S. moniliformis* causes the diseases designated as streptobacillary fever, streptobacillary RBF, or streptobacillosis (McEvoy *et al*., 1987; Rupp, 1992; Heymann, 2008; Fox, 2009). Haverhill fever and epidemic arthritic erythema are diseases associated with ingestion of water, food, or raw milk contaminated with *S. moniliformis.* Sodoku is derived from the Japanese words for rat (*so*) and poison (*doku*), and is used to designate infection with *S. minus.* Spirillosis and spirillary RBF are other names given to the infections caused by *S. minus.*

Reservoir and Incidence These organisms are present in the oral cavity and upper respiratory passages of asymptomatic rodents, usually rats (Wilkins *et al*., 1988). *S. moniliformis* has been isolated as the predominant microorganism from the upper trachea of laboratory rats in one study (Paegle *et al*., 1976). Other surveys indicate isolation of the organism in 0/15, 7/10, 2/20, and 7/14 laboratory rats and 4/6 wild rats (Geller, 1979). The incidence of *S. moniliformis* is probably lower in high-quality, commercially reared specific pathogen-free rats. Surveys in wild rats indicate 0–25% infection with *S. minus* (Hull, 1955) or 50–100% for *S. moniliformis.*

TABLE 28.2 Clinical Signs of RBF[a]

Clinical features	Streptobacillary fever (*Streptobacillus moniliformis*)	Spirillosis (*Spirillum minus*)
Incubation period	2–10 days	1–6 weeks
Fever	+++	+++
Chills	+++	+++
Myalgia	+++	+++
Rash	++	++
	Morbilliform, petechial	Maculopapular
Lymphadenitis	+	++
Arthralgia, arthritis	++	±
Indurated bite wound	–	+++
Recurrent fever/constitutional signs (untreated)	Irregular periodicity	Regular periodicity

[a]*Modified from Lipman (1996).*

Mode of Transmission The bite of an infected rat is the usual source of infection. In some cases, bites from other animals, including mice, gerbils, squirrels, weasels, ferrets, dogs, and cats, or rare traumatic injuries unassociated with animal contact cause the infection.

Clinical Signs RBF is not a reportable disease, which makes its prevalence, geographic location, racial data, and source of infection in humans difficult to assess. The disease, though uncommon in humans, has nonetheless appeared among researchers or students working with laboratory rodents, particularly rats (Anderson *et al.*, 1983). Historically, bites from wild rats and subsequent illness (usually in small children) relate to poor sanitation and overcrowding (Hull, 1955). One survey of rat bites in Baltimore tabulated RBF in 11 of 87 cases (Brooks, 1973). The disease can also occur in individuals who have no history of rat bites but reside or work in rat-infested areas. Exposure to dogs and cats who prey on wild rodents may also be the source of the organism. Ingestion of milk, food, or water contaminated with rat feces can result in RBF (CDC, 1995).

The incubation period for *S. moniliformis* infection varies from a few hours to 2–10 days, whereas the incubation period for *S. minus* infection, most commonly seen in Asia, ranges from 1 to 6 weeks (Table 28.2). Fever is present in either form. Inflammation associated with the bite and lymphadenopathy are frequently accompanied by headache, general malaise, myalgia, and chills. The discrete macular rash that often appears on the extremities may generalize into pustular or petechial sequelae. Arthritis occurs in 50% of all cases of *S. moniliformis* but is less common in *S. minus*. *S. moniliformis* may be cultured from serous to purulent effusion that is recovered from affected larger joints. The organism should be considered in the list of differential diagnosis in cases of septic arthritis, particularly with synovial fluid with high inflammatory cell counts (Dendle *et al.*, 2006).

Most cases of RBF resolve spontaneously within 14 days; however, 13% of untreated cases are fatal (Sens *et al.*, 1989). Prophylactic efficacy of antibiotic treatment following rat bites has not been thoroughly investigated. If antibiotic treatment (intravenous penicillin for 5–7 days, followed by oral penicillin for 7 days) is not instituted early, complications such as pneumonia, hepatitis, pyelonephritis, enteritis, and endocarditis may develop (Anderson *et al.*, 1983). If endocarditis is present, the penicillin should be given parenterally at doses of 15–20 million units daily for 4–6 weeks. Streptomycin and tetracyclines are also effective antibiotics for those individuals with penicillin-associated allergies. Death has occurred in cases of *S. moniliformis* involving preexistent valvular disease. The recent reports of fatalities due to *S. moniliformis* in adults working in a pet store and having rats as pets highlight the need to be vigilant in recognizing the clinical manifestations of RBF in patients with a history of rat bites or intimate exposure to rats (CDC, 2005).

Diagnosis and Prevention *S. minus* does not grow *in vitro* and requires inoculation of culture specimens into laboratory animals, with subsequent identification of the bacteria by dark-field microscopy. Streptobacillary RBF can be diagnosed only by blood culture. *S. moniliformis* grows slowly on artificial media, but only in the presence of 15% blood and sera, usually 10–20% rabbit or horse serum incubated at reduced partial pressures of oxygen (Fox, 2009). Because of its properties as a bacterial growth promoter, sodium polyanethol sulfonate, which is sometimes found in blood-based media, should not be used due to its inhibitory effects on *S. moniliformis*. Growth on agar consists of 1–2 mm gray, glistening colonies. The API ZYM diagnostic system can be used for rapid biochemical analysis and diagnosis. Unfortunately, no serological test is available. Acute febrile diseases, especially if associated with animal bites, are routinely treated with penicillin or other antibiotics.

4. Cat Scratch Disease

Both viruses and chlamydia had been suspected as a cause of cat scratch fever (CSF) until histopathologic examination of lymph nodes from 39 patients with clinical criteria for cat scratch disease (CSD) revealed pleomorphic, gram-negative bacilli in 34 of the 39 nodes. Organisms in lymph node sections exposed to convalescent serum from three patients and to immunoperoxidase stained equally well with all three samples. The authors concluded that the bacilli appear to be the

causative agents of CSD (Wear *et al*., 1983). The following year, using the same staining protocol, researchers demonstrated identical organisms in skin biopsies taken from CSF inoculation papules (Margileth *et al*., 1984). *Bartonella henselae*, a fastidious gram-negative bacteria, is now recognized as the primary cause of CSD. *B. henselae* has been isolated from lymph nodes of CSD patients, and elevated serological titers to *B. henselae* are also noted in these individuals (Dolan *et al*., 1993; Zangwill *et al*., 1993). A second organism, *Afipia felis*, has also been isolated from CSD lesions but is not considered the common etiologic agent of CSD.

Reservoir and Incidence An estimation of 22,000 cases of CSD in the United States, of which approximately 2000 require hospitalization, is based on an analysis of three databases (Jackson *et al*., 1993). Almost all *B. henselae* infections are associated with exposure or ownership of cats; however, not all cases of CSD are associated with a scratch or bite.

Mode of Transmission Patients with CSD commonly have a history of exposure to a cat, and of these patients, the majority have either been bitten or scratched. Most of the patients are under 20 years of age. It is now known that cat fleas are infected with *B. henselae.* It is suspected that the organism is shed in the feces of the flea and can result in the transmission of the organism from cat to cat and from cat to human via mucous membrane or skin contact. Subsequently there is self-inoculation by scratching the flea bite, or alternatively by having the contaminated claws or teeth of cats inoculate the organism into traumatized skin. Importantly, several surveys have shown that cats can be chronically infected with *B. henselae*, with the organism capable of being isolated from blood of asymptomatic cats over an extended period of time (Koehler *et al*., 1994; Goldstein and Greene, 2009). Impounded or stray cats are more likely to be chronically infected than cats maintained in a household long term.

Clinical Signs The natural course of CSD, which consists of a mild or absent fever, few systemic sequelae, and localized lymphadenitis with little or no discomfort, probably results in a large number of unrecognized cases. A primary lesion will develop in 50% of the cases about 10 days after a cat bite or scratch; the erythematous pustule will usually persist for 1–2 weeks. A regional lymphadenopathy develops 14 days after the initial lesion in most cases. Lymphadenitis regresses in about 6 weeks, with 30–50% of the nodes becoming suppurative. Of the approximately 65% of people who develop systemic illness, fever and malaise are the symptoms most often noted. Occasionally observed are generalized lymphadenopathy. Other clinical syndromes include ocular granuloma, thrombocytopenia, encephalitis, osteolytic lesions, pneumonia, liver and spleen abscesses, and erythema nodosum. The disease is benign, and most patients recover spontaneously without sequelae within 2 months, although lymphadenopathy can persist for up to a year. In immunocompromised individuals, CSD is manifested by an unusual vascular growth seen on the skin and given the name bacillary epithelioid angiomatosis (LeBoit *et al*., 1988; Kemper *et al*., 1990). Systemic disease involving the spleen and liver also occurs in these patients.

Diagnosis and Control If lymphadenitis is present, three of the four following criteria should be fulfilled to diagnose CSD: (1) positive serology for *B. hensalae;* a positive titer of 1:64 or greater by IFA assay is considered positive; a recently developed modified IFA has been described with a sensitivity of 85% and specificity of 98% for both IgG and IgM (Metzkor-Cotter *et al*., 2003); (2) history of contact with a cat; (3) characteristic histopathologic changes present in involved lymph node biopsy; (4) absence of other disease; and (5) growth of the organism on rabbit, horse, or sheep blood agar in 5% CO_2. However, growth on human blood agar appears superior (Goldstein and Greene, 2009).

Prevention is based on flea control as well as thorough cleansing of cat bites and scratches.

5. Pasteurella *spp.*

Reservoir and Incidence *Pasteurella* species, particularly *P. multocida*, are considered one of the most prevalent bacterial species known to colonize the upper respiratory tract and oral mucosa of domestic and wild animals (Dewhirst *et al*., 2012).

Mode of Transmission Zoonotic transmission of *P. multocida* most often occurs through animal bites and scratches, or contact with respiratory secretions (Wilson and Ho, 2013). *Pasteurella* species are cultured from infections resulting from 50% of dog bites and 75% of cat bites (Freshwater, 2008; Talan *et al*., 1999; Rempe *et al*., 2009). Other contact, such as kissing infected animals or the animals licking skin abrasions or mucosal surfaces (eyes, mouth, and nose), or exposure to respiratory secretions of infected animals can also account for zoonotic transmission of *Pasteurella* spp. (Myers *et al*., 2012). Immunocompromised, elderly, pregnant individuals, those administrating palliative care, and children are particularly vulnerable to acquiring *P. multocida* from animals' respiratory secretions or contact of patients' skin lesions (through licking).

Clinical Signs Bite wound infections linked to *Pasteurella* spp. infections can be clinically apparent as early as 8–12 hours, and are aggressive in presentation with skin and soft tissue swelling, erythema, local lymphadenopathy, fever, pain, and swelling (Fig. 28.5). Osteomyelitis can also occur in bone underlying the wound, and septicemia can result on occasion (Hombal and Dincsoy, 1992). Cat scratches have also resulted in *P. multocida*-associated corneal ulceration and keratitis

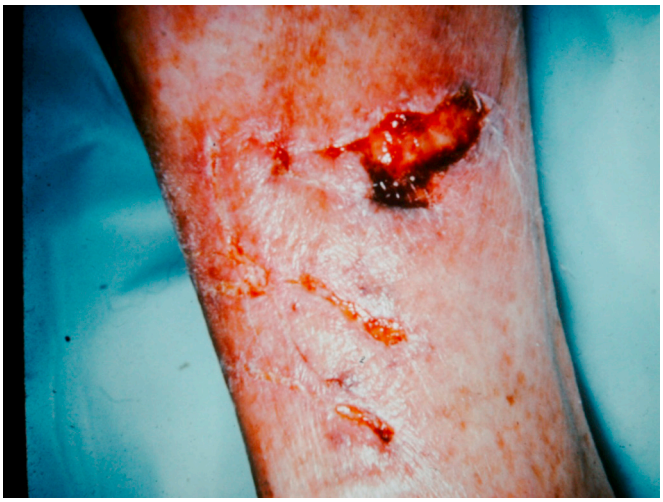

FIGURE 28.5 *Pasteurella multocida*-associated dog bite wound. *Source: John Moses, M.D.*

(Ho and Rapuan, 1993). Routine, prompt prophylactic treatment with broad spectrum antibiotics of animal bite wounds probably accounts for pasteurellosis being a relatively uncommon cause of mortality in humans. Mortality rates, though uncommon, of 25–30% have been reported in human cases of pasteurellosis due to bite wounds, with bacteremia being commonly reported, and to a lesser extent meningitis (Kimura *et al.*, 2004; Myers *et al.*, 2012).

Diagnosis and Control Bacterial culture of the wound is undertaken prior to local cleansing and antisepsis of the traumatic site of injury. The bacteria are gram-negative rods that grow readily on blood agar.

6. Streptococcus iniae

Reservoir and Incidence *Streptococcus iniae* is now recognized as a cause of high mortality in rainbow trout and tilapia (members of the cichlid group of fish) being raised in fish farming environments. *S. iniae* was recognized as a pathogen in 1976 when the bacteria was first cultured from cutaneous abscesses in aquaria-maintained Amazon freshwater dolphins (Pier and Madin, 1976).

Mode of Transmission Many infected patients sustain an injury to the hand when preparing infected fish for consumption. The organism can be readily cultured from these infected fish (Goh *et al.*, 1998).

Clinical Signs *S. iniae* was identified as a zoonotic agent in 1995–1996 when a cluster of cases presented with fever and lymphangitis in individuals handling whole or live fish purchased in Toronto, Canada (CDCP, 1995; Weinstein *et al.*, 1997). *S. iniae* was cultured from the blood of each of these patients.

Diagnosis and Control The organisms are gram-positive cocci, B-hemolytic on 5% sheep blood agar and are nonreactive in the Lancefield sero-grouping system. Unfortunately, *S. iniae* currently is not included in commercial and clinical databases and diagnostic kits, making it likely that human infections are underreported (Fulde and Valentin-Weigand, 2013). A nested PCR assay specific for the 16S–23S ribosomal intergenic spacer and a chaperonin 60 (cpu 60) gene identification method are two molecular techniques that provide accurate, rapid, and specific diagnosis of this organism (Berridge *et al.*, 1998; Goh *et al.*, 1998). Infected individuals respond to parenteral antibiotics within 2–4 days after initiation of treatment.

Other *Streptococcus* spp. associated with zoonosis include *S. canis*, *S. zooepidemicus*, and *S. suis* (Fulde and Valentin-Weigand, 2013) (Fig. 28.6). *S. zooepidemicus* has been recently transmitted from guinea pigs to their owners, resulting in clinical septicemia (Gruszynski *et al.*, 2015).

B. Systemic Diseases

1. Brucellosis

Reservoir and Incidence Of the *Brucella* spp., *Brucella canis* is the most likely zoonotic agent in the laboratory animal facility due to the frequent use of random-source and laboratory-bred dogs in comparison with other large domestic animals known to be infected with other *Brucella* spp.

Mode of Transmission In one study, investigators considered the zoonotic transmission of *B. canis* unlikely, as evidenced by negative serological tests among 12 individuals exposed to five infected dogs. Since 1967, when the first human *B. canis* infection was identified, more than 35 natural and laboratory-acquired infections have been reported; most resulted from contact with aborting bitches (Lucero *et al.*, 2010). Fortunately, humans are relatively resistant to infection; however, *B. canis* is not a reportable disease, and prevalence data are not available. Although *B. canis* is particularly well adapted to dogs and is not readily transmitted to other species, susceptibility has been reported in several wild species of Canidae (Greene and Carmichael, 2011).

Clinical Signs Bacteremia occurred in several infections; other systemic involvement included painful generalized lymphadenophathy and splenomegaly. Additional signs include fever, headache, chills, sweating, weakness, malaise, myalgia, nausea, and weight loss. Rare complications include endocarditis, meningitis, hepatitis, and arthritis. Although *B. canis*-produced clinical disease in humans is similar to that caused by other *Brucella* spp., it is generally not as severe. Seroconversion to *B. canis* has been reported in 0.5% of asymptomatic military personnel who had contact with infected dogs, indicating that inapparent infection may occur (Polt *et al.*, 1982).

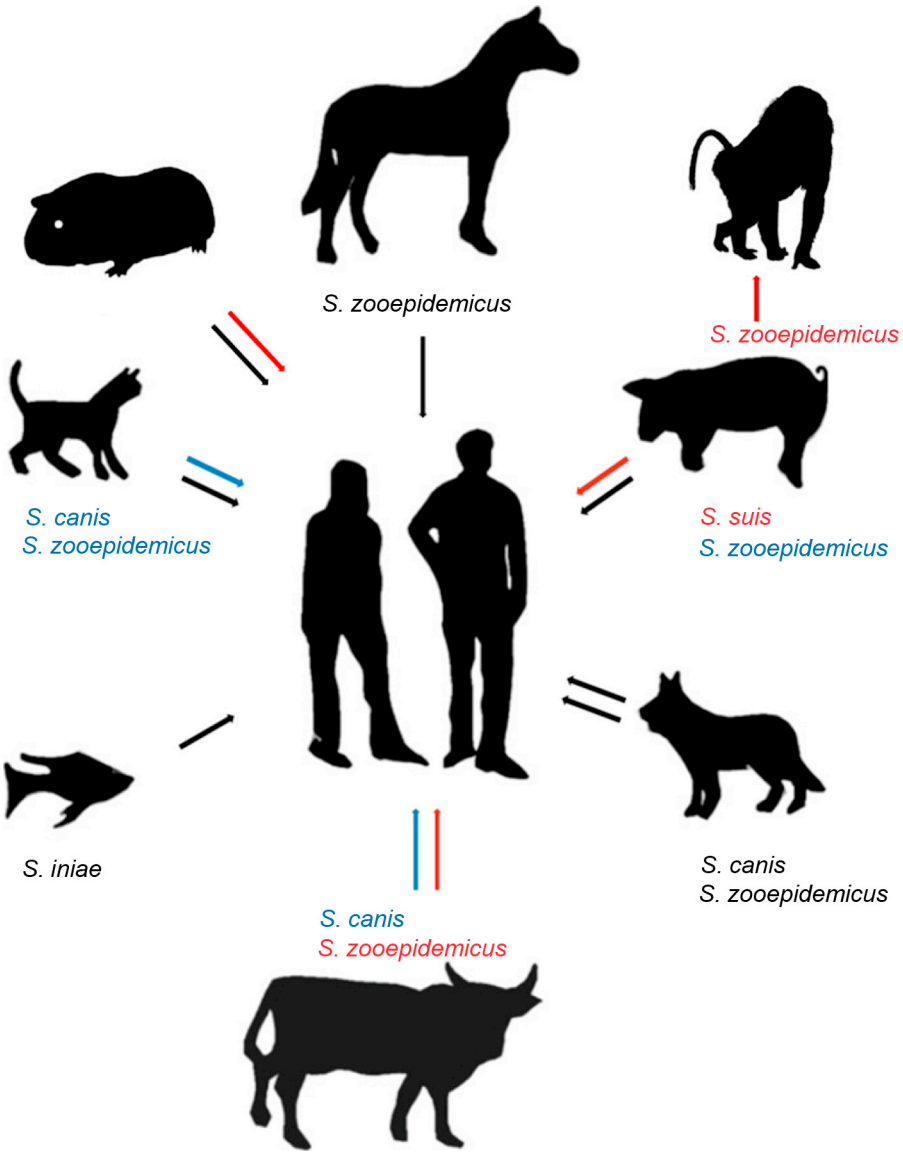

FIGURE 28.6 Schematic figure representing host–pathogen relations of zoonotic streptococci. Black arrows indicate the transmission to one individual, whereas red arrows illustrate the origin of outbreaks. An identification of zoonotic species in animals without a proven transmission to humans is colored blue. *Adapted from Fulde and Valentin-Weigand (2013).*

Diagnosis and Control When a canine's history includes abortions, infertility, testicular abnormalities, and poor semen quality, infection should be considered. A rapid slide agglutination test that produces presumptive diagnostic information is commercially available. To confirm the results of the slide test, one should perform blood cultures and additional serological tests, such as the tube agglutination test (Polt *et al.*, 1982; Serikawa *et al.*, 1989). There have not been any large-scale efforts to eradicate *B. canis* in the general canine population as there have been with *Brucella* spp. of large domestic animals (Forbes and Pantekoek, 1988). Because of the intracellular location of *B. canis*, efficacy of antibiotic therapy is variable, and failures or relapses after therapy are reported in dogs. Ultimate control of *B. canis* in humans relies on elimination of dogs with the disease.

2. *Plague*

Human infections due to *Yersinia pestis*, a gram-negative coccobacillus, in the United States are sporadic and limited, usually resulting from infected flea or rodent contact. Since 1924–1925, when a plague epidemic ravaged Los Angeles, neither urban plague nor rat-borne plague has been diagnosed in the United States (Craven and Barnes, 1991). All reported cases since then have occurred in states located west of the 101st meridian.

Reservoir and Incidence Although plague has occurred repeatedly in recorded history, by the fourteenth century the disease had appeared in the Far East, spread to Asia Minor, and followed the trade routes to Europe. Plague, however, did not make its arrival in the United States until the disease appeared in California in the early 1900s, where it still exists endemically in the ground squirrel and chipmunk.

Wild rat populations still act as the primary reservoir in many parts of the world and remain a continued threat in the United States. Sciurid rodents (rock squirrels, California ground squirrels, chipmunks, and prairie dogs) account for the primary plague reservoir in the western parts of the United States (Kaufman *et al*., 1980; Rosner, 1987). Cricetid rodents, such as the wood rat, are occasionally cited as reservoir hosts. The oriental rat flea, *X. cheopis*, the common vector of plague, is well established throughout the United States, particularly in the southern states and southern California. It is important to remember that more than 1500 species of fleas and 230 species of rodents are infected with *Y. pestis.* Only 30–40 rodent species, however, are permanent reservoirs of the infection (Macy, 1999). Plague is infrequently reported in the United States, with a low of one case in 1972 and a high of 40 cases in 1983 (Craven and Barnes, 1991). Ninety percent of the cases have been diagnosed in New Mexico, Colorado, and California. Urban development (particularly in New Mexico) encroached into plague-enzootic rodent habitats, placing human populations at increased risk of contracting the disease. In addition to rodent epizootics, dogs, and increasingly cats, either have served as passive transporters of the disease or have been actively infected (Rosner, 1987). The disease has seasonal peaks, with the highest proportion occurring May through September.

Mode of Transmission An individual is usually infected by the bite of an infected flea, but infection can also occur via cuts or abrasions in the skin or via infected aerosols coming into contact with the oropharyngeal mucous membrane.

Primary pneumonic plague historically occurred by inhalation of infectious droplets from a pneumonic plague patient. However, in the past several decades, this form of the disease has occurred from exposure to infected animals (usually cats) that have developed secondary pneumonia due to septicemic spread of the organism (Rosner, 1987; Craven and Barnes, 1991). Personnel attending these sick animals are then infected by inhaling infected aerosols.

Clinical Signs Bubonic plague in humans is usually characterized by fever (2–7 days postexposure) and the formation of large, tender, swollen lymph nodes, or buboes. If untreated, the disease may progress to severe pneumonic or systemic plague. Inhaled infective particles, particularly from animals with plague pneumonia, may also result in the pneumonic form of the disease.

Diagnosis and Control A presumptive diagnosis can be made by visualizing bipolar-staining, ovoid, gram-negative rods on the microscopic examination of fluid from buboes, blood, sputum, or spinal fluid; confirmation can be made by culture. Complement fixation, passive hemagglutination, and immunofluorescence staining of specimens can be used for serological confirmation.

Mortality without antibiotic therapy, particularly in cases of pneumonic plague, exceeds 50% in untreated cases. Although *Y. pestis* is susceptible to a wide variety of antibiotics, multiple antibiotic-resistant strains are being isolated with increasing frequency (Dennis and Hughes, 1997). Aminogylcosides, such as streptomycin and gentamicin, are the most effective antibiotics *in vivo* against *Y. pestis.* Chloramphenicol is the drug of choice for treating plague meningitis and endophthalmitis (Craven and Barnes, 1991; Mushatt and Hyslop, 1991). In people exposed to *Y. pestis*, prophylactic therapy with tetracycline for a 7-day period is often prescribed.

An inactivated plague vaccine is available for laboratory personnel working with the organism and in high-risk individuals working in areas where the disease is endemic (e.g., wildlife management employees, Peace Corps volunteers) and where they are exposed to plague reservoirs.

Rodent and flea control, particularly in endemic areas, is an indispensable part of containing exposure to plague, as is restricting certain locales for recreational use. Animal facilities should be constructed and maintained to prevent wild rodent egress. Furthermore, feral or random-source animals acquired from plague-endemic areas should be quarantined and treated with appropriate insecticides to kill fleas.

3. *Leptospirosis*

Leptospirosis is solely a zoonotic disease of livestock, pet and stray dogs, and wildlife, including wild rodents. Human-to-human transmission is extremely rare. *Leptospira interrogans* (comprising >200 serovars) has been isolated worldwide. Although particular serotypes usually have distinct host species, most serotypes can be carried by several hosts. *Leptospira* spp. are well adapted to a variety of mammals, particularly wild animals and rodents. Recent molecular analysis of *Leptospira* spp. has classified these bacteria into over 15 species. In clinical practice, however, *Leptospira* spp. continue to be identified by serotype and importantly used for epidemiological studies (Bharti *et al*., 2003; Levett, 2001).

Reservoir and Incidence *Leptospira icterohaemorrhagiae* was first recovered in 1918 in the United States from wild rats sampled in New York City. In the 1950s, in a study conducted in Baltimore, 45.5% of 1643 rats were infected with *Leptospira;* higher prevalence rates occurred in older rats (approximately 60%). In the late

1970s, more than 90% of adult Brown Norway rats sampled in Detroit were infected with *L. icterohaemorrhagiae* (Thiermann, 1977). Other studies confirm the high prevalence of this organism in wild rats inhabiting U.S. cities (Alexander, 1984; Sanger and Thiermann, 1988). Rodent reservoir hosts of leptospirosis, in addition to rats, include mice, field moles, hedgehogs, gerbils, squirrels, rabbits, and hamsters (Torten, 1979; Fox and Lipman, 1991). Livestock serve as a significant source of primary long-term shedding of at least three serovars. Cattle are the natural carriers of the serotype *L. hardjo*, whereas swine carry *L. pomona* and *L. bratislava;* each animal can shed the organism for extended periods in their urine. Dogs also commonly harbor two other serotypes; feral dogs harbor L. *icterohaemorrhagiae* as well as serve as natural carrier hosts of *L. canicola.* Sheep, goats, and horses can also be infected with a variety of serotypes. Raccoons are reservoirs of *L. autumnalis* and *L. grippotyhosa*, whereas rats, mice, and other wild rodents are common animal hosts for another serotype, *L. ballum.* In wild mice, the infection can persist unnoticed for the animal's lifetime and can also be harbored by laboratory mice, although their carrier rates in the United States are unknown (Torten, 1979). There was, however, a report of leptospirosis in a research colony of mice in the United States in the early 1980s (Alexander, 1984). In several European laboratories, personnel have contracted leptospires from laboratory rats (Geller, 1979).

Mode of Transmission Infection with *Leptospira* most frequently results from handling infected animals (contaminating the hands with urine) or from aerosol exposure during cage cleaning or through exposure to contaminated water or soil. Skin abrasions or mucous membrane exposure may serve as the portal of entry in humans. All secretions and excretions from infected animals should be considered infective. In one instance, a father apparently was infected after his daughter used his toothbrush to clean a contaminated pet mouse cage. Handling infected wild rats increases the risk of contracting leptospires (Luzzi *et al.*, 1987). Also, a young man died of acute leptospirosis by falling into a heavily polluted river contaminated with *L. icterohaemorrhagiae* (Sanger and Thiermann, 1988). In addition, rodent bites can transmit the disease. Children living in rat-infested tenements may be at increased risk of infection. For example, children from inner-city Detroit had significantly higher *L. icterohaemorrhagiae* antibody titers when compared to those of children living in the Detroit suburbs (Demers *et al.*, 1983). It is important to note that leptospirosis can infect hosts on a chronic basis, by colonizing their kidney tubules. Outbreaks of leptospirosis in humans with varying mortality in underdeveloped countries have been documented in 1995–1998.

Clinical Signs The disease may vary from inapparent to severe infection and death. Individuals infected with *Leptospira* spp. experience a biphasic disease (Sanger and Thiermann, 1988; Faine, 1991). They become suddenly ill with weakness, headache, myalgia, malaise, chills, and fever, and usually exhibit leukocytosis. During the second phase of the disease, which is immunologically mediated, conjunctival suffusion and a rash may occur (Fig. 28.7). On examination, renal, hepatic, pulmonary, and gastrointestinal findings may be abnormal. The most severe form of the diseases, known as Weil's disease, is characterized by hepatic and renal dysfunction, hemorrhage, and circulatory collapse (Bharti *et al.*, 2003; Levett, 2001). Treatment of the disease is controversial given the disease is self-limiting. Penicillin is the drug of choice in treating early onset of leptospirosis infection (Vinetz, 2003). Comparison of penicillins to ceftriaxone, cefotaxime, and doxycycline in cases of severe leptospirosis indicated that all of these antibiotics were equally efficacious in reducing fever and clinical complications (Vinetz, 2003). Ampicillin and doxycycline have also been effective in treating people with leptospirosis.

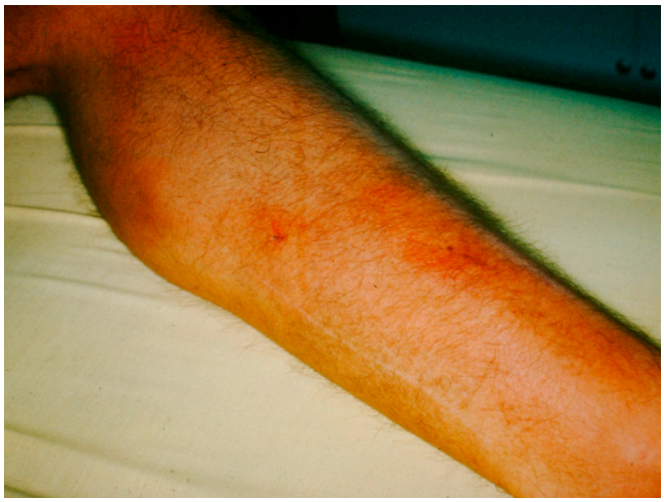

FIGURE 28.7 Leptospirosis causing diffuse redness on a leg of a veterinarian after visiting sick lamb. *Source: John Moses, M.D.*

Diagnosis and Control Leptospirosis in humans is often difficult to diagnose; therefore, the low incidence of reported infection in humans may be misleading. Outbreaks have been documented in the United States from personnel working with laboratory mice (Stoenner and Maclean, 1958; Barkin *et al.*, 1974). In one study, 8 of 58 employees handling infected laboratory mice (80% of breeding females were excreting L. *ballum* in their urine) contracted leptospirosis (Stoenner and Maclean, 1958). Personnel performing field research may be predisposed to developing leptospirosis and other zoonotic diseases, since occupational exposure to wild animal habitats is a work-related risk factor (Adjemian *et al.*, 2012). Because of the variability in clinical symptoms and lack

of pathognomonic findings in humans and animals, serological diagnosis or actual isolation of leptospires is imperative (Bharti *et al.*, 2003; Levett, 2001). As an aid to diagnosis, leptospires can sometimes be observed by examination or direct staining of body fluids or fresh tissue suspensions. The definitive diagnosis in humans or animals is made by culturing the organisms from tissue or fluid samples. Culture media with long-chain fatty acids with 1% bovine serum albumin are routinely used as a detoxicant (Faine, 1991). Serological assessment is accomplished by indirect hemagglutination, agglutination analysis, complement fixation, microscopic agglutination, and fluorescent antibody techniques (Faine, 1991). Growth of the organism is slow, and cultures should be incubated in the dark for 6 weeks at 30°C (Goldstein, 1991; Collins and Lorber, 2009). The serological test most frequently used is the microscopic agglutination test, which employs dark-field microscopy. Titers of 1:100 or greater are considered significant. When comparing serological assays, ELISA and dot ELISA have the highest sensitivities and specificities (Goldstein, 1991; Collins and Lorber, 2009). PCR-based assays are also available for diagnosis (Smythe *et al.*, 2002). Personnel hygiene and protective garments that minimize exposure to infected urine and other infected animal tissue are important for control of zoonotic infection with leptospires.

C. Enteric Diseases

1. *Campylobacteriosis*

Campylobacter spp. have been known as a pathogenic and commensal bacterium in domestic animals for decades. During the past several years, *C. jejuni* and *C. coli* have gained recognition as a leading cause of diarrhea in humans.

Reservoir and Incidence *C. jejuni*, *C. coli*, *C. upsaliensis*, and *C. helveticus* have been isolated from a variety of laboratory animals, including dogs, cats, guinea pigs, hamsters, ferrets, nonhuman primates, poultry, and rabbits (Fox, 1982a; Engvall *et al.*, 2003) and also from healthy swine, sheep, and cattle. *Campylobacter* spp. commonly cause abortion in livestock. They can be shed in the stool for variable periods of time in asymptomatic carriers, and multiple species of *Campylobacter* spp. as well as *Helicobacter* spp. can be isolated from the feces of a single individual or animal (Allos *et al.*, 1995; Shen *et al.*, 1999; Fox, 2011).

Mode of Transmission In most reports citing pet-to-human transmission of *C. jejuni*, diarrheic puppies or kittens recently obtained from animal pounds were the source of the infection (Blaser *et al.*, 1980; Deming *et al.*, 1987; Tenkate and Stafford, 2001). People who live with dogs are at increased risk of acquiring campylobacter infections. In a laboratory animal setting, personnel performing husbandry chores have become infected when handling *Campylobacter*-infected animals (Fox *et al.*, 1989b). Prevalence studies of dogs, cats, newly imported primates, or animals housed in groups suggest that younger animals more easily acquire the infection and, hence, commonly shed the organism. More recently, *C. upsaliensis* and *C. helveticus* have been isolated from dogs and cats. *C. upsaliensis* has also been associated with diarrheal disease in humans (Fox, 2011).

Clinical Signs The clinical features of campylobacter enteritis in humans are usually consistent with an acute gastrointestinal illness. Diarrhea – sometimes watery – with or without blood and leukocytes, abdominal pain, and constitutional symptoms, especially fever, occur routinely. The severity of the illness can be variable, but in most cases it is brief and self-limiting. Complications of *C. jejuni* infections include reactive arthritis, Guillian–Barre syndrome, and rarely myocarditis. In protracted or severe cases, antimicrobial therapy (e.g., erythromycin) is instituted. Erythromycin eliminates *C. jejuni* from the intestine of most infected patients within 72 hours.

Diagnosis and Control There are multiple *C. jejuni/coli* serotypes; the use of serotyping schemes and restriction enzyme analysis of isolates aids in confirming zoonotic spread of the organism (Russell *et al.*, 1990). Additional molecular techniques also can be used to discriminate strain identity. Because animals can be asymptomatic carriers of Campylobacters, protective measures preventing fecal contamination and inadvertent oral ingestion are important for prevention of infection.

2. *Enteric Helicobacteriosis*

Reservoir and Incidence *Helicobacter cinaedi* is primarily recovered from immunocompromised individuals; the organism is also recovered from chronic alcoholics as well as immunocompetent men and women. The hamster is suspected to be the reservoir host for *H. cinaedi* (Gebhart *et al.*, 1989). Even though *H. canis*, *H. cinaedi*, *H. fennelliae*, and *H. rappini* (now classified as *H. bilis)* have been isolated from both dogs and humans, *H. canis* and *H. cinaedi* from cats, and *H. cinaedi* from rhesus monkeys (Fox, 2002; Fox *et al.*, 2001), additional investigations will be required to ascertain whether these enteric helicobacters in dogs, cats, hamsters, non-human primates, and other unrecognized mammalian hosts constitute a potential reservoir for zoonotic transmission to people. Although there are a multitude of *Helicobacter* spp. in rodents, no zoonotic link, other than hamsters, has been associated with these enteric helicobacters (Whary and Fox, 2006). Recently, however, *H. pullorum*, isolated from poultry and humans, has also been cultured from commercially raised mice (Turk *et al.*, 2012).

Mode of Transmission Fecal–oral transmission is the likely route of infection. *H. cinaedi*, a fastidious microaerophile, has been recovered from blood and fecal

specimens of children and of a neonate with septicemia and meningitis. The mother of the neonate had cared for pet hamsters during the first two trimesters of her pregnancy (Orlicek *et al.*, 1993). Because *H. cinaedi* has been isolated from normal intestinal flora of hamsters, it was suggested that the pet hamsters served as a reservoir for transmission to the mother. The mother had a diarrheal illness during the third trimester of pregnancy; the newborn was likely to have been infected during the birthing process, although this was not proven (Orlicek *et al.*, 1993). Furthermore, the hamster has been suggested as possibly infecting other humans with *H. cinaedi* (Gebhart *et al.*, 1989). Studies are needed to confirm zoonotic risk of handling *H. cinaedi*-infected hamsters (Gebhart *et al.*, 1989). Also of interest is the isolation, based on cellular fatty acid and biochemical identification, and molecular analysis, of *H. cinaedi* from the feces of dogs, cats, and nonhuman primates. *H. canis* has also been isolated from blood of a bacteremic 7 month-old child living with a cat (Prag *et al.*, 2007).

Clinical Signs *H. cinaedi* (previously *Campylobacter cinaedi*) was first isolated from the lower bowel of homosexuals with proctitis and colitis. It has also been isolated from the blood of homosexual patients with HIV as well as children and adult women (Orlicek *et al.*, 1993). In a retrospective study of 23 patients with *H. cinaedi*-associated illness, 22 of the cases had the organism isolated from blood by using an automated blood culture system in which a slightly elevated growth index was noted (Kiehlbauch *et al.*, 1994). This study also described a new *H. cinaedi*-associated syndrome consisting of bacteremia and fever, and accompanied by leukocytosis and thrombocytopenia. Recurrent cellulitis and/or arthritis are also noted in a high percentage of infected immunocompromised patients (Kiehlbauch *et al.*, 1994; Burman *et al.*, 1995). Other enteric helicobacters, *H. canis*, *H. pullorum*, *H. bilis*, *H. fenneliae*, *H. canadensis*, and *H. westmeadii*, have been isolated from diarrheic patients as well as bacteremic immunocompromised individuals (Fox, 2002).

Diagnosis and Control It should be stressed that many hospital and veterinary laboratories have difficulty isolating this organism. Because of the slow growth of *H. cinaedi* and other enteric helicobacters, laboratory diagnosis is unlikely if blood culture procedures that rely on visual detection of the culture media are used (Kiehlbauch *et al.*, 1994; Burman *et al.*, 1995; Kiehlbauch *et al.*, 1995). Use of dark-field microscopy or acridine orange staining of blood culture media, rather than gram staining, increases likelihood of seeing the organism. Likewise, fecal isolation is difficult; selective antibiotic media are required, and recovery is facilitated by passing fecal homogenates through a 0.45-pm filter (Gebhart *et al.*, 1989). In one study, several strains of both *H. cinaedi* and *H. fennelliae* were inhibited by concentrations of cephalothin and cetazolin used frequently in selective media for isolation of enteric microaerophilic bacterium. These organisms also require an environment rich in hydrogen for optimum *in vitro* growth. Until diagnostic laboratories embark on routine isolation attempts of *Helicobacter* spp. from feces, the extent of their presence in companion and pocket pets and their zoonotic potential will be unknown.

3. Gastric Helicobacter Infections

Reservoir and Incidence Because gastric helicobacter-like organisms (GHLOs) (i.e., '*H. heilmannii*' (now classified as *H. suis*) or *H. felis*, and *H. bizzozeronii* in dogs) cause a small percentage of gastritis in humans and no environmental source for these bacteria has been recognized, various animals, particularly dogs and cats, have been implicated in zoonotic transmission. In colony-reared dogs, cats, and nonhuman primates, GHLO infection may approach 100%. *H. pylori*, the primary gastric pathogen in humans, has been isolated from only one colony of commercial cats and macaque species. If *H. pylori*, as demonstrated in commercially reared cats (Handt *et al.*, 1994; Fox *et al.*, 1996), is isolated from pet cats, the zoonotic potential of helicobacteriosis from cats would obviously increase substantially. *H. pylori* infection is an important cause of human gastritis; however, most epidemiologic studies do not incriminate animal contact as a cause of human infection. An epidemiologic survey conducted in Germany did not show an increased risk of *H. pylori* because of cat ownership. In a serological survey measuring antibodies to *H. pylori*, lower socioeconomic status, and not pet ownership or day care, was associated with seropositivity (Staat *et al.*, 1996).

Mode of Transmission Oral–oral transmission is likely, but fecal–oral transmission may also occur. In one case study, a researcher performing physiologic studies with cat stomachs developed an acute gastritis, presumably resulting from *H. felis* on the basis of electron microscopy (EM) (Lavelle *et al.*, 1994). Gastric spiral bacteria were demonstrated in gastric mucosa of cats being used by this scientist. In Germany, a survey of 125 individuals infected with GHLOs provided information in a questionnaire regarding animal contact. Of these patients, 70.3% had contact with one or more animals compared with 37% in the clinically healthy control population (Stolte *et al.*, 1994).

Clinical Signs Infection with GHLOs in animals (although associated with gastritis in the majority of humans) does not cause characteristic clinical illness with any consistency or reproducibility. In people with GHLO infections, bismuth subsalicylate, amoxicillin, tetracycline, and metronidazole in various combinations successfully eradicated GHLOs from the gastric mucosa with resolution of gastritis (Heilmann and Borchard, 1991). No systematic antibiotic trials have

been conducted in dogs and cats to test for efficacy in eradicating either '*H. heilmannii*' or *H. felis* from gastric mucosa.

Diagnosis and Control A diagnosis of chronic gastritis in animals, as in humans, cannot be made by gross visual examination of the gastric mucosa by endoscopy. Histologic evaluation of gastric biopsy samples is required, utilizing a special silver stain or modified Giemsa stain to reveal the presence of GHLOs. Unfortunately, *H. bizzozeronii* is the most common spiral organism in dogs and cats, and it has been extremely difficult to culture on artificial media (Hanninen *et al*., 1996). '*H. heilmannii*,' (now *H. suis)* also common in primates, has been cultured successfully from pigs and humans (Baele *et al*., 2008). *H. felis* is also difficult to isolate. In practice, histological findings of inflammatory changes accompanied by gastric spiral organisms on the gastric mucosa or in the gastric mucous layer have been used for diagnosis. *H. felis* cannot be distinguished from '*H. heilmannii*' by histologic examination; EM evaluation is necessary.

Because oral bacteria and bacteria refluxed from the duodenum may overgrow the fastidious *Helicobacter* species, selective antibiotic media are available for isolation. Helicobacters, like campylobacters, require special environmental and cultural conditions for their growth. The organisms are thermophilic and grow at 37°C, and some species at 42°C. Growth on chocolate or blood agar takes 3–5 days (Hanninen *et al*., 1996). For *H. bizzozeronii* isolation, incubation requires 5–10 days. A provisional diagnosis of gastric helicobacters takes advantage of a biochemical feature of these organisms: the ability to produce large quantities of urease. Gastric biopsy samples can be placed in a urea broth containing a pH indicator (phenol red) and a preservative (sodium azide). A similar test is available commercially. Serological assays are being employed to diagnose *H. pylori* in humans (Staat *et al*., 1996; Fox and Megraud, 2007), as are *H. pylori* antigen-based fecal assays. However, serological tests currently do not provide a reliable, noninvasive diagnostic test for gastric helicobacter infection in dogs and cats or primates.

4. Salmonellosis

The genus *Salmonella* are gram-negative bacteria of which there are two species, *S. bongori* which infects mainly poikilotherms and rarely humans, and *S. enterica* which includes approximately 2500 serovars. *Salmonella* are properly designated using their serovar (which was often formerly a species name), for example, *S. enterica* subsp. *enterica* serovar Typhimurium (aka *S. Typhimurium*) and serovar Enteritidis (*S. Enteritidis*). Nontyphoidal salmonellosis is caused by any of these serotypes. *Salmonella* are flagellated, nonsporulating, aerobic gram-negative bacilli that can be readily isolated from feces on selective media designed to suppress bacterial growth of other enteric bacteria.

Reservoir and Incidence Salmonellosis occurs worldwide and is important in humans and animals. *Salmonella* isolates, because of molecular taxonomics, are now divided between *S. enterica* and *S. bongori.* Salmonellae are pathogenic to a variety of animals.

Although the reported prevalence of *Salmonella* in laboratory animals has decreased in the past several decades because of management practices (e.g., pasteurizing animal feeds), environmental contamination with *Salmonella* continues to be a potential source of infection for these animals and for the personnel handling them. Until all animal feeds in the United States and Europe are *Salmonella*-free and animals are procured from *Salmonella*-free sources, laboratory animal-associated cases of salmonellosis in humans will continue. The increasing number of recalls due to *Salmonella*-contaminated, commercially available dog and cat food, presumably manufactured in facilities with improper quality control procedures, is particularly of concern (CDC, 2012c). Endemic salmonellosis in commercially raised guinea pigs as well as dogs, cats, and nonhuman primates has also been a source of infection in personnel working with these animals. Prevalence data from eight studies conducted worldwide indicated that a wide range (0.6–27%) of cats were culture positive for *Salmonella*, and a conservative estimate for the U.S. canine population would be 10%. Rats are extremely susceptible to infection with *Salmonella*. In studies performed in the 1920s through 1940s, the prevalence of *Salmonella* in wild rats surveyed in the United States varied from 1% to 18%, compared to 19% in Europe (Geller, 1979; Weisbroth, 1979; Alexander, 1984). In experimental studies, when rats were dosed orally with *Salmonella*, 10% shed the organism in the 2 months after inoculation, and a few remained carriers when examined 5 months after experimental challenge. These rats, when placed with other naive rats, were capable of initiating new epizootics. Fortunately, the disease in laboratory rats, although common prior to 1939, has been isolated rarely in U.S. commercially reared rats since that time. Birds and reptiles are particularly dangerous sources of *Salmonella;* as much as 94% of all reptiles harbor *Salmonella*. (Chiodini and Sundberg, 1981). Turtles have received a great deal of zoonotic attention and in 1970 alone may have caused 280,000 human cases of salmonellosis. In the late 1960s, with annual sales of 15 million turtles, zoonotic salmonellosis became a growing problem. In 1972, the U.S. Food and Drug Administration (FDA) banned importation of turtles and turtle eggs and the interstate shipment of turtles that were not certified as free of *Salmonella* or *Arizona hinshawii* in their state of origin. However, the unreliable effectiveness of this method forced the FDA in 1975 to rule against the sale of viable turtle eggs or

live turtles with a carapace length less than 10.2 cm, with exceptions made for educational or scientific institutions and marine turtles. Subsequently, there was a substantial decrease in turtle-associated salmonellosis, indicating the efficacy of this regulation. These restrictions are difficult to enforce, and other reptiles, e.g., iguanas, are increasingly cited in zoonotic outbreaks of salmonellosis, particularly in children. Also of note, because of repeated reports of chick- and duckling-associated salmonellosis, some states have also restricted their sale as pets.

An outbreak of multidrug resistant *S. enterica* serovar Typhimurium associated with commercially distributed pet rodents, including rats, mice, and hamsters, was recently reported (Swanson *et al.*, 2007). Twenty-eight matching isolates identified by PFGE of *S. enterica* serotype Typhimurium from humans were identified from humans; 13 (59%) had previously had contact with rodents purchased from retail pet stores and 2 patients (9%) had secondarily acquired the infection from a patient who had been exposed to an infected rodent. These 15 patients whose median age was 16 years (neonate-43) resided in 10 different states. No single source of rodents was common in all cases and each case household had purchased the rodents from a different retail pet store. It was ascertained that several of the rodent breeders and distributors routinely used antimicrobials (e.g., spectinomycin, leptomycin, tetracycline, and nitrofurazone) in the drinking water as a preventative measure for nonspecific rodent enteritis. Interestingly, all human animal and environmental samples of *S. enterica* serovar Typhimurium isolates tested in this outbreak were uniformly resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline (R-type ACSSuT). Patients infected with multiple antibiotic resistant strains of *S. enterica* serotype Typhimurium have higher hospitalization rates than patients infected with susceptible strains (Martin, 2004; Varma, 2005). There are also reports of increased risk of septicemia, treatment failure, and mortality associated with multidrug resistant *S. enterica* serotype Typhimurium (Helms *et al.*, 2002). The spread of these multiple antibiotic resistant strains in rodents may have been facilitated by the widespread use of antibiotics as a prophylactic measure in the pocket pet retail industry. Indeed treatment with oral antibiotics may eliminate normal enterobacteriacae enteric flora and facilitate colonization with antibiotic resistant *Salmonella*, as observed in mice treated with antimicrobials (Que, 1985; van der Waaij, 1968; van der Waaij *et al.*, 1971. The authors of this outbreak urged heightened disease surveillance in pet retail facilities, as well as increased hygiene and husbandry practices to minimize the need for prophylactic antimicrobial therapy. Individuals purchasing rodents as pets or for food consumption by reptiles should be alerted to the possibility that these animals' feces are potentially infectious. For example, additional outbreaks of Salmonellosis have been traced to households that have pet snakes. The source of *Salmonella* infection in humans, particularly children, was caring for the pet snakes that, as part of their diet, were fed *Salmonella*-infected frozen rats and mice sold commercially in the United States, as well as the United Kingdom (Fuller, 2008; Harker *et al.*, 2011). Aquatic frogs, particularly African dwarf frogs, can also be a source of *Salmonella* infection (CDC, 2010b; CDC, 2011). This highlights the importance of ascertaining pet status of prospective animal technicians who have applied for positions in vivaria. Another multistate outbreak of *S. enterica* serovar Typhimurium has been recently reported due to exposure to infected pet hedgehogs (Marsden-Haug *et al.*, 2013). The increased incidence of *Salmonella* infections can be reduced by hand washing with soap and water after handling of rodents, their cages, and bedding.

Mode of Transmission *Salmonella* spp. are ubiquitous in nature and are routinely found in water or food contaminated with animal or human excreta. Fecal–oral transmission is the primary mode for spread of infection from animal to animal or to humans. Rat feces can remain infective for 148 days when maintained at room temperature. *Salmonella* is routinely associated with food-borne disease outbreaks, is a contaminant of sewage, and is found in many environmental water sources. Transmission is enhanced by crowding and poor sanitation.

Both humans and animals can be asymptomatic carriers and periodic shedders; they may have mild, unrecognized disease, or they may be completely asymptomatic. In the biomedical laboratory, asymptomatic animals can easily infect other animals, technicians, and investigators. Personnel at veterinary hospitals are at increased risk because of outbreaks of salmonellosis in hospitalized animals (Ikeda *et al.*, 1986). The prevalence of human salmonellosis acquired from laboratory animals or *vice versa* is unknown; however, the literature is replete with examples of cases of this infection obtained from pets; this is particularly true for exotic pets such as iguanas, turtles, sugar gliders, and hedgehogs (Woodward *et al.*, 1997).

Clinical Signs Clinical signs of salmonellosis in humans include acute sudden gastroenteritis, abdominal pain, diarrhea, nausea, and fever. Diarrhea and anorexia may persist for several days. Organisms invading the intestine may create septicemia without severe intestinal involvement; most clinical signs are attributed to hematogenous spread of the organisms. As with other microbial infections, the severity of the disease relates to the serotype of the organism, the number of bacteria ingested, and the susceptibility of the host. In experimental studies with volunteers, several serovars induced a

spectrum of clinical disease, from brief enteritis to serious debilitation. Incubation varied from 7 to 72 h. Cases of asymptomatic carriers, persisting for several weeks, were common (Hull, 1955).

Salmonella gastroenteritis is usually mild and self-limiting. With careful management of fluid and electrolyte balance, antimicrobial therapy is not necessary. In humans, antimicrobial therapy may prolong rather than shorten the period that *Salmonella* is shed in the feces (Nelson *et al*., 1980; Pavia and Tauxe, 1991). In one double-blind placebo study of infants, oral antibiotics did not significantly affect the duration of *Salmonella* carriage. Bacteriological relapse after antibiotic treatment occurred in 53% of the patients, and 33% of these suffered a recurrence of diarrhea, whereas none of the placebo group relapsed (Nelson *et al*., 1980). Also of interest is the fact that in outbreaks of DT104 *S. enterica* serotype Typhimurium infection, a high percentage of patients had been recently on antibiotics before becoming infected with the *S. enterica* serovar Typhimurium strain DT104 (Molba *et al*., 1999).

Diagnosis and Control As with other fecal–oral transmitted diseases, control depends on eliminating contact with feces, food, or water contaminated with *Salmonella* or animal reservoirs excreting the organism. *Salmonella* survive for months in feces and are readily cultured from sediments in ponds and streams previously contaminated with sewage or animal feces. Fat and moisture in food promote survival of *Salmonella.* Pasteurization of milk and proper cooking of food (56°C for 10–20 min) effectively destroy *Salmonella.* In the laboratory, control and prevention of salmonellosis depends on the rapid detection, removal, or treatment of both acute and chronic animal infections, particularly during the quarantine period. Multiple antibiotic resistance is commonly encountered in *Salmonella* strains. For example, multiple-resistant *S. enterica* serotype Typhimurium strain DT104 has been increasingly cited (in Europe and recently in the United States) as a cause of human infections (Tauxe, 1999). Importantly, this organism has been isolated from farm animals, cats, wild birds, rodents, foxes, and badgers. It definitely has been transmitted from cattle and sheep to humans and has caused epizootic gastroenteritis and fatal bacteremia in dairy cattle (Besser *et al*., 1997).

5. Shigellosis

Reservoir and Incidence Shigellosis is a significant zoonotic disease in nonhuman primates (Fox, 1975; Richter *et al*., 1984). *Shigella flexneri, S. sonnei*, and *S. dysenteriae* are the most common species found in nonhuman primates. Humans are the main reservoir of the disease, which occurs worldwide. Nonhuman primates acquire the disease following capture and subsequent contact with other infected primates or contaminated premises, food, or water. Shigellosis is one of the most commonly identified causes of diarrhea in nonhuman primates.

Mode of Transmission *Shigella* organisms may be shed from clinically ill as well as asymptomatic humans and nonhuman primates. In humans, transmission occurs by ingestion of fecally contaminated food or water, or by direct contact (even if only minimal) with infected animals. Pet monkeys shedding *Shigella* are a particular threat to owners, and pet store proprietors, unless cautious, can contract the disease (Fox, 1975).

Clinical Signs Humans are generally susceptible to shigellosis, although it is much more severe in children than in adults. The disease varies from completely asymptomatic to a bacillary dysentery syndrome characterized by blood and mucus in the feces, abdominal cramping, tenesmus, weight loss, and anorexia. Usually, the disease presents only as a clinically mild diarrhea. However, fatal shigellosis has been reported in children and adults who have had contact with infected pet or zoo monkeys (Fox, 1975); survivors can remain asymptomatic carriers. The clinical disease in nonhuman primates is similar to that in humans but may be associated with higher mortality rates.

Diagnosis and Control When humans or nonhuman primates experience acute diarrhea (especially if traced with blood or mucus), *Shigella* spp. may be the cause (Richter *et al*., 1984; Dupont, 2000). A definitive diagnosis requires the isolation of the organism from inoculation of fresh feces or gingival swabs onto selective media. An identification can be confirmed by agglutination with polyvalent *Shigella* antisera. Because many *Shigella* spp. from nonhuman primates have plasmid-mediated antibiotic resistance markers, determination of antibiotic sensitivities of these isolates is mandatory before instituting treatment.

To prevent shigellosis in the laboratory, quarantine and screening of all newly arrived primates to detect carriers of *Shigella* spp. are required. As in the treatment of the disease in humans, trimethoprim and sulfamethodoxazole can be effective in eliminating the *Shigella* spp. carrier state in rhesus monkeys. Enrofloxacin is also used to eliminate subclinical *Shigella* spp. in macaques.

D. Respiratory Infections

1. Bordetella bronchiseptica

Bordetella bronchiseptica, a gram-negative bacteria, is commonly recovered from the respiratory tract of dogs, cats, rabbits, and a variety of laboratory rodents. Despite its widespread occurrence in animals, it is seldom cultured from diseased tissues of humans, with few cases reported in the literature. Its isolation is often from immunocompromised patients (Woolfrey and Moody, 1991) who have pneumonia and/or bacteremia,

or cystic fibrosis (Spilker *et al.*, 2008). It has also been isolated from AIDS patients (Ng *et al.*, 1992). In children with respiratory infection due to *B. bronchiseptica*, a 'whooping cough'-like syndrome is described. This is not surprising given that *B. bronchiseptica* produces a dermatonecrotoxin, tracheal cytotoxin, and adenylate cyclase similar to that isolated from *B. pertussis.* In one interesting report, three children with *B. bronchiseptica* infection developed whooping cough-like symptoms; both their pet rabbits and cats subsequently died of *B. bronchiseptica* pneumonia (Kristensen and Lautrop, 1962). Fluoroquinolones have been used successfully to treat the disease in humans (Carbone *et al.*, 1999; Spilker *et al.*, 2008).

2. *Tuberculosis*

Reservoir and Incidence Tuberculosis is an important zoonosis associated with laboratory animals and a potential concern in wildlife research programs or when wild-caught animals are brought into the laboratory. It is caused by acid-fast bacilli of the genus *Mycobacterium.* Natural reservoir hosts for the etiologic agent of this disease correspond to the three most common species of *Mycobacterium*: *M. bovis*, *M. avium* complex, and M. *tuberculosis.* Although cattle, birds, and humans are the major reservoir hosts, many animals, including swine, sheep, goats, monkeys, cats, dogs, and ferrets, are susceptible and contribute to the spread of disease (Marini *et al.*, 1989; Fox and Marini, 2014; Swennes and Fox, 2014). This susceptibility varies according to the immune response of the host and to the particular *Mycobacterium* spp. infecting the host. In nonhuman primates, outbreaks of tuberculosis still occur, particularly in the Old World species of monkeys. They initially contract the disease in the wild through human contact, and then the organism is transmitted from monkey to monkey (Richter *et al.*, 1984).

Mode of Transmission *Mycobacterium* bacilli are transmitted from infected animals or tissue samples via the aerosol route. The disease is spread beyond the natural host range through animal-to-animal and human-to-human contact, usually by airborne infectious particles. Laboratory workers have the highest risk of contracting the disease when caring for or performing autopsies on infected animals. In the laboratory, certain situations can enhance disease transmission, such as exposure to (1) dusty bedding of infected animals, (2) aerosolized organisms from a high-pressure water sanitizer, and (3) the coughing of clinically affected animals. The disease may also be contracted by direct ingestion of bacilli. Reports have documented an increase of tuberculin skin conversion in personnel working with primates infected with *Mycobacterium* spp. (Kalter *et al.*, 1978).

Clinical Signs Clinical signs of tuberculosis in humans are dependent on the organ system or systems involved. Most familiar are the signs related to the pulmonary form. Although this form of the disease often remains asymptomatic for months or years, it may eventually produce a cough with sputum and hemoptysis. In addition, general symptoms include anorexia, weight loss, lassitude, fatigue, fever, chills, and cachexia (Division of Tuberculosis Elimination, 2000).

Diagnosis and Control A positive diagnosis is often quite difficult to obtain. Three widely used tools for a presumptive diagnosis are the intradermal tuberculin test, radiographic analysis, and positive acid-fast-stained sputum smears. Serological assays for diagnosis of tuberculosis have been recently introduced as an adjunct or replacement for intradermal testing (Mazurek *et al.*, 2010). A more definitive diagnosis of the organisms from body fluids or biopsy specimens is obtained by culture, PCR analysis, and confirmation using standard biochemical techniques.

Control of tuberculosis infection, particularly within the biomedical research arena, requires a multifaceted approach. This includes personnel education, a regular health surveillance program for personnel and nonhuman primates, isolation and quarantine of suspect animals, and rapid euthanasia and careful disposal of confirmed positive animals. Vaccination or chemoprophylaxis may be considered, but certain precautions are necessary (Division of Tuberculosis Elimination, 2000). Vaccination with Bacillus Calmette–Guerin (BCG), a strain of *M. bovis*, is an effective means of preventing active tuberculosis. Vaccination is suggested in high-risk groups. However, this vaccine often elicits a positive tuberculin test, thereby negating the best diagnostic indicator of early disease. Vaccination in the United States is therefore reserved for demonstrated high-risk individuals and children in locations where 20% or more of school-age children are tuberculin-positive (Division of Tuberculosis Elimination, 2000).

Chemoprophylaxis with effective antituberculosis agents used to treat humans, such as isoniazid, rifampin, and ethambutol, has been used to treat valuable nonhuman primates (Wolf *et al.*, 1988). A well-conceived tuberculosis control program will include some or all of the above methods tailored to the needs and special circumstances of individual animal resource programs.

VI. FUNGAL DISEASES

The superficial mycoses are commonly referred to as ringworm due to the characteristic circular erythematous lesion found on the skin of the host. The most common of the fungi responsible for disease in animals and humans are the three genera of the dermatophytes:

Microsporum, *Epidermophyton*, and *Trichophyton.* Species of dermatophytes are subcategorized as anthropophilic (primarily infect humans), geophilic (soil inhabitants), and zoophilic (parasitic on animals). The zoophilic dermatophytes are known to infect humans.

Reservoir and Incidence Dermatophytes are distributed worldwide, with particular species found more frequently in specific geographic regions. Ringworm in laboratory animals is common, particularly among random-source animals, such as dogs, cats, and livestock. *Microsporum canis* is the common isolate from dogs and cats, whereas *Trichophyton verrucosum* and *T. equinum* are the species usually isolated from ruminants and horses. *T. mentagrophytes* is the most common isolate from laboratory rodents, and human transmission has occurred (Hironaga *et al.*, 1981; Kraemer *et al.*, 2013).

Mode of Transmission Transmission to humans occurs from direct or indirect contact with symptomatic or asymptomatic carrier animals; contaminated bedding, caging, or other equipment; or fungal contamination of the environment. The resultant disease in humans, tinea, is frequently self-limiting and often goes unnoticed. When lesions occur, they are generally on the extremities, particularly on the arm or hand. Lesions are focal, annular, scaling, and erythematous with central clearing resembling a ring. Occasionally, vesicles or fissures are reported. In contrast with anthropophilic species, zoophilic dermatophytes generally produce more eczematous and inflammatory lesions, which regress rapidly.

Clinical Signs Generally, dermatophytes grow only in dead, keratinized tissue. Advancing infection is halted when contact with live cells and inflammation occurs. Dermatophytes are species-adapted and rarely cause severe inflammatory lesions in the specific-host species. When zoophilic species infect humans, the inflammatory response usually restricts the progress of the infection. Contact with the dermatophyte does not necessarily result in infection in the animal or human host. A number of factors, including but not limited to age; immune, hormonal, and nutritional status; and prior exposure, all are important in disease expression.

When observed, disease in animals is often mild and goes undetected. Disease in cats, usually seen in kittens, is quite variable. Lesions, generally seen on and around the head, are crusting and mildly erythemic. The areas may be alopecic with numerous broken hairs. In dogs, lesions consist of circular, alopecic, crusting patches. In laboratory rodents, lesions are generally absent. Presence of the organism may not be detected until personnel become infected and manifest lesions (Fig. 28.8).

Diagnosis and Control Diagnosis in humans and animals is similar, and is best approached by a combination of direct microscopy on hairs and skin scrapings, Wood's lamp examination (approximately 50% of *Microsporum canis* isolates fluoresce when examined with a cobalt-filtered ultraviolet lamp) and fungal culture (Bond, 2010). Specialized dermatophyte test media (DTM) or Sabouraud's agar may be used.

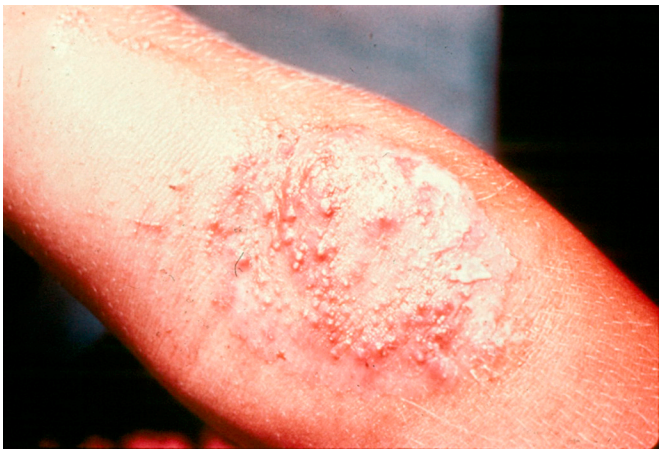

FIGURE 28.8 Ringworm on the forearm. Note the circumscribed lesion with multiple vesicles.

The risk of zoonotically acquired dermatophytosis can be reduced among laboratory and animal care personnel by wearing protective garments, specifically long-sleeved clothing or laboratory coats; practicing effective personal hygiene; handling random-source animals with disposable gloves; screening newly acquired animals for suggestive lesions; and isolating and treating animals with lesions.

Treatment consists of either systemic therapy with griseofulvin or topical therapy with any one of a number of antifungal agents, such as miconazole. Infectious spores will persist on the animal despite successful treatment of active lesions. Eradication of spores is generally unfeasible, as it may require extensive depilation and the use of sporicidal dips.

VII. PROTOZOAL DISEASES

A. Enteric Diseases

1. Amebiasis

Amebiasis is a parasitic infection of the large intestine caused by the protozoan parasite *Entamoeba histolytica* (Ravdin, 1995).

Reservoir and Incidence The disease occurs worldwide in humans, with a greater prevalence in tropical areas. The parasite is found routinely in clinically normal monkeys and anthropoid apes but may occasionally cause severe clinical disease in these species. The reported incidence of *E. histolytica* has ranged from 0–21% in rhesus monkeys, 2–67% in chimpanzees, and up to 30% in other nonhuman primates. Molecular

techniques can be used to characterize potentially virulent strains found in captive primates (Rivera *et al.*, 2010; Tachibana *et al.*, 2009).

Mode of Transmission *E. histolytica* exists as either resistant cysts or the more fragile trophozoites (Visvesvar and Stehr-Green, 1990). Cysts are the infectious form of the parasite and are usually found in the normal stool of asymptomatic carriers or humans with mild disease (Ravdin, 2000). Cysts may remain viable in moist, cool conditions for over 12 days and in water for up to 30 days. Epidemics of amebiasis in humans usually result from ingestion of fecally contaminated water containing amebic cysts. Laboratory animal workers handling nonhuman primates are potentially exposed to infection from infected fecal matter transferred through the workers' skin or clothing. The infective cyst forms may be subsequently ingested.

Clinical Signs Most human infections with *E. histolytica* have few or no detectable symptoms (Ravdin, 2000). Clinical signs result when trophozoites invade the large bowel wall causing an amebic colitis. Signs begin with a mild, watery diarrhea with bad-smelling stool, which is frequently preceded by constipation in early stages. There may be gas, abdominal cramps, and tenderness progressing to an acute fulminating bloody or mucoid dysentery with fever, chills, and muscle ache. The disease may have periods of remission and exacerbation over months to years (Ravdin, 2000). Rarely, extraintestinal amebic abscesses may form in the liver, lung, pericardium, or central nervous system. Involvement of the liver may lead to tenderness in the right abdomen and can progress to jaundice.

Diagnosis and Control The diagnosis of amebiasis is commonly made via the microscopic identification of trophozoites or cysts in fresh stool specimens. The organism must be carefully measured to differentiate it from other nonpathogenic amebas. As is the case with many infectious agents potentially present in stool samples, PCR screening methods have also been developed (Rivera *et al.*, 2010). Control measures to prevent amebiasis should include strict adherence to sanitation and personal hygiene practices. Water supplies should be protected from fecal contamination since usual water purification chlorine levels do not destroy the cysts (Chin, 2000). A chlorine concentration of 10 ppm is necessary to kill amebic cysts (Ravdin, 2000). Cysts may also be killed by heating to 50°C. Nonhuman primates should be screened during quarantine to identify carriers of *E. histolytica* and should be appropriately treated. Nonhuman primates with acute diarrhea or dysentery should also have stool examined for the presence of *E. histolytica* and should be treated as necessary. Recommended drugs for treatment of *E. histolytica* infection include metronidazole, paromomycin, emetine, and iodoquinol (diiodohydroxyquin). The benzoate salt of metronidazole does not posess the bitterness inherent in standard preparations and is useful for oral regimens. Both asymptomatic carriers and symptomatic patients should be treated (Ravdin, 2000).

2. Balantidiasis

Balantidiasis is a zoonotic disease caused by the large ciliated protozoan *Balantidium coli.*

Reservoir and Incidence *Balantidium coli* is distributed worldwide and is common in domestic swine. It may also be found in humans, great apes, and several monkey species. The incidence in nonhuman primate colonies has ranged from 0 to 63%. These infections are usually asymptomatic in most animals, although clinical disease characterized by diarrhea or dysentery may occur.

Mode of Transmission Infection usually results from the ingestion of trophozoites or cysts from the feces of infected animals or humans. Transmission may also occur from ingestion of contaminated food or water.

Clinical Signs Balantidiasis may cause ulcerative colitis characterized by diarrhea or dysentery, tenesmus, nausea, vomiting, and abdominal pain. In severe cases, blood and mucus may be present in the stool. Humans apparently have a high natural incidence, and infections are often asymptomatic (Chin, 2000).

Diagnosis and Control Balantidiasis is diagnosed by the detection of trophozoites or cysts in fresh fecal samples. Control measures to prevent balantidiasis should be directed at maintaining good sanitation and personal hygiene practices in nonhuman primate and swine colonies. Water supplies should be protected from fecal contamination, especially since usual water chlorination does not destroy cysts (Chin, 2000). Nonhuman primates exhibiting acute diarrhea should be examined for the presence of *B. coli* organisms in the feces. Positive animals should be isolated and the infection appropriately treated. Tetracyclines, metronidazole, and paromomycin have been used successfully to eliminate *B. coli* infections (Teare and Loomis, 1982) and iodoquinol is also used in humans.

3. Cryptosporidiosis

Cryptosporidiosis was first described in the mouse. The genus *Cryptosporidium* now contains over 10 named species (Levine, 1980), many of which have been incriminated as opportunistic, pathogenic parasites (Angus, 1983). Cryptosporidiosis, once considered an infrequent, inconsequential protozoan infection in mammals and reptiles, is now considered a significant enteric pathogen. *Cryptosporidium parvum* and *C. hominis* are considered the human pathogens, but a variety of species and genotypes have been identified and mixed infections can occur (Ng-Hublin *et al.*, 2013).

Reservoir and Incidence *Cryptosporidium* spp. are coccidian parasites known to infect a variety of mammals, including humans, monkeys, livestock, ferrets, pigs, guinea pigs, mice, fish, reptiles, and birds. Neonates of mammalian domestic species are uniquely susceptible to this infection, in comparison with the adults, who are resistant. In humans, however, both children and adults are susceptible. The host-specificity of cryptosporidia isolated from mammals is controversial (Monis and Thompson, 2003), but it is clear that the bovine strains are zoonotic (Levine *et al.*, 1988). Bovine cryptosporidia from calves can also cause infection in newborn pigs, lambs, chicks, mice, rats, and guinea pigs.

Mode of Transmission The life cycle of cryptosporidia is direct, with infection generally limited to the small intestine; however, infections of the respiratory tract, stomach, and conjunctiva have been reported. The life cycle of cryptosporidia is similar to that of other coccidia except that cryptosporidial oocysts do not require time outside the host to sporulate but are infectious at the time of excretion. Large epidemics have occurred in humans ingesting the organism in contaminated municipal drinking water. Sporulated oocysts can exist in the intestine before being excreted. Disease transmission is through ingestion of infectious oocysts. The organisms are small (4–5 pm in diameter) and are located on the apical surface of the parasitized epithelial cell, where they protrude from the brush border. The organisms are intracellular, as the plasma membrane of the host cell envelops the parasite.

Clinical Signs Recorded cases of this disease generally occur in children, particularly in developing countries with poor sanitation, and in immunosuppressed (compromised) individuals. Zoonotic disease has been reported among animal handlers and veterinary students working with neonatal ruminants, principally calves, infected before 6 weeks of age (Levine *et al.*, 1988). Another transmission was recorded in an individual who became infected performing a survey of *Cryptosporidium* spp. in calves (Reese *et al.*, 1982). In this patient, clinical remission occurred by day 13, and oocytes of cryptosporidium were no longer apparent on fecal flotation (Fig. 28.9). Disease in neonatal ruminants may be subclinical or may present with protracted watery diarrhea, very similar to what occurs in humans. Symptoms in humans occur 1–2 weeks after contact with infected calves, and diarrhea may be accompanied by vomiting, severe abdominal cramps, lassitude, fever, and headache. Disease is generally self-limiting except in immunocompromised individuals (Fayer and Ungar, 1986). Most of the recorded cases of protracted human cryptosporidiosis have occurred in immunodeficient individuals, particularly AIDS patients, and are regarded as opportunistic infections (Chin, 2000). Disease in these individuals produced low-grade fever, malaise, anorexia, nausea, abdominal cramps, and a protracted, watery diarrhea. Repeated intestinal biopsies in a patient have documented indigenous cryptosporidial stages for as long as 1 year; clinical signs also persisted in this patient.

Diagnosis and Control Diagnosis is made by examination of feces for the characteristic oocysts. Direct wet mounts may be satisfactory in heavy infections; the organism can be concentrated by the Sheather sugar

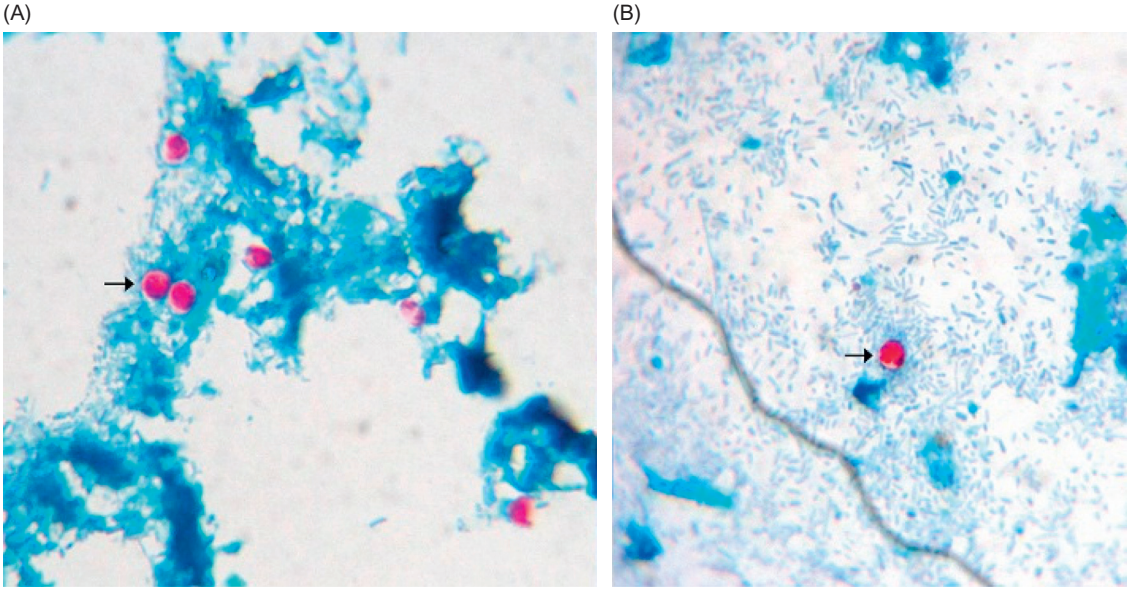

FIGURE 28.9 *Cryptosporidium* oocysts in calf (A) and human (B) feces stained with cold modified Ziehl–Neelsen staining method. *Source: Jafari et al., JRHS 2013; 13(1): 86–89.*

flotation or the formalin-ethyl acetate method. A modified acid-fast stain can be used to detect oocytes in fecal specimens or biopsies. Histologic evaluation of intestinal and rectal biopsies can also be used for diagnosis. Fecal antigen IFA and PCR tests have also been developed. Currently, no pharmaceutic agent is considered completely effective in treating cryptosporidiosis, but agents such as paramomycin and nitazoxanide may have some utility and are used in human treatment. The infection is considered to persist until the host's immune response clears the parasite, which may never occur in severely immunocompromised patients.

4. *Giardiasis*

Giardiasis is usually a mild intestinal illness, caused by the protozoan parasite *Giardia duodenalis* (syn. *G. lamblia*). The parasite can be found in the feces of infected animals (dogs, cats, beavers, and rodents).

Reservoir and Incidence *Giardia* spp. are found worldwide among all classes of vertebrates and occur among numerous laboratory animals. Historical classification schemes have speciated *Giardia* based on host origin, since the recovered cysts are for the most part morphologically indistinguishable. However, based on experimental infections, it is known that cross-species transmission can occur. Considering the cosmopolitan distribution of the parasite in wild and domestic animals, the potential for zoonotic transmission appears significant. When infected beavers were identified in the watersheds associated with human waterborne outbreaks, this circumstantial evidence led to supposition that beavers were the cause (Dykes *et al.*, 1980; Keifer *et al.*, 1980) and resulted in the disease being referred to as 'beaver fever.' Experimental transmission studies showed that cysts from a beaver source can infect dogs as well as human volunteers (Davies *et al.*, 1979). However, further studies comparing the infectious dose of homologous and heterologous isolates determined that host-adapted strains are more readily transmitted, and the significantly higher innolum required for cross-species transmission in some cases is enough to lend some doubt to the likelihood of natural transmission (Erlandsen *et al.*, 1988). Wildlife giardiasis may be a reverse zoonosis whereby human contamination of the environment leads to animal infection (Thompson *et al.*, 2011). To paraphrase a veterinary school lecture comment by parasitologist Dr. W.J. Bemrick (attended by author GO), "Show me a stream where humans contracted giardiasis and I'll show you a stream contaminated by humans."

Nonhuman primates have also been implicated in human disease, and theoretically primate-to-man cross-transmission could be more likely due to the close genetic similarity. A clinically ill gibbon was presumed to be the source of infection for three zoo attendants and six apes that subsequently developed clinical giardiasis (Armstrong and Hertzog, 1979). Dogs (and puppies in particular) are often considerd sources of human infection, and a cross-sectional survey of laboratory animal workers resulted in self-reporting of giardiasis associated with canine exposure (Weigler *et al.*, 2005). Ruminants are another potential source of human contamination.

Advanced classification methods for *G. duodenalis* isolates based on genetic techniques have now established a classification consisting of various assemblages (genotypes) which has provided evidence that certain assemblages are more commonly associated with particular species (Feng *et al.*, 2011). The addition of genetic studies to future epidemiologic investigations may shed more light on the comparative risks of zoonotic transmission, but at this time the genetic studies suggest that zoonotic risks may be lower than previously thought (Yoder *et al.*, 2012).

Mode of Transmission The life cycle of *Giardia* is direct, with trophozoites, the feeding stage of the organism, residing in the upper gastrointestinal tract. They multiply and develop into infective cysts that are shed in the feces and ingested by subsequent hosts (Fig. 28.10).

Clinical Signs The disease in humans and animals is often similar. Giardiasis in humans is characterized by chronic or intermittent diarrhea, bloating, abdominal cramping, anorexia, fatigue, and weight loss. The stool

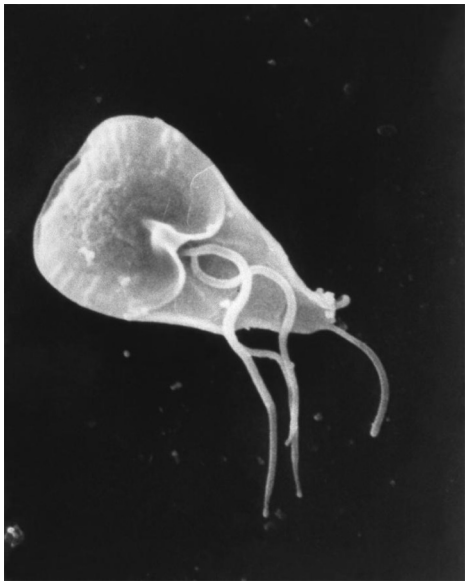

FIGURE 28.10 Scanning electron micrograph (SEM) revealing some of the external ultrastructural details displayed by a flagellated *Giardia lamblia* protozoan parasite. *G. lamblia* is the organism responsible for causing the diarrheal disease 'giardiasis.' Once an animal or person has been infected with this protozoan, the parasite lives in the intestine and is passed in the stool. Because the parasite is protected by an outer shell, it can survive outside the body and in the environment for long periods of time. *Source: PHIL 8698.*

frequently is mucus-laden, light-colored, and soft, but not watery. Symptoms may persist for several weeks and then resolve spontaneously. Fever is usually not present, and many persons infected with *Giardia* may have no symptoms at all. Individuals with the disease are contagious for the entire period of infection and may recover without treatment.

Prevention and Control Although many species of domesticated laboratory animals can be infected experimentally with *Giardia* pathogenic for humans, the majority have not been demonstrated to harbor human-related assemblages naturally. *Giardia* infections of nonhuman primates and wild-caught species may present a greater public health risk. Isolation and treatment of symptomatic shedders is certainly indicated, and personnel handling these animals should take appropriate safety measures. Metronidazole is commonly used for treatment, but quinacrine, furazolidone, and paromomycin are also used. The risk and benefit of attempted eradication when dealing with asympomatic carriers should be considered before initiating prophylactic treatment.

B. Systemic Infections

First discovered in 1908, toxoplasmosis is caused by infection with a microscopic parasite called *Toxoplasma gondii.* Toxoplasmosis has been found in humans and most warm-blooded animals. An estimated 500 million humans have been infected with the organism, and nearly one-third of all adult humans in the United States and in Europe have antibodies to toxoplasma, which provides evidence that they have been exposed to this parasite.

Reservoir and Incidence The life cycle of *T. gondii* consists of definitive and intermediate hosts. *Toxoplasma* infection has spread throughout the animal kingdom to include hundreds of species of mammals and birds as its intermediate hosts. Mice, rats, hamsters, guinea pigs and other rodents, rabbits, dogs, sheep, cattle, and nonhuman primates include some of the laboratory animals that could serve as intermediate hosts (Teutsch *et al*., 1979; Wright, 1985). These laboratory animal hosts have not been shown to be important in zoonotic infection by *T. gondii* in the laboratory environment because the organism replicates only asexually in extraintestinal sites (Parker and Holliman, 1992; Herwaldt and Juranek, 1993). Serological surveys conducted in the United States have demonstrated *T. gondii* infection in 30–80% of cats with the highest prevalence in stray or outdoor cats (Ladiges *et al*., 1982; Dubey *et al*., 2002). Presumably, all serologically positive cats have shed *Toxoplasma* oocysts and could again shed organisms by reinfection or by reactivation.

Mode of Transmission Domestic and wild felids develop extraintestinal invasion with *T. gondii* analogous to that of the nonfelid hosts. In addition, as the definitive hosts in the *T. gondii* life cycle, felines develop intestinal infection, with the shedding of oocysts. Thus, the domestic cat is the primary reservoir for the zoonotic transmission of *T. gondii* in the laboratory environment. The three common modes of transmission are congenital infection, ingestion of *T. gondii*-infected tissue, and ingestion of toxoplasma oocytes or from direct exposure and consumption of contaminated food or water (Dubey, 1998). Most postnatally acquired infections in cats are asymptomatic and have a variable prepatent period and pattern of oocyst shedding. The prepatent period can be as brief as 3 days if the cat has ingested mice or meat containing *T. gondii* cysts, or it can be as long as several weeks if oocysts have been ingested. Shedding of oocysts in the feces occurs for 1–2 weeks, during which time cats are considered a public health risk (Dubey, 1998). Oocysts become infectious after sporulation, which occurs in 1–5 days. Oocysts survive best in warm, moist soil. Oocyst shedding is less likely to occur if the cat was infected by oocysts or tachyzoites than if infection resulted from the ingestion of *Toxoplasma* cysts. Oocyst shedding can be reactivated by induction of hypercorticism or by superinfection with other feline microorganisms, such as *Isospora felis* (Chessman, 1972). Oocysts of *T. gondii* have been observed infrequently in the feces of naturally infected cats (Ladiges *et al*., 1982), and shedding usually precedes the development of antibody titers to *T. gondii.* The oocyst is very hardy and can survive freezing and as much as several months of extreme heat and dehydration. Importantly, high IgG titers do not prove recent or active infection (Dubey *et al*., 1995).

Clinical Signs *Toxoplasma* infection in humans and animals is very common, but clinical disease occurs only sporadically and has a low incidence. In addition to sporadic clinical cases, occasional epidemics can occur when humans are exposed to oocyst-contaminated environments (Teutsch *et al*., 1979). Populations at high risk of infection are pregnant women and immunodeficient individuals. Congenital infection in humans results in systemic disease, frequently with severe neuropathological changes. Postnatal infection results in disease that is less severe and commonly presents as nondescript, consisting of fever, myalgia, and generalized lymphadenopathy that may resolve without treatment in a few weeks. Asymptomatic infection may recrudesce with encephalitis if patients become immunocompromised. Although rare, serious systemic toxoplasmosis can be acquired by older individuals. This is manifested by fever, maculopapular eruption, malaise, myalgia, arthralgia, posterior cervical lymphadenopathy, pneumonia, myocarditis, and meningoencephalitis. Ocular toxoplasmosis, usually chorioretinitis, is commonly seen in postnatal infections but can also occur in infections of older individuals. Clinically severe and progressive

illness is most likely to develop in immunocompromised individuals. As high as 10% of AIDS patients have toxoplasmosis (Gill and Stone, 1992). These patients develop neurologic disease and can experience convulsions, paralysis, or coma or even die from toxoplasmosis, even after treatment is administered. Infection in these cases is considered in most cases to be reactivation of tissue cysts from a chronic infection.

Diagnosis and Control Diagnosis can be made by histopathologic demonstration of the organisms, demonstration of serum antibody, testing for antigenemia, or skin test. Chemotherapeutic treatment is indicated in patients with diagnosed clinical disease, active ocular lesions, or congenital infection, and in immunocompromised individuals with disease suggestive of toxoplasmosis. The preferred therapy in humans is pyrimethamine administered in combination with a sulfa drug. Laboratory-acquired infections are likely restricted to the use and handling of laboratory cats (DiGiacomo *et al*., 1990). Rigorous sanitation should effectively prevent human toxoplasmosis from occurring in the laboratory environment. Since oocysts must sporulate before they are infectious, daily cleaning of litter plans will prevent accumulation of infectious oocysts. Personnel should wear gloves when handling litter pans and wash their hands thoroughly before eating. Pregnant women should completely avoid contact with cat feces. Most cats acquire infection shortly after weaning and shed the oocysts for a short period of time (<3 weeks). Nevertheless, unsporulated oocysts are more susceptible to proper disinfection, and control of exposure should be centered around disinfection of litter pans at this stage.

VIII. HELMINTH INFECTIONS

Many of the helminth parasites common to animals and humans have an indirect life cycle that is interrupted in the laboratory environment, thus precluding cross-infection of animals and humans. Although numerous helminths of laboratory animals should be regarded as zoonotic (Soulsby, 1969; Flynn, 1973), the risk of human infection from laboratory-housed animals appears to be minimal. One exception may be the dwarf tapeworm of humans, *Hymenolepis* (*Rodentolepsis*) *nana*, a common parasite of house mice and occasionally diagnosed in mice used for research. It is conservatively estimated that over 20 million people (mostly children) are infected with this parasite (Markell *et al*., 1999). *H. (Rodentolepsis) nana* is unique among cestodes in that the adult worm develops following ingestion of the egg by humans and does not require an intermediate host for its life cycle (Table 28.3).

Nematodes in aberrant hosts are a potential cause of visceral and ocular larval migrans. Ingested eggs of several nematode larvae may be shed in the feces and ingested by humans. These ingested eggs hatch in the abnormal host and migrate into deep tissues, but development proceeds no further. Larvae may persist in the visceral organs or the eyes and cause granulomatous lesions, resulting in hepatosplenomegaly, fever, and eosinophilia (visceral larval migrans) (Edelglass *et al*., 1982; Davies *et al*., 1993) or leucocoria, eye pain, strabismus, or loss of vision (ocular larval migrans) (Bathrick, 1981). The most frequent cause of these diseases is *Toxocara canis* (dog) (Wolfrom *et al*., 1995) and *T. cati* (cat) (Glickman and Magnava, 1993), but *Baylisascaris procyonis* in the raccoon is much more aggressive and therefore more pathogenic (Fox *et al*., 1988). Fatal or severe central nervous system disorders have been documented for mice, woodchucks, pigeons, domestic quail, turkeys, captive prairie dogs, and armadillos, and two human fatalities have been reported. Several other animal parasites have been associated with larval migrans-like syndromes. These include *Ascaris suum* (swine), *Capillaria hepatica* (rat), *Angiostrongylus cantonensis* (rat), *Gnathostoma spinigerum* (dogs and cats) (Bathrick, 1981), and *Angiostrongylus costaricensis* (cotton rats) (Levine, 1980). Human involvement has been reported with each of the above.

The practices encountered in a properly managed animal facility are not conducive to the transmission of these parasites. Proper quarantine, surveillance, and treatment procedures drastically reduce the endoparasitic burden of laboratory animals. Routine sanitation eliminates most parasitic ova before they have undergone the embryonation necessary for infectivity. Education of personnel on standard hygiene practices further reduces the likelihood of zoonotic infection.

Laboratory-housed nonhuman primates are presumed to be the most likely, although infrequent, source of parasitic infection for animal handlers (Orihel, 1970; Nasher, 1988). However, literature reports of captive primate-to-human transmission are restricted to exposures to pet animals, not laboratory primates.

IX. ARTHROPOD INFESTATIONS

Health hazards to humans due to ectoparasite infestations from arthropods associated with laboratory animals are most often mild and limited to manifestations of allergic dermatitis. However, arthropods can serve as vectors to systemic illnesses such as rickettsial pox, tularemia, and Lyme disease. Those working with laboratory animals, particularly those species arriving directly from their natural habitat, should be familiar with the arthropods capable of transmitting these diseases.

TABLE 28.3 Zoonotic Helminth Parasites in the Laboratory Environment

Disease	Etiology	Natural host(s)	Aberrant hosts	Comments
Cestodiasis	*Hymenolepis* (*Rodentolepsis*) *nana*	Rats, mice, hamsters, nonhuman primates	Humans	Intermediate host is not essential to the life cycle of this cestode. Direct infection and internal autoinfection can also occur. Heavy infections result in abdominal distress, enteritis, anal pruritis, anorexia, and headache.
Strongyloidiasis	*Strongyloides stercoralis, S. fulleborni*	Nonhuman primates, dogs, cats, humans, Old World nonhuman primates	Humans	Oral and transcutaneous infections can occur in animals and humans. Heavy infections can produce dermatitis, verminous pneumonitis, enteritis. Internal autoinfection can occur.
Ternidens infection	*Ternidens deminutus*	Old World primates	Humans	Rare and asymptomatic
Ancylostomiasis	*Ancylostoma duodenale*	Humans	Nonhuman primates, pigs	Oral and transcutaneous routes of infection occur. Heavy infections produce transient respiratory signs during larval migration followed by anemia due to gastrointestinal blood loss.
	Necator americanus	Humans	Nonhuman primates, pigs	
Trichostrongylosis	*Trichostrongylus colubriformis, T. axei*	Ruminants, pigs, dogs, rabbits, Old World nonhuman primates	Humans	Heavy infections produce diarrhea.
Oesophagostomiasis	*Oesophagostomum* spp.	Old World primates	Humans	Heavy infections result in anemia. Encapsulated parasitic granulomas are usually an inocuous sequella to infection.
Ascariasis	*Ascaris lumbricoides*	Old World primates	Humans	Infection occurs by ingestion of embryonated eggs only. Embryonation, requiring 2 or more weeks, ordinarily would not occur in laboratory. Heavy infections can produce severe respiratory and gastrointestinal tract disease.
Enterobiasis	*Enterobias vermicularis*	Humans	Old world primates	Oral and inhalational infection can occur. Disease in humans characterized by perianal pruritis, irritability, and disturbed sleep.
Trichuriasis	*Trichuris trichiura*	Humans	Old world primates	Three-week embryonation makes laboratory infection highly unlikely. Heavy infection in humans results in intermittent abdominal pain, bloody stools, diarrhea, and occasionally rectal prolapse.
Larval migrans (viscera)	*Toxocara canis*	Dogs and other canids	Humans	Chronic eosinophilic granulomatous lesions distributed throughout various organs. Should not be encountered in laboratory.
	T. cati	Cats and other felids	Humans	
	T. leonina	Dogs, cats, wild canids, felids	Humans	
	Baylisascaris procyonis	Raccoons	Humans and other animals	Infections in aberrant host produce granulomas in visceral organs with a predilection for the central nervous system.
Larval migrans (cutaneous)	*Ancylostoma caninum*	Dogs	Humans	Transcutaneous infection causes a parasitic dermatitis called 'creeping eruption'.
	A. braziliense	Dogs, cats	Humans	
	A. duodenale	Dogs, cats	Humans	
	Uncinarla stenocephala	Dogs, cats	Humans	
	N. americanus	Dogs, cats	Humans	

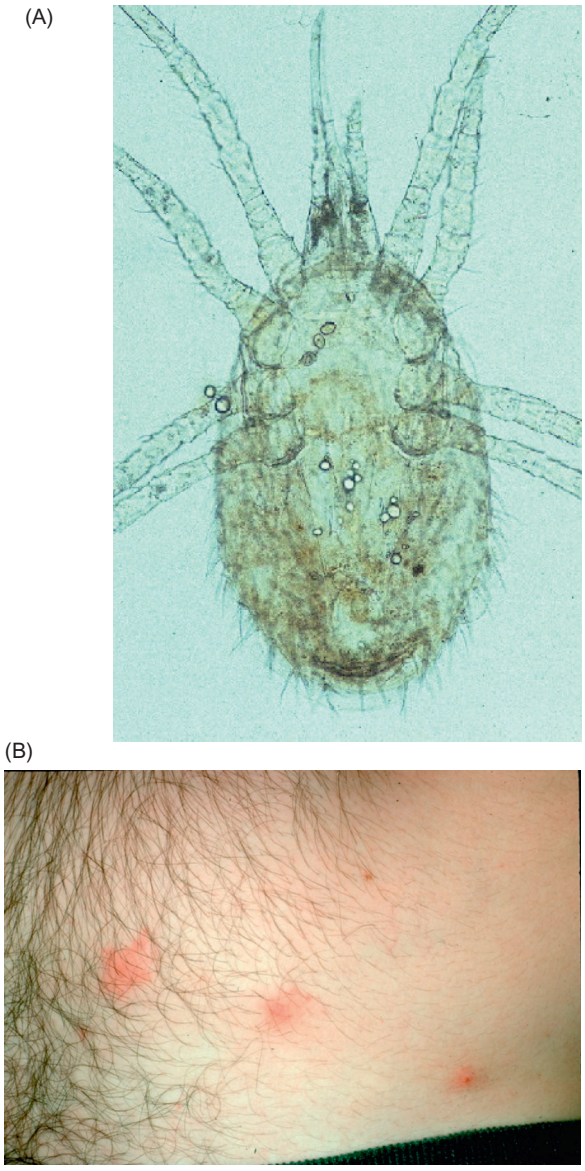

FIGURE 28.11 (A) Tropical rat mite (*Ornithonyssus bacoti*). (B) Tropical rat mite dermatitis. Note the three bites, referred to as 'breakfast, lunch, and dinner.' *Beck, 2009 Travel Medicine and Infectious Disease "Occurrence of a house-infesting Tropical rat mite (Ornithonyssus bacoti) on murides and human beings"; and Fox* et al., *2009 Arch Derm.)*

Mites probably pose the greatest health hazard, not only because they are the most common inhabitants in number and variety of species, but because they also readily transmit agents from almost every major group of pathogens: bacteria, chlamydia, rickettsia, viruses, protozoa, spirochetes, and helminths (Yunker, 1964). In addition, most of these mites are capable of producing severe allergic papular dermatitis in humans (Fox and Reed, 1978; Fox, 1982b) (Fig. 28.11). Control of mite infestation is primarily dependent on their habitats. Some, such as *Sarcoptes* spp. and *Notoedres* spp., are obligate parasites that require treatment of the host. Other mites, such as *Ornithonyssus bacoti*, which live most of the time off the animal, require treatment of the environment with appropriate insecticides (Markell *et al.*, 1999; Fox, 2009, Fox, 1982b).

Ticks, with the exception of those in newly arrived dogs or wild animals brought into the laboratory, are rarely found in the well-managed animal facility. The brown dog tick, *Rhipicephalus sanguineus*, is an exception. It readily infests kennels and vivaria. Ticks, like mites, can transmit a variety of diseases, including Rocky Mountain spotted fever, tick-borne typhus, Lyme disease, and others (Table 28.4). Lyme borreliosis is a commonly reported tick-borne infection in Europe and North America. The illness is caused by a spirochete, *Borrelia burgdorferi*, which is transmitted during the blood feeding of ticks of the genus *Ixodes.* The larvae and nymphs feed readily on a wide range of hosts, including birds, and an abundance of reservoir hosts exists, usually small and medium-sized animals. Larger animals, such as deer, sheep, cows, or horses, must be present for the maintenance of the tick population since adult ticks only engorge successfully on larger animals. Transmission occurs through salivation during the feeding process on a host. Control of ticks indoors is aimed primarily at the resting places of the unattached ticks and proper treatment of newly arrived animals, which are noted for harboring ticks.

Fleas are notorious for their ability to transmit disease to humans, particularly plague and murine typhus. Three rodent fleas, *X. cheopis*, *Nasopsyllus fasciatus*, and *Leptopsylla segnis*, have been found in a high percentage of urban dwellings in certain areas of the United States and are potential transmitters of disease in the laboratory. Apparently, *X. cheopis* in the past was readily established in animal facilities. At a Midwestern U.S. university, it inhabited rooms housing laboratory mice, where on two separate occasions fleas bit students (Yunker, 1964). *L. segnis*, the mouse and rat flea, bites humans and is a vector for plague and typhus, serious diseases in humans. *L. segnis* can also serve as an intermediate host for the rodent tapeworms *H. (Rodentolepsis) nana* and *H. diminuta*, both of which can infect humans (Markell *et al.*, 1999). The flea bite can be irritating and can cause allergic dermatitis. The cat flea, *Ctenocephalides felis*, is the most common flea in and around human dwellings in the United States. This flea is capable of experimentally transmitting plague and murine typhus, and therefore, the potential exists for transmitting the disease to humans. Control of fleas consists of treatment of infested areas as well as the primary host; in the case of rodent fleas, the animal facility must be free of feral rodents and their entry to prevent introduction of these arthropods.

TABLE 28.4 Ectoparasites[a,b]

Species	Disease in humans	Animal host	Agent
Mites			
Obligate skin mites			
Sarcoptes scabiei subspecies	Scabies	Mammals	
Notoedres cati	Mange	Cats, dogs, rabbits	
Nest-inhabiting parasites			
Ornithonyssus bacoti	Dermatitis, murine typhus	Rodents and other vertebrates, including birds	WEE,[c] ShE[d] virus Rickettsia mooseri
O. bursa	Dermatitis	Birds	WEE, EEE,[e] SLE viruses
O. sylviarum	Dermatitis, encephalitis	Birds	
Dermanyssus gallinae	Dermatitis, encephalitis	Birds	
Allodermanyssus sanguineus	Dermatitis, rikettsialpox	Rodents, particularly *Mus musculus*	*Rickettsia mooseri*
Ophionyssus natricis	Dermatitis	Reptiles	
Haemogamasus pontiger	Dermatitis	Rodents, insectivores, straw bedding	
H. casalis	Dermatitis	Birds, mammals, straw, hay	
Eulaelaps stabularis	Dermatitis, tularemia	Small mammals, straw bedding	*Francisella tularensis*
Glycyphagus cadaverum	Dermatitis, psittacosis	Birds	*C. psittaci*
Acaropsis docta	Dermatitis, psittacosis	Birds	*C. psittaci*
Trixacarus caviae	Dermatitis	Guinea pigs	
Facultative mites			
Cheyletiella spp.	Dermatitis	Cats, dogs, rabbits, bedding	
Dermatophagoides scheremtewskyi	Dermatitis, urinary infections, pulmonary acariasis	Feathers, animal feed, bird nests	
Eutrombicula spp.	Human pest (chiggers), local pruritis	Chickens, occasional mammals obtained from natural habitat	
Laelaps echidninus			Potential Argentine hemorrhagic fever
Ixodids (ticks)			
Rhipicephalus sanguineus	Irritation, RMSF,[f] tularemia, other diseases	Dogs	*Rickettsia rickettsii, Francisella tularensis*
Dermacentor variabilis	Irritation, RMSF,[f] tularemia tick paralysis, other diseases	Wild rodents, cottontail rabbits, dogs from endemic areas	See above
D. andersoni	Irritation, Colorado tick fever, Q fever, RMSF,[f] other diseases	Small mammals, uncommon on dogs	See above Ungrouped rhabdoviruses
D. occidentalis	Irritation, Colorado tick fever, RMSF,[f] tularemia	Small mammals, uncommon on dogs	See above
Ambylomma americanum	Irritation, RMSF,[f] tularemia	Wild rodents, dogs	
Ixodes scapularis	Irritation, possible tularemia	Dogs, wild rodents	
Ixodes spp.	Lyme disease	Dogs, cats, wild rodents	*Borrelia burgdonferi*
Omithodorus spp.	Irritation, relapsing fever	Captive reptiles, wild animals, pigs	*B. recurrentis*
Argas persicus	Irritation, seldom bites humans, but can transmit anthrax, Q fever	Domestic fowl	*B. recurrentis*

(*Continued*)

TABLE 28.4 (Continued)

Species	Disease in humans	Animal host	Agent
Fleas			
Ctenocephalides felis	Dermatitis, vector of *Hymenolepis diminuta*, *Dipylidium caninum*	Dogs, cats	
C. canis (cat and dog fleas)			
Xenopsylla cheopis	Dermatitis, plague vector, *Hymenolepis nana*, *H. diminuta*	Mouse, rat, wild rodents	*Yersinia pestis*
Nasopsyllus fasciatus	Dermatitis, plague vector,		
	Hymenolepis nana, *H. diminuta*, murine typhus	Mouse, rat, wild rodents	*Y. pestis*
Leptopsylla segnis	*Hymenolepis diminuta*, *H. nana*, murine typhus vector	Rat	Harbors salmonella
Echidnophaga gallinacea (sticktight flea)	Potential plague vector	Poultry	
Pulex irritans	Irritation	Domestic animals (especially pigs) and humans	

[a]*Found in laboratory animals that cause allergic dermatitis or from which zoonotic agents have been recovered in nature.*
[b]*Modified from Fox* et al. *(1984).*
[c]*WEE, Western equine encephalitis.*
[d]*SLE, St. Louis encephalitis.*
[e]*EEE, Eastern equine encephalitis.*
[f]*RMSF, Rocky Mountain spotted fever.*

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References

Abbott, Y., Acke, E., Khan, S., Muldoon, E.G., Markey, B.K., Pinilla, M., et al., 2010. Zoonotic transmission of Streptococcus equi subsp. zooepidemicus from a dog to a handler. J. Med. Microbiol. 59, 120–123.

Adams, W.H., Emmons, R.W., Brooks, J.E., 1970. The changing ecology of murine (endemic) typhus in southern California. Am. J. Trop. Med. Hyg. 19, 311–318.

Adams, J.R., Schmidtmann, E.T., Azad, A.F., 1990. Infection of colonized cat fleas, *Ctenocephalides felis* (Bouche), with a rickettsia-like microorganism. Am. J. Trop. Med. Hyg. 43, 400–409.

Adjemian, J., Weber, I.B., Mcquiston, J., Griffith, K.S., Mead, P.S., Nicholson, W., et al., 2012. Zoonotic infections among employees from Great Smoky Mountains and Rocky Mountain National Parks, 2008–2009. Vector Borne Zoonotic Dis. 12, 92–431.

Advisory Committee on Immunization Practices (ACIP), 2006. Prevention of hepatitis a through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 55, 1–23.

Advisory Committee on Immunization Practices (ACIP), 2007. Update: prevention of hepatitis a after exposure to hepatitis a virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 56, 1080–1084.

Alexander, A.D., 1984. Leptospirosis in laboratory mice. Science 224, 1158.

Allos, B.M., Lastovica, A.J., Blaser, M.J., 1995. Atypical campylobacters and related microorganisms. In: Blaser, M.J., Smith, P.D., Ravdin, J.I., Greenberg, H.B., Guerrant, R.L. (Eds.), Infections of the Gastrointestinal Tract. Raven Press, New York, pp. 849–865.

Ambrus, J.L., Strandstrom, H.V., 1966. Susceptibility of Old World monkeys to Yaba virus. Nature 211, 876.

Ambrus, J.L., Strandstrom, H.V., Kawinski, W., 1969. "Spontaneous" occurrence of a Yaba tumor in a monkey colony. Experimentia 25, 64–65.

Anderson, A., Bijlmer, H., Fournier, P.E., Graves, S., Hartzell, J., Kersh, G.J., et al., 2013. Diagnosis and management of Q fever-United States, 2013: recommendations from CDC and the Q fever working group. MMWR Recomm. Rep. 62 (RR-03), 1–30.

Anderson, L.C., Leary, S.L., Manning, P.J., 1983. Rat-bite fever in animal research laboratory personnel. Lab. Anim. Sci. 33, 292.

Angus, K.N., 1983. Cryptosporidiosis in man, domestic animals, and birds: a review. J. R. Soc. Med. 76, 62–70.

Armstrong, J., Hertzog, R.E., 1979. Giardiasis in apes and zoo attendants, Kansas city, Missouri. Vet. Public Health Notes 1, 7–8.

Asher, M.S., 1989. Rickettsial diseases. In: Schmidt, N.J., Emmons, R.W. (Eds.), Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections. American Public Health Association, Washington, DC, pp. 1141–1164.

Ayres, J.G., Flint, N., Smith, E.G., Tunnicliffe, W.S., Fletcher, T.J., Hammond, K., et al., 1998. Post-infection fatigue syndrome following Q fever. QJM 91, 105–123.

Babudieri, B., 1959. Q fever: a zoonosis. Adv. Vet. Sci. 5, 82–182.

Baele, M., Decostere, A., Vandamme, P., Ceelen, L., Hellemans, A., Mast, J., et al., 2008. Isolation and characterization of *Helicobacter suis* sp. nov. from pigs stomachs. Int. J. Syst. Evol. Microbiol. 58, 1350–1358.

Baiano, J.C., Barnes, A.C., 2009. Towards control of *Streptococcus iniae*. Emerg. Infect. Dis. 15, 1891–1896.

Baker, D.G., 1998. Natural pathogens of laboratory mice, rats, and rabbits and their effects on research. Clin. Microbiol. Rev. 11, 231–266.

Balayan, M.S., 1997. Epidemiology of hepatitis E virus infection. J. Viral Hepat. 4, 155–165.

Banyard, A., Fooks, A., 2011. Rabies and rabies-related lyssaviruses. In: Palmer, S.R., Soulsby, L., Torgerson, P., Brown, D. (Eds.), Oxford Textbook of Zoonoses: Biology, Clinical Practice, and Public Health Control Oxford University Press, New York, pp. 398–422.

Barkin, R.M., Guckian, J.C., Glosser, J.W., 1974. Infections by *Leptospira ballum:* a laboratory-associated case. South Med. J. 67, 155–176.

Barkley, W.E., Richardson, J.H., 1984. The control of biohazards associated with the use of experimental animals. In: Fox, J.G., Cohen, B.J., Loew, F.M. (Eds.), Laboratory Animal Medicine. Academic Press, Orlando, FL, pp. 595–602.

Bathrick, M.E., 1981. Intraocular gnathostomiasis. Ophthalmology 99, 1293–1295.

Bearcroft, W.G.C., Jamieson, M.F., 1958. An outbreak of subcutaneous tumors in rhesus monkeys. Nature 182, 195–196.

Beaver, P.C., Jung, R.C., 1985. Animal Agents and Vectors of Human Disease, fifth ed. Lea & Febiger, Philadelphia, PA.

Belser, J.A., Katz, J.M., Tumpey, T.M., 2011. The ferret as a model organism to study influenza a virus infection. Dis. Model. Mech. 4, 575–579.

Bengis, R.G., Leighton, F.A., Fischer, J.R., Artois, M., Mörner, T., Tate, C.M., 2004. The role of wildlife in emerging and re-emerging zoonoses. Rev. Sci. Tech. Int. Off. Epizoot. 23, 497–511.

Bennett, S.G., Comer, J.A., Smith, H.M., Webb, J.P., 2007. Serologic evidence of a Rickettsia akari-like infection among wild-caught rodents in Orange County and humans in Los Angeles County, California. J. Vec. Ecol. 32, 198–201.

Benson, P.M., Malane, S.L., Banks, R., Hicks, C.B., Hilliard, J., 1989. B virus (*Herpesvirus simiae*) and human infection. Arch. Dermatol. 125, 1247–1248.

Bernard, K.W., Parham, G.L., Winkler, W.G., Helmick, C.G., 1982. Q fever control measures: recommendations for research facilities using sheep. Infect. Control 3, 461–465.

Berridge, B.R., Fuller, J.D., de Azavedo, J.C., Low, D.E., Bercovier, H., Frelier, P.F., 1998. Development of specific nested oligonucleotide PCR primers for the *Streptococcus iniae* 16S-23S ribosomal DNA intergenic spacer. J. Clin. Microbiol. 36, 2778–2781.

Bert, F., Lambert-Zechovsky, N., 1997. Septicemia caused by *Streptococcus canis* in a human. J. Clin. Microbiol. 35, 777–779.

Besser, T.E., Gay, C.C., Gay, J.M., Hancock, D.D., Rice, D., Pritchett, L.C., et al., 1997. Salmonellosis associated with *S. typhimurium* DT104 in the USA [letter; comment]. Vet. Rec. 140, 73.

Bharti, A.R., Nally, J.E., Ricaldi, J.N., Mathhias, M.A., Diaz, M.M., Lovett, M.A., et al., 2003. Leptospirosis: a zoonotic disease of global importance. Lancet Infect. Dis. 3, 757–771.

Bhatt, P.N., Jacoby, R.O., Barthold, S.W., 1986. Contamination of transplantable murine tumors with lymphocytic choriomeningitis virus. Lab. Anim. Sci. 36, 136–139.

Bi, Z., Formenty, P.B.H., Roth, C.E., 2008. Hantavirus infection: a review and global update. J. Infect. Dev. Ctries. 2, 3–23.

Biggar, R.J., Woodall, J.P., Walter, P.D., Haughie, G.E., 1975. Lymphocytic choriomeningitis outbreak associated with pet hamsters. J. Am. Vet. Med. Assoc. 232, 494–500.

Blanchard, J.L., Russell-Lodrigue, K.E., 2012. Biosafety in laboratories using nonhuman primates. In: Abee, C.R., Mansfield, K., Tardif, S.D., Morris, T. (Eds.), Nonhuman Primates in Biomedical Research: Biology and Management. Elsevier, pp. 437–492.

Blaser, M.J., LaForce, F.M., Wilson, N.A., Wang, W.L.L., 1980. Reservoirs for human campylobacteriosis. J. Infect. Dis. 141, 665–669.

Bodetti, T.J., Jacobson, E., Wan, C., Hafner, L., Pospischil, A., Rose, K., et al., 2002. Molecular evidence to support the expansion of the hostrange of Chlamydophila pneumoniae to include reptiles as well as humans, horses, koalas and amphibians. Syst. Appl. Microbiol. 25, 146–152.

Bond, R., 2010. Superficial veterinary mycoses. Clin. Dermatol. 28, 226–236.

Boneva, R.S., Grindon, A.J., Orton, S.L., Switzer, W.M., Shanmugam, V., Hussain, A.I., et al., 2002. Simian foamy virus infection in a blood donor. Transfusion 42, 886–891.

Bonthius, D.J., 2012. Lymphocytic choriomeningitis virus: an underrecognized cause of neurologic disease in the fetus, child, and adult. Semin. Pediatr. Neurol. 19, 89–95.

Boostrom, A., Beier, M.S., Macaluso, J.A., Macaluso, K.R., Sprenger, D., Hayes, J., et al., 2002. Geographic association of Rickettsia felis-infected opossums with human murine typhus, Texas. Emerg. Infect. Dis. 8, 549–554.

Bowen, G.S., Calisher, C.H., Winkler, W.G., Kraus, A.L., Fowler, E.H., Garmon, D.W., et al., 1975. Laboratory studies of lymphocytic choriomeningitis virus outbreak in man and laboratory animals. Am. J. Epidemiol. 102, 233–240.

Brooks, J.E., 1973. A review of commensal rodents and their control. Rev. Eviron. Control 3, 405–453.

Brown, C.M., Conti, L., Ettestad, P., Leslie, M.J., Sorhage, F.E., Sun, B., 2011. Compendium of animal rabies prevention and control. J. Am. Vet. Med. Assoc. 239, 609–617.

Burgos-Rodriguez, A.G., 2011. Zoonotic diseases of primates. Vet. Clin. North Am. Exot. Anim. Pract. 14, 557–575.

Burman, W.J., Cohn, D.L., Reves, R.R., Wilson, M.L., 1995. Multifocal cellulitis and monoarticular arthritis as manifestations of *H. cinaedi* bacteremia. Clin. Infect. Dis. 20, 564–570.

Carbone, M., Fera, M.T., Pennisi, M.G., Masucci, M., De Sarro, A., Macri, C., 1999. Activity of nine fluoroquinolones against strains of *Bordetella bronchiseptica*. Int. J. Antimicrob. Agents 12, 355–358.

Centers for Disease Control and Prevention (CDC), n.d.-a. Known Cases and Outbreaks of Ebola Hemorrhagic Fever, in Chronological Order [online]. Available at: <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/ebola/ebolatable.htm>(accessed 08.09.13).

Centers for Disease Control and Prevention (CDC), n.d.-b. Known Cases and Outbreaks of Marburg Hemorrhagic Fever, in Chronological Order [online]. Available at: <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/marburg/marburg-table.htm>(accessed 08.09.13.).

Centers for Disease Control and Prevention (CDC), n.d.-c. National Select Agent Registry, Select Agents and Toxins List [online] Available at: <http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html>(accessed 08.09.13).

Centers for Disease Control and Prevention (CDC), n.d.-f. Reported Cases of HPS – Hantavirus [online]. Available at: <http://www.cdc.gov/hantavirus/surveillance/index.html>(accessed 09.09.13).

Centers for Disease Control and Prevention (CDC), n.d.-g. Dog Bite: Fact Sheet [online]. Available at: <http://www.cdc.gov/homeandrecreationalsafety/dog-bites/dogbite-factsheet.html>(accessed 11.11.13).

Centers for Disease Control and Prevention (CDC), 1977. Rabies in a laboratory worker. MMWR 26, 183–184.

Centers for Disease Control and Prevention (CDC), 1987. Guidelines for the prevention of *Herpesvirus simiae* (B virus) infection in monkey handlers. MMWR 36, 680–689.

Centers for Disease Control and Prevention (CDC), 1989a. Epidemiologic notes and reports B virus infections in humans – Michigan. MMWR 38, 453–454.

Centers for Disease Control and Prevention (CDC), 1989b. Ebola virus infection in imported primates – Virginia. MMWR 38, 831–832.

Centers for Disease Control and Prevention (CDC), 1989c. Epidemiologic notes and reports B virus infections in humans – Michigan. MMWR 38, 453–454.

Centers for Disease Control and Prevention (CDC), 1990. Update: Ebola-related filovirus infection in nonhuman primates and interim guidelines for handling nonhuman primates during transit and quarantine. MMWR 39, 22–30.
Centers for Disease Control and Prevention (CDC), 1992a. Anonymous survey for simian immunodeficiency virus (SIV) seropositivity in SIV-laboratory researchers–United States. MMWR 41, 814–815.
Centers for Disease Control and Prevention (CDC), 1995. Outbreak of acute febrile illness and pulmonary hemorrhage – Nicaragua. MMWR 44, 841–843.
Centers for Disease Control and Prevention (CDCP), 1996. Invasive infection due to *Streptococcus iniae* – Ontario, 1995–1996. MMWR 45, 650–653.
Centers for Disease Control and Prevention (CDCP), 1997. Human monkeypox – Kasai Oriental, Democratic Republic of Congo, February 1996–October 1997. MMWR 46, 1168–1171.
Centers for Disease Control and Prevention (CDCP), 1998. Fatal *cercopithecine herpesvirus* 1 (B virus) infection following a mucocutaneous exposure and interim recommendations for worker protection. MMWR 47, 1073–1076.
Centers for Disease Control and Prevention (CDC), 2003. Update: multistate outbreak of monkeypox – Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR 52, 561–564.
Centers for Disease Control and Prevention (CDC), 2005. Fatal Rat-Bite Fever – Florida and Washington, 2003. MMWR 53, 1198–1202.
Centers for Disease Control and Prevention (CDC), 2008. Brief report: lymphocytic choriomeningitis virus transmitted through solid organ transplantation – Massachusetts, 2008. MMWR 57, 799–801.
Centers for Disease Control and Prevention (CDC), 2010a. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies-recommendations of the advisory committee on immunization practice. Ann. Emerg. Med. 56, 64–67.
Centers for Disease Control and Prevention (CDC), 2010b. Multistate outbreak of human salmonella typhimurium infections associated with aquatic frogs – United States, 2009. MMWR 58, 1433–1436.
Centers for Disease Control and Prevention (CDC), 2011. Notes from the field: update on human salmonella typhimurium infections associated with aquatic frogs – United States, 2009–2011. MMWR 60, 628.
CDC. Human Orf virus infection from household exposures – United States, 2009–2011. MMWR Morb Mortal Wkly Rep. 2012 Apr 13;61(14):245–8.
Centers for Disease Control and Prevention (CDC), 2012a. Measles. In: Atkinson, W., Wolfe, C., Hamborsky, J. (Eds.), Epidemiology and Prevention of Vaccine – Preventable Diseases, twelfth ed. Public Health Foundation, Washington DC, pp. 173–192. second printing.
Centers for Disease Control and Prevention (CDC), 2012b. Notes from the field: lymphocytic choriomeningitis virus infections in employees of a rodent breeding facility – Indiana, May–June 2012. MMWR 61, 622–623.
Centers for Disease Control and Prevention (CDC), 2012c, Multistate Outbreak of Human *Salmonella Infantis* Infections Linked to Dry Dog Food (Final Update) [online]. Available at: <http://www.cdc.gov/salmonella/dog-food-05-12/>.
Centers for Disease Control and Prevention (CDC), 2013. Measles – United States, January 1–August 24, 2013. MMWR 62, 741–743.
Centers for Disease Control and Prevention–National Institutes of Health (CDCP–NIH), 2009. Biosafety in Microbiological and Biomedical Laboratories, fifth ed. U.S. Government Printing Office, Washington, DC, HHS Publ. (CDC) 21–1112.
Charrel, R.N., de Lamballerie, X., 2010. Zoonotic aspects of arenavirus infections. Vet. Microbiol. 140, 213–220.
Chen, Z., Telfier, P., Gettie, A., Reed, P., Zhang, L., Ho, D.D., et al., 1996. Genetic characterization of new West African simian immunodeficiency virus SIVsm: geographic clustering of household-derived SIV strains with human immunodeficiency virus type 2 subtypes and genetically diverse viruses from a single feral sooty mangabey troop. J. Virol. 70, 3617–3627.
Chessman, B.S., 1972. Reactivation of toxoplasm oocyst production in the cat by infection with *Isospora felis*. Br. Vet. J. 128, 33–36.
Childs, J.E., Colby, L., Krebs, J.W., Strine, T., Feller, M., Noah, D., et al., 1997. Surveillance and spatiotemporal associations of rabies in rodents and lagomorphs in the United States, 1985–1994. J. Wildl. Dis. 33, 20–27.
Chin, J. (Ed.), 2000. Control of communicable diseases manual: an official report of the American Public Health Association. American Public Health Association, Washington, DC.
Chiodini, R.J., Sundberg, J.P., 1981. Salmonellosis in reptiles: a review. Am. J. Epidemiol. 113, 494.
Chosewood, L.C., Wilson, D.E., 2009. Biosafety in Microbiological and Biomedical Laboratories. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institutes of Health, Washington, DC.
Cohen, J.I., Davenport, D.S., Stewart, J.A., Deitchman, S., Hilliard, J.K., Chapman, L.E., 2002. Recommendations for prevention of and therapy for exposure to B virus (*Cercopithecine Herpesvirus* 1). Clin. Infect. Dis. 35, 1191–1203.
Collins, J.M., Lorber, B., 2009. With man's best friend. In: Schlossberg, D. (Ed.), Infections of Leisure, fourth ed. ASM Press, Washington, DC, pp. 127–153.
Committee on Urban Pest Management, 1980. Urban Pest Management. National Academies Press, Washington, DC.
Cossaboom, C.M., Córdoba, L., Dryman, B.A., Meng, X.J., 2011. Hepatitis E virus in rabbits, Virginia, USA. Emerg. Infect. Dis. 17, 2047–2049.
Cossaboom, C.M., Córdoba, L., Sanford, B.J., Piñeyro, P., Kenney, S.P., Dryman, B.A., et al., 2012. Cross-species infection of pigs with a novel rabbit, but not rat, strain of hepatitis E virus isolated in the United States. J. Gen. Virol. 93, 1687–1695.
Cotton, M.M., Partridge, M.R., 1998. Infection with feline *Chlamydia psittaci*. Thorax 53, 75–76.
Craven, R.B., Barnes, A.M., 1991. Plague and tularemia in animal associated human infections. Infect. Dis. Clin. North Am. 1, 165–175.
Dalgard, D.W., Hardy, S.L., Pearson, G.J., Pucak, G.J., Quander, Z., Zack, P.M., et al., 1992. Combined simian hemorrhagic fever and Ebola virus infection in cynomolgus monkeys. Lab. Anim. Sci. 42, 152–159.
Damon, I.K., 2011. Status of human monkeypox: clinical disease, epidemiology and research. Vaccine 29 (Suppl. 4), D54–D59.
Davies, H.D., Sakuls, P., Keystone, J.S., 1993. Creeping eruption. A review of clinical presentation and management of 60 cases presenting to a tropical disease unit. Arch. Dermatol. 129, 588–591.
Davies, R.B., Hibler, C.P., 1979. Animal reservoirs and cross-species transmission of Giardia. In: Jakubowski, W., Hoff, J.C. (Eds.), Waterborne Transmission of Giardiasis. Environmental Protection Agency, Cincinnati, OH, pp. 104–126.
Demers, R.Y., Thiermann, A., Demers, P., Frank, R., 1983. Exposure to *Leptospira icterohaemorrhagiae* in inner-city and suburban children: a serologic comparison. J. Fam. Prac. 17, 1007–1011.
Deming, M.S., Tauxe, R.V., Blake, B.A., Dixon, S.E., Fowler, B.S., Jones, T.S., et al., 1987. *Campylobacter* enteritis at a university: transmission from eating chicken and from cats. Am. J. Epidemiol. 126, 526–534.
Dendle, C., Woolley, I.J., Korman, T.M., 2006. Rat-bite fever septic arthritis: illustrative case and literature review. Eur. J. Clin. Microbiol. Infect. Dis. 25, 791–797.
Dennis, D.T., Hughes, J.M., 1997. Multidrug resistance in plague. N. Engl. J. Med. 337, 702–704.
De Vleeschauwer, A., Atanasova, K., Van Borm, S., van den Berg, T., Rasmussen, T.B., Uttenthal, A., et al., 2009. Comparative pathogenesis of an avian H5N2 and a swine H1N1 influenza virus in pigs. PLoS One 4, e6662.

Dewhirst, F.E., Klein, E.A., Thompson, E.C., Blanton, J.M., Chen, T., Miella, L., et al., 2012. The canine oral microbiome. PLoS One 7, e36067.

Dienstag, J.L., Davenport, F.M., McCollum, R.W., Hennessy, A.V., Klatskin, G., Purcell, R.H., 1976. Nonhuman primate-associated viral hepatitis type A. Serologic evidence of hepatitis a virus infection. JAMA 236, 462–464.

DiGiacomo, R.F., Harris, N.V., Huber, N.L., Cooney, M.K., 1990. Animal exposures and antibodies to *Toxoplasma gondii* in a university population. Am. J. Epidemiol. 131, 729–733.

Division of Tuberculosis Elimination, 2000. Core Curriculum on Tuberculosis: What the Clinician Should Know, fourth ed. Centers for Disease Control and Prevention, Atlanta, GA.

Dolan, M.J., Wong, M.T., Regnery, R.L., Jorgensen, J.H., Garcia, M., Peters, J., et al., 1993. Syndrome of *Rochalimaea henselae* adenitis suggesting cat scratch disease. Ann. Intern. Med. 118, 331–336.

Dubey, J.P., 1998. Advances in the life cycle of *Toxoplasma gondii*. Int. J. Parasitol. 28, 1019–1024.

Dubey, J.P., Lappin, M.R., Thulliez, P., 1995. Long-term antibody responses of cats fed *Toxoplasma gondii* tissue cysts. J. Parasitol. 81, 887–893.

Dubey, J.P., Saville, W.J., Stanek, J.F., Reed, S.M., 2002. Prevalence of Toxoplasma gondii antibodies in domestic cats from rural Ohio. J. Parasitol. 88, 802–803.

Dupinay, T., Gheit, T., Roques, P., Cova, L., Chevallier-Queyron, P., Tasahsu, S.I., et al., 2013. Discovery of naturally occurring transmissible chronic hepatitis B virus infection among *Macaca fascicularis* from Mauritius Island. Hepatolology 58, 1610–1620.

Dupont, H.L., 2000. *Shigella* species (bacillary dysentery). In: Mandell, G.L., Bennett, J.E., Dolin, R. (Eds.), Practices and Principles in Infectious Diseases. Churchill Livingston, Philadelphia, PA, pp. 2363.

Dyer, J.L., Wallace, R., Orciari, L., Hightower, D., Yager, P., Blanton, J.D., 2013. Rabies surveillance in the United States during 2012. J. Am. Vet. Med. Assoc. 243, 805–815.

Dykes, A.C., Juranek, D.D., Lorenz, R.A., Sinclair, S., Jakubowski, W., Davies, R., 1980. Municipal waterborne giardiasis: an epidemiologic investigation. Beavers implicated as a possible reservoir. Ann. Intern. Med. 92, 165–170.

Dykewicz, C.A., Dato, V.M., Fisher-Hoch, S., Horwath, M.V., Perez-Oronoz, G., Ostroff, S.M., et al., 1992. Lymphocytic choriomeningitis outbreak associated with nude mice in a research institute. J. Am. Med. Assoc. 267, 1349–1353.

Edelglass, J.W., Douglass, M.C., Stiefler, R., Tessler, M., 1982. Cutaneous larva migrans in northern climates. A dream vacation. J. Am. Acad. Dermatol. 7, 353–358.

Engvall, E.O., Brandstrom, B., Andersson, L., Baverud, V., Trowald-Wigh, G., Englund, L., 2003. Isolation and identification of thermophilic *Campylobacter* species in faecal samples from Swedish dogs. Scand. J. Infect. Dis. 35, 713–718.

Eremeeva, M.E., Karpathy, S.E., Krueger, L., Hayes, E.K., Williams, A.M., Zaldivar, Y., et al., 2012. Two pathogens and one disease: detection and identification of flea-borne Rickettsiae in areas endemic for murine typhus in California. J. Med. Entomol. 49, 1485–1494.

Erlandsen, S.L., Sherlock, L.A., Januschka, M., Schupp, D.G., Schaefer III, F.W., Jakubowski, W., et al., 1988. Cross-species transmission of Giardia spp.: inoculation of beavers and muskrats with cysts of human, beaver, mouse, and muskrat origin. Appl. Environ. Microbiol. 54, 2777–2785.

Essbauer, S., Pfeffer, M., Meyer, H., 2010. Zoonotic poxviruses. Vet. Microbiol. 140, 229–236.

Estep, R.D., Messaoudi, I., Wong, S.W., 2010. Simian herpesviruses and their risk to humans. Vaccine 28 (Suppl. 2), B78–B84.

Everett, K.D., Bush, R.M., Andersen, A., 1999. Emended description of the order Chlamydiales, proposal of Parachlamydiaceae fam. nov. and Simkaniaceae fam. nov. each containing one monotypic genus, revised taxonomy of the family Chlamydiaceae, including a new genus and five new species, and standards for the identification of the organisms. Int. J. Syst. Bacteriol. 49, 415–440.

Faine, S., 1991. Leptospirosis. In: Evans, A.S., Brachman, P.S. (Eds.), Bacterial Infections of Humans. Plenum Medical Book Co., New York, pp. 367–393.

Farhang-Azad, A., Traub, R., Baqar, S., 1985. Transovarial transmission of murine typhus, rickettsiae in *Xenopsylla cheopis* fleas. Science 227, 543–545.

Fayer, R., Ungar, B.L.P., 1986. *Cryptosporidium* spp. and cryptosporidiosis. Microbiol. Rev. 50, 458.

Feldmann, H., Geisbert, T.W., 2011. Ebola haemorrhagic fever. Lancet 377, 849–862.

Feng, Y., Xiao, L., 2011. Zoonotic potential and molecular epidemiology of Giardia species and giardiasis. Clin. Microbiol. Rev. 24, 110–140.

Fenner, F., 1990. Poxviruses of laboratory animals. Lab. Anim. Sci. 40, 469–480.

Fischer, S.A., Graham, M.B., Kuehnert, M.J., Kotton, C.N., Srinivasan, A., Marty, F.M., et al., 2006. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N. Engl. J. Med. 354, 2235–2249.

Fitzpatrick, J.L., Dyer, J.L., Blanton, J.D., Kuzmin, I.V., Rupprecht, C.E., 2014. Rabies in rodents and lagomorphs in the United States, 1995–2010. JAVMA 245, 333–337.

Flowers, D.J., 1970. Human infection due to *Mycobacterium marinum* after a dolphin bite. J. Clin. Pediatr. 23, 475–477.

Flynn, R.J., 1973. Parasites of Laboratory Animals. Iowa State University Press, Ames, IA.

Forbes, L.B., Pantekoek, J.F., 1988. *Brucella canis* isolates from Canadian dogs. Can. Vet. J. 29, 149.

Fox, A.S., Kazacos, K.R., Gould, N.S., Heydemann, P.T., Thomas, C., Boyer, K.M., 1988. Fatal eosinophilic meningoencephalitis and visceral larva migrans caused by the raccoon ascarid *Baylisascaris procyonis*. N. Engl. J. Med. 312, 1619.

Fox, J.G., 1975. Transmissible drag resistance in *Shigella* and *Salmonella* isolated from pet monkeys and their owners. J. Med. Primatol. 4, 164.

Fox, J.G., 1982a. Campylobacteriosis – a "new" disease in laboratory animals. Lab. Anim. Sci. 32, 625.

Fox, J.G., 1982b. Outbreak of tropical rat mite dermatitis in laboratory personnel. Arch. Dermatol. 118, 676–678.

Fox, J.G., 2002. The non-*H. pylori* helicobacters: their expanding role in gastrointestinal and systemic diseases. Gut 50, 273–283.

Fox, J.G., 2009. With man's worst friend: the rat. In: Schlossberg, D. (Ed.), Infections of Leisure, fourth ed. ASM Press, Washington, DC, pp. 221–251.

Fox, J.G., 2011. *Campylobacter* infections. In: Greene, C.E. (Ed.), Infectious Diseases of the Dog and Cat, second ed. Elsevier-Saunders, St. Louis, MO, pp. 370–373.

Fox, J.G., Lipman, N.S., 1991. Infections transmitted from large and small laboratory animals. In: Weinberg, A., Weber, D. (Eds.), Infectious Diseases of North America. Saunders, Philadelphia, PA, pp. 131–163.

Fox, J.G., Marini, R.P., 2014. Biology and Diseases of the Ferret, third ed. Wiley-Blackwell, Ames, IA.

Fox, J.G., Megraud, F., 2007. Helicobacter. In: Murray, P.R., Baron, E.J., Jorgensen, J.H., Landry, M.L., Pfaller, M.A. (Eds.), Manual for Clinical Microbiology, ninth ed. ASM Press, Washington, DC, pp. 947–962.

Fox, J.G., Reed, C., 1978. Cheyletiella infestation of cats and their owners. Arch. Dermatol. 117, 1233–1234.

Fox, J.G., Taylor, N.S., Penner, J.L., Shames, B., Gurgis, R.V., Thomson, F.N., 1989b. Investigation of a zoonotically acquired *Campylobacter jejuni* enteritis with serotyping and restriction endonuclease DNA analysis. J. Clin. Microbiol. 27 (11), 2423–2425.

Fox, J.G., Perkins, S., Yan, L., Shen, Z., Attardo, L., Pappo, J., 1996. Local immune response in *Helicobacter pylori* infected cats and identification of *H. pylori* in saliva, gastric fluid, and feces. Immunology 88, 400–406.

Fox, J.G., Handt, L., Sheppard, B.J., Xu, S., Dewhirst, F.E., Motzel, S., et al., 2001. Isolation of Helicobacter cinaedi from the colon, liver and mesenteric lymph node of a rhesus monkey with chronic colitis and hepatitis. J. Clin. Microbiol. 39, 1580–1585.

Franz, D.R., Jahrling, P.B., Friedlander, A.M., McClain, D.J., Hoover, D.L., Bryne, W.R., et al., 1997. Clinical recognition and management of patients exposed to biological warfare agents. J. Am. Med. Assoc. 278, 399–411.

Freshwater, A., 2008. Why your housecat's trite little bite could cause you quite a fright: a study of domestic felines on the occurrence and antibiotic susceptibility of *Pasteurella multocida*. Zoonoses Public Health 55, 507–513.

Fulde, M., Valentin-Weigand, P., 2013. Epidemiology and pathogenicity of zoonotic streptococci. Curr. Top. Microbiol. Immunol. 368, 49–81.

Fuller, C., 2008. A multi-state *Salmonella* Typhimurium outbreak associated with frozen vacuum-packed rodents used to feed snakes. Zoonoses Public Health 55, 481–487.

Gao, F., Bailes, E., Robertson, D.L., Chen, Y., Rodenburg, C.M., Michael, S.F., et al., 1999. Origin of HIV-1 in the chimpanzee (*Pan troglodytes troglodytes*). Nature 397, 436–441.

Gardner, C.L., Ryman, K.D., 2010. Yellow fever: a reemerging threat. Clin. Lab. Med. 30, 237–260.

Gebhart, C.J., Fennell, C.L., Murtaugh, M.P., Stamm, W.E., 1989. *Campylobacter cinaedi* is normal intestinal flora in hamsters. J. Clin. Microbiol. 27, 1692–1694.

Geisbert, T.W., Hensley, L.E., Geisbert, J.B., Leung, A., Johnson, J.C., Grolla, A., et al., 2010. Postexposure treatment of Marburg virus infection. Emerg. Infect. Dis. 16, 1119–1122.

Geller, E.H., 1979. Health hazards for man. In: Baker, H.J., Lindsey, J.R., Weisbroth, S.H. (Eds.), The Laboratory Rat. Academic Press, New York, p. 402.

Gessain, A., Rua, R., Betsem, E., Turpin, J., Mahieux, R., 2013. HTLV-3/4 and simian foamy retroviruses in humans: discovery, epidemiology, cross-species transmission and molecular virology. Virology 435, 187–199.

Gibbons, R.V., 2002. Cryptogenic rabies, bats, and the question of aerosol transmission. Ann. Emerg. Med. 39, 528–536.

Gill, D.M., Stone, D.M., 1992. The veterinarian's role in the AIDS crisis. J. Am. Vet. Med. Assoc. 201, 1683–1684.

Glickman, L.T., Magnava, J.F., 1993. Zoonotic roundworm infections. Infect. Dis. Clin. North Am. 7, 717–732.

Goebel, S.J., Taylor, J., Barr, B.C., Kiehn, T.E., Castro-Malaspina, H.R., Hedvat, C.V., et al., 2007. Isolation of avian paramyxovirus 1 from a patient with a lethal case of pneumonia. J. Virol. 81, 12709–12714.

Goh, S.H., Driedger, D., Gillett, S., Low, D.E., Hemmingsen, S.M., Amos, M., et al., 1998. *Streptococcus iniae*, a human and animal pathogen: Specific identification by the chaperonin 60 gene identification method. J. Clin. Microbiol. 36, 2164–2166.

Goldstein, E.J.C., 1991. Household pets and human infections. Infect. Dis. Clin. North Am. 5, 117–130.

Goldstein, E.J.C., Greene, C.E., 2009. Around cats. In: Schlossberg, D. (Ed.), Infections of Leisure, fourth ed. ASM Press, Washington, DC, pp. 153–173.

Greene, C.E., Carmichael, L.E., 2011. Canine brucellosis. In: Greene, C.E. (Ed.), Infectious Diseases of the Dog and Cat. Elsevier-Saunders, St. Louis, MO, pp. 398–411.

Gruszynski, K., Young, A., Levine, S.J., Garvin, J.P., Brown, S., Turner, L., et al., 2015. Streptococcus equi subsp. zooepidemicus infections associated with guinea pigs. Emerg. Infect. Dis. 21 (January).

Guarner, J., Johnson, B.J., Paddock, C.D., Shieh, W.J., Goldsmith, C.S., Reynolds, M.G., et al., 2004. Monkeypox transmission and pathogenesis in prairie dogs. Emerg. Infect. Dis. 10, 426–431.

Haig, D.M., McInnes, C., Deane, D., Reid, H., Mercer, A., 1997. The immune and inflammatory response to orf virus. Comp. Immunol. Microbiol. Infect. Dis. 20, 197–204.

Handt, L.K., Fox, J.G., Dewhirst, F.E., Fraser, G.J., Paster, B.J., Yan, L., et al., 1994. *Helicobacter pylori* isolated from the domestic cat: public health implications. Infect. Immun. 62, 2367–2374.

Hanninen, M.L., Happonen, I., Saari, S., Jalava, K., 1996. Culture and characteristics of *Helicobacter bizzozeronii*, a new canine gastric *Helicobacter* sp. Int. J. Syst. Bacteriol. 46, 160–166.

Harder, T.C., Vahlenkamp, T.W., 2010. Influenza virus infections in dogs and cats. Vet. Immunol. Immunopathol. 134, 54–60.

Harker, K.S., Lane, C., De Pinna, E., Adak, G.K., 2011. An outbreak of Salmonella Typhimurium DT191a associated with reptile feeder mice. Epidemiol. Infect. 139, 1254–1261.

Hayami, M., Ido, E., Miura, T., 1994. Survey of simian immunodeficiency virus among nonhuman primate populations. Curr. Top. Microbiol. Immunol. 188, 1–20.

Heilmann, K.L., Borchard, F., 1991. Gastritis due to spiral shaped bacteria other than *Helicobacter pylori:* clinical, histological, and ultrastructural findings. Gut 32, 137–140.

Helms, M., Vastrup, P., Gerner-Smidt, P., Molbak, K., 2002. Excess mortality associated with antimicrobial drug-resistant *Salmonella* Typhimurium. Emerg. Infect. Dis. 8, 490–495.

Hemachudha, T., Ugolini, G., Wacharapluesadee, S., Sungkarat, W., Shuangshoti, S., Laothamatas, J., 2013. Human rabies: neuropathogenesis, diagnosis, and management. Lancet Neurol. 12, 498–513.

Heneine, W., Switzer, W.M., Sandstrom, P., Brown, J., Vedapuri, S., Schable, C.A., et al., 1998. Identification of a human population infected with simian foamy viruses. Nat. Med. 4, 391–392, 644–645.

Herwaldt, B.L., Juranek, D.D., 1993. Laboratory acquired malaria, leishmaniasis, trypanosomiasis, and toxoplasmosis. Am. J. Trop. Med. Hyg. 48, 313–323.

Heymann, D.L. (Ed.), 2008. Control of Communicable Diseases. Manual American Public Health Association, Washington, DC.

Hinman, A.R., Fraser, D.W., Douglas, R.D., Bowen, G.S., Krause, A.L., Winkler, W.G., et al., 1975. Outbreaks of lymphocytic choriomeningitis infection in medical center personnel. Am. J. Epidemiol. 101, 103–110.

Hinthorn, D.R., Foster Jr., M.T., Bruce, H.L., Aach, R.D., 1974. An outbreak of chimpanzee associated hepatitis. J. Occup. Med. 16, 388–391.

Hironaga, M., Fujigaki, T., Watanabe, S., 1981. Trichophyton mentagrophytes skin infections in laboratory animals as a cause of zoonosis. Mycopathologia 73, 101–104.

Hjelle, B., Torrez-Martinez, N., Koster, F.T., Jay, M., Ascher, M.S., Brown, T., et al., 1996. Epidemiologic linkage of rodent and human hantavirus genomic sequences in case investigation of hantavirus pulmonary syndrome. J. Infect. Dis. 173, 781–786.

Ho, A.C., Rapuan, C.J., 1993. *Pasteurella multocida* keratitis and corneal laceration from a cat scratch. Ophthalmic. Surg. 24, 346–348.

Hombal, S.M., Dincsoy, H.P., 1992. *Pasteurella multocida* endocarditis. Am. J. Clin. Pathol. 98, 565–568.

Hosamani, M., Scagliarini, A., Bhanuprakash, V., McInnes, C.J., Singh, R.K., 2009. Orf: an update on current research and future perspectives. Expert Rev. Anti. Infect. Ther. 7, 879–893.

Huang, F., Wang, H., Jing, S., Zeng, W., 2012. Simian foamy virus prevalence in *Macaca mulatta* and Zookeepers. AIDS Res. Hum. Retroviruses 28, 591–593.

Huang, F.F., Haqshenas, G., Guenette, D.K., Halbur, P.G., Schommer, S.K., Pierson, F.W., et al., 2002. Detection by reverse transcription-PCR and genetic characterization of field isolates of swine hepatitis E virus from pigs in different geographic regions of the United States. J. Clin. Microbiol. 40, 1326–1332.

Huff, J.L., Barry, P.A., 2003. B-virus (*Cercopithecine herpesvirus* 1) infection in humans and macaques: potential for zoonotic disease. Emerg. Infect. Dis. 9, 246–250.

Hull, T.G., 1955. Diseases Transmitted from Animals to Man, fourth ed. Thomas, Springfield, IL.
Hyde, S.R., Benirschke, K., 1997. Gestational psittacosis: case report and literature review. Mod. Pathol. 10, 602–607.
Ikeda, J.S., Hirsch, D.C., Jang, S.S., Biberstein, E.L., 1986. Characteristics of *Salmonella* isolated from animals at a veterinary medical teaching hospital. Am. J. Vet. Res. 47, 232–235.
Institute of Laboratory Animal Resources (ILAR), Committee on Occupational Safety and Health in Research Animal Facilities, 1997. Occupational Health and Safety in the Care and use of Research Animals. National Academies Press, Washington, DC.
Jaax, N.K., Davis, K.J., Geisbert, T.J., Vogel, P., Jaax, G.P., Topper, M., et al., 1996. Lethal experimental infection of rhesus monkeys with Ebola-Zaire (Mayinga) virus by the oral and conjunctival route of exposure. Arch. Pathol. Lab. Med. 120, 140–155.
Jackson, L.A., Perkins, B.A., Wenger, J.D., 1993. Cat scratch disease in the United States: an analysis of three national databases. Am. J. Public Health 83, 1707–1711.
Jahrling, P.B., Peters, D.J., 1992. Lymphocytic choriomeningitis virus, a neglected pathogen of man. Arch. Pathol. Lab. Med. 116, 486–488.
Jay, M., Hjelle, B., Davis, R., Ascher, M., Baylies, H.N., Reilly, K., et al., 1996. Occupational exposure leading to hantavirus pulmonary syndrome. Clin. Infect. Dis. 22, 841–844.
Jones, B.A., Grace, D., Kock, R., Alonso, S., Rushton, J., Said, M.Y., et al., 2013. Zoonosis emergence linked to agricultural intensification and environmental change. Proc. Natl. Acad. Sci. USA 110, 8399–8404.
Jones, J.W., Pether, J.V.S., Rainey, H.A., Swinburn, C.R., 1993. Recurrent *Mycobacterium bovis* infection following a ferret bite [letter]. J. Infect. 26, 225–226.
Jorgesen, D.M., 1997. Gestational psittacosis in a Montana sheep rancher. Emerg. Infect. Dis. 3, 191–194.
Kalish, M.L., Wolfe, N.D., Ndongmo, C.B., McNicholl, J., Robbins, K.E., Aidoo, M., et al., 2005. Central African hunters exposed to simian immunodeficiency virus. Emerg. Infect. Dis. 11, 1928–1930.
Kalter, S.S., Milstein, C.H., Bocyk, L.H., Cummins, L.B., 1978. Tuberculosis in nonhuman primates as a threat to humans. Dev. Biol. Stand. 41, 85–91.
Kalter, S.S., Heberling, R.L., Cooke, A.W., Barry, J.D., Tian, P.Y., Northam, W.J., 1997. Viral infections of nonhuman primates. Lab. Anim. Sci. 47, 461–467.
Kalthoff, D., Globig, A., Beer, M., 2010. (Highly pathogenic) avian influenza as a zoonotic agent. Vet. Microbiol. 140, 237–245.
Karp, B.E., Ball, N.E., Scott, C.R., Walcoff, J.B., 1999. Rabies in two privately owned domestic rabbits. J. Am. Vet. Med. Assoc. 215, 1824–1827.
Katz, D., Shi, W., Patrusheva, I., Perelygina, L., Gowda, M.S., Krug, P.W., et al., 2012. An automated ELISA using recombinant antigens for serologic diagnosis of B Virus infections in macaques. Comp. Med. 62, 527–534.
Kaufman, A.F., Boyce, J.M., Martone, W.J., 1980. Trends in human plague in the United States. J. Infect. Dis. 141, 522.
Kawamata, J., Yamanouchi, T., Dohmae, K., Miyamoto, H., Takahaski, M., Yamanishi, K., et al., 1987. Control of laboratory acquired hemorrhagic fever with renal syndrome (HFRS) in Japan. Lab. Anim. Sci. 37, 431–436.
Keifer, A., Lynch, G., Conwill, D., 1980. Water-borne giardiasis–California, Colorado, Pennsylvania, Oregon. MMWR 29, 121–123.
Kelt, D.A., Van Vuren, D.H., Hafner, M.S., Danielson, B.J., Kelly, M.J., 2007. Threat of hantavirus pulmonary syndrome to field biologists working with small mammals. Emerg. Infect. Dis. 13, 1285–1287.
Kemper, C.A., Lombard, C.M., Deresinki, S.C., Tompkins, L.S., 1990. Visceral bacillary epithelioid angiomatosis: possible manifestations of disseminated cat scratch disease in the immunocompromised host: a report of two cases. Am. J. Med. 89, 216–222.
Khabbaz, R.R., Heneine, W.M., George, J.R., Parekh, B.S., Rowe, T., Woods, T., et al., 1994. Brief report: infection of a laboratory worker with simian immunodeficiency virus. N. Engl. J. Med. 330, 172–177.
Khan, A.S., 2009. Simian foamy virus infection in humans: prevalence and management. Expert Rev. Anti. Infect. Ther. 7, 569–580.
Khan, A.S., Kumar, D., 2006. Simian foamy virus infection by whole-blood transfer in rhesus macaques: potential for transfusion transmission in humans. Transfusion 46, 1352–1359.
Kiehlbauch, J.A., Tauxe, R.V., Baker, C.N., Wachsmuth, I.K., 1994. *Helicobacter cinaedi-associated* bacteremia and cellulitis in immunocompromised patients. Ann. Intern. Med. 121, 90–93.
Kiehlbauch, J.A., Brenner, D.J., Cameron, D.N., Steigerwalt, A.G., Makowski, J.M., Baker, C.N., et al., 1995. Genotypic and phenotypic characterization of *H. cinaedi* and *H. fennelliae* strains isolated from humans and animals. J. Clin. Microbiol. 22, 2940–2947.
Kimura, R., Hayashi, Y., Takeuchi, T., 2004. *Pasteurella multocida* septicemia caused by close contact with a domestic cat: case report and literature review. J. Infect. Chemother. 10, 250–252.
Koehler, J.E., Glaser, C.A., Tappero, J.W., 1994. *Rochalimaea henselae* infection: new zoonosis with the domestic cat as reservoir. J. Am. Med. Assoc. 271, 531–535.
Kopecny, L., Bosward, K.L., Shapiro, A., Norris, J.M., 2013. Investigating *Coxiella burnetii* infection in a breeding cattery at the centre of a Q fever outbreak. J. Feline Med. Surg. 15, 1037–1045.
Kornegay, R.W., Giddens Jr., W.E., Van Hoosier Jr., J.L., Morton, W.R., 1985. Subacute nonsuppurative hepatitis associated with hepatitis B virus infection in two cynomolgus monkeys. Lab. Anim. Sci. 35, 400–404.
Kraemer, A., Hein, J., Heusinger, A., Mueller, R.S., 2013. Clinical signs, therapy and zoonotic risk of pet guinea pigs with dermatophytosis. Mycoses 56, 168–172.
Kristensen, K.H., Lautrop, H., 1962. A family epidemic caused by the whooping cough bacillus *Bordetella bronchiseptica* (Danish). Ugeskr. Laeger 124, 303–308.
Krug, P.W., Schinazi, R.F., Hilliard, J.K., 2010. Inhibition of B Virus (*Macacine herpesvirus* 1) by conventional and experimental antiviral compounds. Antimicrob. Agents Chemother. 54, 452–459.
Krusell A, Comer JA and Sexton DJ. Rickettsialpox in North Carolina: A Case Report. Emerg Infect Dis. [serial on the Internet]. 2002 Jul. Available from: <http://wwwnc.cdc.gov/eid/article/8/7/01-0501>.
Ksiazek, T.G., West, C.P., Rollin, P.E., Jahrling, P.B., Peters, C.J., 1999. ELISA for the detection of antibodies to Ebola viruses. J. Infect. Dis. 179, S192–S198.
Kuo, C.-C., Stephens, R., 2010. Phylum XXIV. Chlamydiae Garrity and Holt 2001. In: Krieg, N., Staley, J., Brown, D. (Eds.), Bergey's Manual® of Systematic Bacteriology. Springer, New York, pp. 843–877.
Kupper, J.L., Casey, H.W., Johnson, D.K., 1970. Experimental Yaba and benign epidermal monkeypox in rhesus monkeys. Lab. Anim. Care 20, 979–988.
Ladiges, W.C., DiGiacomo, R.F., Yamaguchi, R.A., 1982. Prevalence of *Toxoplasma gondii* antibodies and oocytes in pound source cats. J. Am. Vet. Med. Assoc. 180, 1334–1335.
Langley, J.M., Marrie, T.H., Covert, A., 1988. Poker player's pneumonia: an urban outbreak of Q fever following exposure to a parturient cat. N. Engl. J. Med. 319, 354–356.
Animal handlersLangley, R.L. (Ed.), 1999. Occupational Medicine: State of the Art Reviews. Hanley and Belfus, Philadelphia, PA.
Lavelle, J.P., Landas, S., Mitros, F.A., Conklin, J.L., 1994. Acute gastritis associated with spiral organisms from cats. Dig. Dis. Sci. 39, 744–750.
LeBoit, P.E., Berger, T.G., Egbert, B.M., Yen, T.S.B., Stoler, M.H., Bonfiglio, T.A., et al., 1988. Epithelioid haemangioma-like vascular proliferations in AIDS: manifestation of cat scratch disease bacillus infection? Lancet 1, 960–963.

LeDuc, J.W., 1987. Epidemiology of Hantaan and related viruses. Lab. Anim. Sci. 37, 413.
Lee, H.W., Johnson, K.M., 1982. Laboratory acquired infections with Hantaan virus, the etiologic agent of Korean hemorrhagic fever. J. Infect. Dis. 146, 645–651.
Leitman, T., Brooks, D., Moncada, J., Schachter, J., Dawson, D., Dean, D., 1998. Chronic follicular conjunctivitis associated with *Chlamydia psittaci* or *Chlamydia pneumoniae*. Clin. Infect. Dis. 26, 1335–1340.
Lemon, S.M., Binn, K.N., Marchwicki, R., Murphy, P.C., Ping, L.H., Jansen, R.W., et al., 1990. *In vivo* replication and reversal to wild type of a neutralization resistant antigenic variant of hepatitis a virus. J. Infect. Dis. 161, 7–13.
Leroy, E.M., Kumulungui, B., Pourrut, X., Rouquet, P., Hassanin, A., Yaba, P., et al., 2005. Fruit bats as reservoirs of Ebola virus. Nature 438, 575–576.
Levett, P.N., 2001. Leptospirosis. Clin. Microbiol. Rev. 14, 296–326.
Levine, J.E., Levy, M.G., Walker, R.L., Crittenden, S., 1988. Cryptosporidiosis in veterinary students. J. Am. Vet. Med. Assoc. 193, 1413–1414.
Levine, N.D., 1980. Nematode Parasites of Domestic Animals and of Man. Burgess Publishing Co., Minneapolis, MN.
Lhomme, S., Dubois, M., Abravanel, F., Top, S., Bertagnoli, S., Guerin, J.L., et al., 2013. Risk of zoonotic transmission of HEV from rabbits. J. Clin. Virol. 58, 357–362.
Ligon, B.L., 2004. Monkeypox: a review of the history and emergence in the Western hemisphere. Semin. Pediatr. Infect. Dis. 15, 280–287.
Lipman, N.S., 1996. Rat bite fevers. In: Schlossberg, D. (Ed.), Current Therapy of Infectious Disease. Mosby-Yearbook, Philadelphia, PA, pp. 451–455.
Lloyd, G., 2011. Marburg and Ebola viruses. In: Palmer, S.R., Soulsby, L., Torgerson, P.R., Brown, W.G.B. (Eds.), Oxford Textbook of Zoonoses: Biology, Clinical Practice, and Public Health Control. Oxford University Press, New York, pp. 353–368.
Locatelli, S., Peeters, M., 2012. Cross–species transmission of simian retroviruses: how and why they could lead to the emergence of new diseases in the human population. AIDS 26, 659–673.
Lorenz, H.J., Cornelie, J., Willems, H., Baljer, G., 1998. PCR detection of *Coxiella burnetii* from different clinical specimens, especially bovine milk, on the basis of DNA preparation with silica matrix. Appl. Environ. Microbiol. 64, 4234–4237.
Lucero, N.E., Corazza, R., Almuzara, M.N., Reynes, E., Escobar, G.I., Boeri, E., et al., 2010. Human *Brucella canis* outbreak linked to infection in dogs. Epidemiol. Infect. 138, 280–285.
Luzzi, G.A., Milne, L.W., Waitkins, S.A., 1987. Rat-bite acquired leptospirosis. J. Infect. 15, 57–60.
MacDonald, D.M., Holmes, E.C., Lewis, J.C., Simmonds, P., 2000. Detection of hepatitis B virus infection in wild-born chimpanzees (*Pan troglodytes verus*): phylogenetic relationships with human and other primate genotypes. J. Virol. 74, 4253–4257.
Maclachlan, N.J., Dubovi, E.J., Fenner, F., 2011a. Bunyaviridae Fenner's Veterinary Virology. Elsevier Academic Press, Boston, MA, pp. 371–384.
Maclachlan, N.J., Dubovi, E.J., Fenner, F., 2011b. Arenaviridae Fenner's Veterinary Virology. Elsevier Academic Press, Boston, MA, pp. 385–392.
Maclachlan, N.J., Dubovi, E.J., Fenner, F., 2011c. Other Viruses: Hepeviruses, Hepadnaviridae, Deltaviruses, Anelloviruses, and Unclassified Viruses Fenner's Veterinary Virology. Elsevier Academic Press, Boston, MA, pp. 483–488.
Maclachlan, N.J., Dubovi, E.J., Fenner, F., 2011d. Paramyxoviridae Fenner's Veterinary Virology. Elsevier Academic Press, Boston, MA, pp. 299–324.
Macneil, A., Ströher, U., Farnon, E., Campbell, S., Cannon, D., Paddock, C.D., et al., 2012. Solid organ transplant-associated lymphocytic choriomeningitis, United States, 2011. Emerg. Infect. Dis. 18, 1256–1262.
Macy, D.W., 1999. Plague. In: Greene, C.E. (Ed.), Infectious Diseases of the Dog and Cat, second ed. Saunders, Philadelphia, PA.
Maetz, H.M., Sellers, C.A., Bailey, W.C., Hardy Jr., G.E., 1976. Lymphocytic choriomeningitis from pet hamster exposure: a local public health experience. Am. J. Public Health 66, 1082–1085.
Mak, P.W.Y., Jayawardena, S., Poon, L.L.M., 2012. The evolving threat of influenza viruses of animal origin and the challenges in developing appropriate diagnostics. Clin. Chem. 58, 1527–1533.
Margileth, A.W., Wear, D.J., Hadfield, T.L., Schlagel, C.J., Spigel, G.T., Muhlbauer, J.E., 1984. Cat-scratch disease. Bacteria in skin at the primary inoculation site. JAMA 252, 928–931.
Marini, R.P., Adkins, J.A., Fox, J.G., 1989. Proven or potential zoonotic diseases of ferrets. J. Am. Vet. Med. Assoc. 195, 990.
Markell, E.K., John, D.T., Krotoski, W.A., 1999. Medical Parasitology, eighth ed. Saunders, Philadelphia, PA.
Marrie, T.J., 1990. Epidemiology of Q fever. In: Marrie, T.J. (Ed.), Q Fever: The Disease. CRC Press, Boca Raton, FL, pp. 49–70.
Marrie, T.J., Williams, J.C., Schlech, W.F., Yates, L., 1986. Q fever pneumonia associated with exposure to wild rabbits. Lancet 1, 427–429.
Marsden-Haug, N., Bidol, S.A., Culpepper, W., Behravesh, C.B., Morris, J., Anderson, T.A., 2013. Multistate outbreak of human *Salmonella* typhimurium infections linked to contact with pet hedgehogs – United States, 2011–2013. MMWR 61, 73.
Martin, L.J., Fyfe, M., Doré, K., 2004. Increased burden of illness associated with antimicrobial-resistant *Salmonella enterica* serotype Typhimurium infections. J. Infect. Dis. 189, 377–384.
Mazurek, G.H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., Castro, K., 2010. Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection – United States, 2010. MMWR Recomm. Rep. 59, 1–25.
McEvoy, M.B., Noah, N.D., Pilsworth, R., 1987. Outbreak of fever caused by *Streptobacillus moniliformis*. Lancet 2, 1361–1363.
Mehedi, M., Groseth, A., Feldmann, H., Ebihara, H., 2011. Clinical aspects of Marburg hemorrhagic fever. Future Virol. 6, 1091–1106.
Meng, X.J., 2005. Hepatitis E virus: cross-species infection and zoonotic risk. Clin. Microbiol. Newsl. 27, 43–48.
Meng, X.J., 2010a. Recent advances in hepatitis E virus. J. Viral Hepat. 17, 153–161.
Meng, X.J., 2010b. Hepatitis E virus: animal reservoirs and zoonotic risk. Vet. Microbiol. 140, 256–265.
Meng, X.J., 2011. From barnyard to food table: the omnipresence of hepatitis E virus and risk for zoonotic infection and food safety. Virus Res. 161, 23–30.
Meng, X.J., Purcell, R.H., Halbur, P.G., Lehman, J.R., Webb, D.M., Tsareva, T.S., et al., 1997. A novel virus in swine is closely related to the human hepatitis E virus. Proc. Natl. Acad. Sci. USA 94, 9860–9865.
Mercer, A., Fleming, S., Robinson, A., Nettleton, P., Reid, H., 1997. Molecular genetic analyses of parapoxviruses pathogenic for humans. Arch. Virol. Suppl. 13, 25–34.
Metzkor-Cotter, E., Kletter, Y., Avidor, B., Varon, M., Golan, Y., Ephros, M., et al., 2003. Long-term serological analysis and clinical follow-up of patients with cat scratch disease. Clin. Infect. Dis. 37, 1149–1154.
Miranda, M.E., Ksiazek, T.G., Retuya, T.J., Khan, A.S., Sanchez, A., Fulhorst, C.F., et al., 1999. Epidemiology of Ebola (subtype Reston) in the Philippines, 1996. J. Infect. Dis. 179, S115–S119.
Molba, K., Baggesen, D.L., Aarestrup, F.M., Ebbesen, J.M., Engberg, J., Frydendahl, K., et al., 1999. An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype *typhimurium* DT104. N. Engl. J. Med. 341, 1420–1425.
Monath, T.P., Staples, J.E., 2011. Yellow fever. In: Palmer, S.R., Soulsby, L., Torgerson, P., Brown, D. (Eds.), Oxford Textbook of Zoonoses: Biology, Clinical Practice, and Public Health Control. Oxford University Press, New York, pp. 443–453.

Monis, P.T., Thompson, R.C., 2003. Cryptosporidium and Giardia-zoonoses: fact or fiction? Infect. Genet. Evol. 3, 233–244.
Montali, R.J., Ramsay, E.C., Stephensen, C.B., Worley, M., Davis, J.A., Holmes, K.V., 1989. A new transmissible viral hepatitis of marmosets and tamarins. J. Infect. Dis. 160, 759–765.
Montali, R.J., Scanga, C.A., Pernikoff, D., Wessner, D.R., Ward, R., Holmes, K.V., 1993. A common-source outbreak of callitrichid hepatitis in captive tamarins and marmosets. J. Infect. Dis. 167, 946–950.
Montali, R.J., Connolly, B.M., Armstrong, D.L., Scanga, C.A., Holmes, K.V., 1995. Pathology and immunohistochemistry of callitrichid hepatitis, an emerging disease of captive New World primates caused by lymphocytic choriomeningitis virus. Am. J. Pathol. 147, 1441–1449.
Morita, C., Tsuchiya, K., Ueno, H., Muramatsu, Y., Kojimahara, A., Suzuki, H., et al., 1996. Seroepidemiological survey of lymphocytic choriomeningitis virus in wild house mice in China with particular reference to their subspecies. Microbiol. Immunol. 40, 313–315.
Murphy, H.W., Miller, M., Ramer, J., Travis, D., Barbiers, R., Wolfe, N.D., et al., 2006. Implications of simian retroviruses for captive primate population management and the occupational safety of primate handlers. J. Zoo Wildl. Med. 37, 219–233.
Murray, S.M., Linial, M.L., 2006. Foamy virus infection in primates. J. Med. Primatol. 35, 225–235.
Mushatt, D.M., Hyslop, N.E., 1991. Neurologic aspects of North American zoonoses. Infect. Dis. North Am. 5, 703–731.
Myers, E.M., Ward, S.L., Myers, J.P., 2012. Life-threatening respiratory pasteurellosis associated with palliative pet care. Clin. Infect. Dis. 54, e55–e57.
Nasher, A.K., 1988. Zoonotic parasitic infections of the Arabian sacred baboon *Papio hamadryas arabicus*, Thomas in Asir Province, Saudi Arabia. Ann. Parasitol. Hum. Comp. 63, 448–454.
National Research Council, 1997. Occupational Health and Safety in the Care and Use of Research Animals. National Academies Press, Washington, DC, p. 154.
Nelson, J.D., Kusmiesz, H., Jackson, L.H., Woodman, E., 1980. Treatment of *Salmonella* gastroenteritis with ampicillin, amoxicillin, and placebo. Pediatrics 65, 1125–1130.
Newcomer, C.E., Anver, M.R., Simmons, J.L., Wilcke, B.W., Nace, G.W., 1982. Spontaneous and experimental infections of *Xenopus laevis* with *Chlamydia psittaci*. Lab. Anim. Sci. 32, 680–686.
Newcomer, C.E., Fox, J.G., 2007. Zoonoses and other human health hazards. In: Fox, J.G., Barthold, S., Davisson, M., Newcomer, C.E., Quimby, F.W., Smith, A. (Eds.), The Mouse in Biomedical Research: Diseases. Elsevier, Boston, MA, pp. 719–745.
Ng, V.L., Boggs, J.M., York, M.K., Golden, J.A., Hollander, H., Hadley, W.K., 1992. Recovery of *Bordetella bronchiseptica* from patients with AIDS. Clin. Infect. Dis. 15, 376–377.
Ng-Hublin, J.S., Combs, B., Mackenzie, B., Ryan, U., 2013. Human cryptosporidiosis diagnosed in Western Australia: a mixed infection with *Cryptosporidium meleagridis*, the *Cryptosporidium* mink genotype, and an unknown *Cryptosporidium* species. J. Clin. Microbiol. 51, 2463–2465.
Nicklas, W., Kraft, V., Meyer, B., 1993. Contamination of transplantable tumors, cell lines, and monoclonal antibodies with rodent viruses. Lab. Anim. Sci. 43, 296–300.
Niven, S.J.F., 1961. Subcutaneous "growths" in monkeys with Yaba pox virus. J. Pathol. Bacteriol. 81, 1–14.
Oehler, R.L., Velez, A.P., Mizrachi, M., Lamarche, J., Gompf, S., 2009. Bite-related and septic syndromes caused by cats and dogs. Lancet Infect. Dis. 9, 439–447.
Ordog, G.J., 1985. Rat bites: fifty cases. Ann. Emerg. Med. 14, 126.
Orihel, T.C., 1970. The helminth parasites of nonhuman primates and man. Lab. Anim. Care 20, 395–401.
Orlicek, S.L., Welch, D.F., Kuhls, T.L., 1993. Septicemia and meningitis caused by *Helicobacter cinaedi* in a neonate. J. Clin. Microbiol. 31, 569–571.
Paegle, R.D., Tweari, R.P., Bernhard, W.N., Peters, E., 1976. Microbial flora of the larynx, trachea, and large intestine of the rat after long-term inhalation of 100 percent oxygen. Anesthesiology 44, 287–290.
Palmer, A.E., 1987. *Herpesvirus simiae:* historical perspective. J. Med. Primatol. 16, 99–130.
Parker, S., Holliman, R.E., 1992. Toxoplasmosis and laboratory workers: a case control assessment of risk. Med. Lab. Sci. 49, 103–106.
Parker, S., Nuara, A., Buller, R.M.L., Schultz, D.A., 2007. Human monkeypox: an emerging zoonotic disease. Future Microbiol. 2, 17–34.
Pavia, A.T., Tauxe, R.V., 1991. Salmonellosis: nontyphoidal. In: Evans, A.S., Brachman, P.S. (Eds.), Bacterial Infections of Humans. Epidemiology and Control, second ed. Plenum Press, New York, pp. 573–592.
Pavio, N., Meng, X.J., Renou, C., 2010. Zoonotic hepatitis E: animal reservoirs and emerging risks. Vet. Res. 41, 46.
Perez-Osorio, C.E., Zavala-Velazquez, J.E., Arias Leon, J.J., Zavala-Castro, J.E., 2008. *Rickettsia felis* as emergent global threat for humans. Emerg. Infect. Dis. 14, 1019–1023.
Pier, G.B., Madin, S.H., 1976. *Streptococcus iniae* sp. nov., a beta-hemolytic streptoccus isolated from an Amazon freshwater dolphin, *Inia geoffrensis*. Int. J. Syst. Bacteriol. 26, 545–553.
Polt, S.S., Dismukes, W.E., Flint, A., Schaefer, J., 1982. Human brucellosis caused by *Brucella canis*: clinical features and immune response. Ann. Intern. Med. 97, 717–719.
Prag, J., Blom, J., Krogfelt, K.A., 2007. *Helicobacter canis* bacteraemia in a 7-month old child. FEMS Immun. Med. Microbiol. 50, 264–267.
Ravdin, J.L., 1995. Amebiasis. Clin. Infect. Dis. 20, 1453–1466.
Ravdin, J.I., 2000. Entamoeba histolytica. In: Mandell, G.L., Bennett, J.E., Dolin, R. (Eds.), Principles and Practice of Infectious Diseases. Churchill Livingstone, Philadelphia, PA, pp. 2798–2810.
Reese, N.C., Current, W.L., Ernst, J.V., Barley, W.S., 1982. Cryptosporidiosis of man and calf: a case report and results of experimental infections in mice and rats. Am. J. Trop. Med. Hyg. 31, 226–229.
Reid, H.W., Dagleish, M.P., 2011. Poxviruses. In: Palmer, S.R., Soulsby, L., Torgerson, P., Brown, D. (Eds.), Oxford Textbook of Zoonoses: Biology, Clinical Practice, and Public Health Control. Oxford University Press, New York, pp. 380–385.
Reimer, L.G., 1993. Q fever. Clin. Microbiol. Rev. 6, 193–198.
Rempe, B., Aloi, M., Iskyan, K., 2009. Evidence-based management of mammalian bite wouds. Pediatr. Emerg. Med. Pract. 6, 1–22.
Reynolds, M.G., Krebs, J.S., Comer, J.A., Sumner, J.W., Rushton, T.C., Lopez, C.E., et al., 2003. Flying squirrel-associated typhus, United States. Emerg. Infect. Dis. 9, 1341–1343.
Reynolds, M.G., Carroll, D.S., Karem, K.L., 2012. Factors affecting the likelihood of monkeypox's emergence and spread in the post-smallpox era. Curr. Opin. Virol. 2, 335–343.
Richter, C.P., Lehner, N.D.M., Henrickson, R.V., 1984. Primates. In: Fox, J.G., Cohen, B.J., Loew, F.M. (Eds.), Laboratory Animal Medicine. Academic Press, Orlando, FL, p. 298.
Rivera, W.L., Yason, J.A., Adao, D.E., 2010. Entamoeba histolytica and *E. dispar* infections in captive macaques (*Macaca fascicularis*) in the Philippines. Primates 51, 69–74.
Roberts, J.A., Lerche, N.W., Markowits, J.E., Maul, D.H., 1988. Epizootic measles at the CRPRC. Lab. Anim. Sci. 38, 492.
Roest, H.I., van Solt, C.B., Tilburg, J.J., Klaassen, C.H., Hovius, E.K., Roest, F.T., et al., 2013. Search for possible additional reservoirs for human Q fever, The Netherlands. Emerg. Infect. Dis. 19, 834–835.
Rosner, W.W., 1987. Bubonic plague. J. Am. Med. Assoc. 191, 406–409.
Roulis, E., Polkinghorne, A., Timms, P., 2013. *Chlamydia pneumoniae*: modern insights into an ancient pathogen. Trends Microbiol. 21, 120–128.

Rousseau, M.C., Saron, M.F., Brouqui, P., Boureade, A., 1997. Lymphocytic choriomeningitis in France: four case reports and a review of the literature. Eur. J. Epidemiol. 13, 817–823.

Rupp, M.E., 1992. *Streptobacillus moniliformis* endocarditis: case report and review. Clin. Infect. Dis. 14, 769–772.

Russell, R.G., Sarmiento, J.I., Fox, J.G., Panigrahi, P., 1990. Evidence of reinfection with multiple strains of *C. jejuni* and C. *coli* in *Macaca nemestrina* housed under hyperendemic conditions. Infect. Immun. 58, 2149.

Ryabchikova, E.I., Kolesnikova, L.V., Luchko, S.V., 1999. An analysis of features of pathogenesis in two animal models of Ebola virus infection. J. Infect. Dis. 179, S199–S202.

Sacks, J.J., Sinclair, L., Gilchrist, J., Lockwood, R., 2000. Breeds of dogs involved in fatal human attacks in the United States between 1979 and 1998. J. Am. Vet. Med. Assoc. 217, 836–840.

Sanger, J.G., Thiermann, A.B., 1988. Leptospirosis. J. Am. Vet. Med. Assoc. 193, 1250–1254.

Schafer, I.L., Miller, R., Strother, U., Knust, B., Nichol, S.T., Rollin, P.E., 2014. Notes from the field: a cluster of lymphocytic choriomeningitis virus infections transmitted through organ transplantation. MMWR 63, 249.

Schmaljohn, C., Hjelle, B., 1997. Hantaviruses: a global disease problem. Emerg. Infect. Dis. 3, 95–104.

Schou, S., Hansen, A.K., 2000. Marburg and Ebola virus infections in laboratory non-human primates: a literature review. Comp. Med. 50, 108–123.

Schweizer, M., Falcone, V., Gange, J., Turek, R., Neumann-Haefelin, D., 1997. Simian foamy virus isolated from an accidentally infected human individual. J. Virol. 71, 4821–4824.

Sejvar, J.J., Chowdary, Y., Schomogyi, M., Stevens, J., Patel, J., Karem, K., et al., 2004. Human monkeypox infection: a family cluster in the midwestern United States. J. Infect. Dis. 190, 1833–1840.

Sens, M.A., Brown, E.W., Wilson, L.R., Crocker, T.P., 1989. Fatal *Streptobacillus moniliformis* infection in a two month old infant. Am. J. Clin. Pathol. 91, 612–616.

Serikawa, T., Iwaki, S., Mori, M., Muraguchi, T., Yamada, J., 1989. Purification of *Brucella canis* cell wall antigen using immunosorbent columns and use of the antigen in enzyme-linked immunosorbent assay for specific diagnosis of canine brucellosis. J. Clin. Microbiol. 27, 837–842.

Shen, Z., Feng, Y., Fox, J.G., 1999. Co-infection with enteric *Helicobacter* spp. and *Campylobacter* spp. in cats. J. Clin. Micro. 39, 2166–2172.

Shevtsova, Z.V., Lapin, B.A., Doroshenko, N.V., Krilova, R.L., Korzaja, L.I., Lomovskaya, I.B., et al., 1988. Spontaneous and experimental hepatitis A in Old World monkeys. J. Med. Primatol. 17, 177–194.

Simmons, J.H., 2010. Herpesvirus infections of laboratory macaques. J. Immunotoxicol. 7, 102–113.

Smith, A.L., Singleton, G.R., Hansen, G.M., Shellam, G., 1993. A serologic survey for viruses and *Mycoplasma pulmonis* among wild house mice (*Mus domesticus*) in southeastern Australia. J. Wildl. Dis. 29, 219–229.

Smith, A.L., Black, D.H., Eberle, R., 1998. Molecular evidence for distinct genotypes of monkey B virus (*Herpesvirus simiae*) which are related to the macaque host species. J. Virol. 72, 9224–9232.

Smith, T.F., 1989. Chlamydia. In: Schmidt, N.J., Emmons, R.W. (Eds.), Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infections. American Public Health Association, Washington, DC, pp. 1335–1340.

Smythe, L.D., Smith, I.L., Smith, G.A., Dohnt, M.F., Symonds, M.L., Barnett, L.J., et al., 2002. A quantitative PCR (TaqMan) assay for pathogenic *Leptospira* spp. BMC Infect. Dis. 2, 13–19.

Soulsby, E.J.L., 1969. Helminths, Arthropods, and Protozoa of Domesticated Animals, sixth ed. Williams & Wilkins, Baltimore, MD.

Spilker, T., Liwienski, A.A., LiPuma, J.J., 2008. Identification of *Bordetella* spp. in respiratory speciments from individuals with cystic fibrosis. Clin. Microbiol. Infect. 14, 504–506.

Staat, M.A., Kruszon-Moran, D., McQuillan, G.M., Kaslow, R.A., 1996. A population-based serologic survey of *Helicobacter pylori* infection in children and adolescents in the United States. J. Infect. Dis. 174, 1120–1123.

Stephensen, C.B., Blount, S.R., Lanford, R.E., Holmes, K.V., Montali, R.J., Fleenor, M.E., et al., 1992. Prevalence of serum antibodies against lymphocytic choriomeningitis virus in selected populations from two U.S. cities. J. Med. Virol. 38, 27–31.

Stephensen, C.B., Park, J.Y., Blount, S.R., 1995. cDNA sequence analysis confirms that the etiologic agent of callitrichid hepatitis is lymphocytic choriomeningitis virus. J. Virol. 69, 1349–1352.

Stoenner, H.G., Maclean, D., 1958. Leptospirosis (ballum) contracted from Swiss albino mice. Arch. Intern. Med. 101, 706–710.

Stolte, M., Wellens, E., Bethke, B., Ritter, M., Eidt, H., 1994. *Helicobacter heilmannii* (formerly *Gastrospirillum hominis*) gastritis: an infection transmitted by animals? Scand. J. Gastroenterol. 29, 1061–1064.

Storz, J., 1971. Chlamydia and Chlamydia-Induced Diseases. Thomas, Springfield, IL.

Swanson, S., Snider, C., Braden, R., 2007. Multidrug-resistant *Salmonella enterica* serotype Typhimurium associated with pet rodents. NEJM 356, 21–28.

Swayne, D.E., King, D.J., 2003. Avian influenza and Newcastle disease. J. Am. Vet. Med. Assoc. 222, 1534–1540.

Swennes, A.G., Fox, J.G., 2014. Bacterial and Mycoplasmal Diseases. In: Fox, J.G., Marini, R.P. (Eds.), Biology and Diseases of the Ferret. Wiley-Blackwell, Ames, IA.

Switzer, W.M., Bhullar, V., Shanmugam, V., Cong, M.E., Parekh, B., Lerche, N.W., et al., 2004. Frequent simian foamy virus infection in persons occupationally exposed to nonhuman primates. J. Virol. 78, 2780–2789.

Tachibana, H., Yanagi, T., Akatsuka, A., Kobayashi, S., Kanbara, H., Tsutsumi, V., 2009. Isolation and characterization of a potentially virulent species *Entamoeba nuttalli* from captive Japanese macaques. Parasitology 136, 1169–1177.

Takeda, N., Kikuchi, K., Asano, R., Harada, T., Totsuka, K., Sumiyoshi, T., et al., 2001. Recurrent septicemia caused by *Streptococcus canis* after a dog bite. Scand. J. Infect. Dis. 33, 927–928.

Talan, D.A., Citron, D.M., Abrahamian, F.M., Moran, G.R., Goldstein, E.J.C., 1999. Bacteriologic analysis of infected dog and cat bites. N. Engl. J. Med. 340, 85–92.

Tauxe, R.V., 1999. *Salmonella enteritidis* and *Salmonella typhimurium* DT104: successful subtypes in the modern world. In: Scheld, W.M., Craig, W.A., Hughes, J.M. (Eds.), Emerging Infections 3. ASM Press, Washington, DC, pp. 37–52.

Taylor, J.P., Istre, G.R., McChesney, T.C., Satalowich, F.T., Parker, R.L., McFarland, L.M., 1991. Epidemiologic characteristics of human tularemia in the southwest-central states, 1981–1987. Am. J. Epidemiol. 133, 1032–1038.

Teare, J.A., Loomis, M.R., 1982. Epizootic of balantidiasis in lowland gorillas. J. Am. Vet. Med. Assoc. 181, 1345–1347.

Tenkate, T.D., Stafford, R.J., 2001. Risk factors for *Campylobacter* infections in infants and young children: a matched case-control study. Epidem. Infect. 127, 399–404.

Teutsch, S.M., Juranek, D.D., Sulzer, A., Dubey, J.P., Sikes, R.K., 1979. Epidemic toxoplasmosis associated with infected cats. N. Engl. J. Med. 300, 695–699.

Thi, E.P., Mire, C.E., Ursic-Bedoya, R., Geisbert, J.B., Lee, A.C.H., Agans, K.N., et al., 2014. Marburg virus infection in nonhuman primates: therapeutic treatment by lipid-encapsulated siRNA. Sci. Transl. Med. 6, 250ra116.

Thiermann, A.B., 1977. Incidence of leptospirosis in the Detroit rat population. Am. J. Trop. Med. Hyg. 26, 970–974.

Thomas, N., Brook, I., 2011. Animal bite-associated infections: microbiology and treatment. Expert Rev. Anti. Infect. Ther. 9, 215–226.

Thompson, R.C., Smith, A., 2011. Zoonotic enteric protozoa. Vet. Parasitol. 182, 70–78.
Tissot-Dupont, H., Torres, S., Nezri, M., Raoult, D., 1999. Hyperendemic focus of Q fever related to sheep and wind. Am. J. Epidemiol. 150, 67–74.
To, H., Sakai, R., Shirota, K., Kano, C., Abe, S., Sugimoto, T., et al., 1998. Coxiellosis in domestic and wild birds from Japan. J. Wildl. Dis. 34, 310–316.
Torres-Perez, F., Wilson, L., Collinge, S.K., Harmon, H., Ray, C., Medina, R.A., et al., 2010. Sin Nombre virus infection in field workers, Colorado, USA. Emerg. Infect. Dis. 16, 308–310.
Torten, M., 1979. Leptospirosis. In: Steele, J.H. (Ed.), CRC Handbook Series in Zoonoses, 1. CRC Press, Cleveland, OH, pp. 363–421.
Towner, J.S., Pourrut, X., Albariño, C.G., Nkogue, C.N., Bird, B.H., Grard, G., et al., 2007. Marburg virus infection detected in a common African bat. PLoS One 2, e764.
Tsai, T.F., 1987. Hemorrhagic fever with renal syndrome: mode of transmission to humans. Lab. Anim. Sci. 37, 428.
Tsai, T.F., Bauer, S.P., Sasso, D.R., Whitfield, S.G., McCormick, J.B., Caraway, T.C., et al., 1985. Serological and virological evidence of a hantaan virus-related enzootic in the United States. J. Infect. Dis. 152, 126–136.
Turk, M.L., Cacioppo, L.D., Ge, Z., Shen, Z., Whary, M.T., Parry, N., et al., 2012. Persistent *Helicobacter pullorum* colonization in C57BL/6NTac mice: a new mouse model for an emerging zoonosis. J. Med. Microbiol. 61, 720–728.
van der Waaij, D., 1968. The persistent absence of Enterobacteriaceae from the intestinal flora of mice following antibiotic treatment. J. Infect. Dis. 118, 32–38.
van der Waaij, D., Berghuis-de Vries, J., Lekkerkerk-van der Wees, J., 1971. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. J. Hyg. (Lond.) 69, 405–411.
Varma, J.K., Molbak, K., Barrett, T.J., Beebe, J.L., Jones, T.F., Rabatsky-Ehr, T., et al., 2005. Antimicrobial-resistant nontyphoidal *Salmonella* is associated with excess bloodstream infections and hospitalizations. J. Infect. Dis. 191, 554–561.
Vinetz, J.M., 2003. A mountain out of a molehill: do we treat acute leptospirosis, and if so, with what? Clin. Infect. Dis. 36, 1514–1515.
Visvesvar, G.S., Stehr-Green, J.K., 1990. Epidemiology of free-living amoebae infections. J. Protozool. 37, 25S–33S.
Vitral, C.L., Yoshida, C.F., Gaspar, A.M., 1998. The use of non-human primates as animal models for the study of hepatitis viruses. Braz. J. Med. Biol. Res. 31, 1035–1048.
Wachtman, L., Mansfield, K., 2012. Viral diseases of nonhuman primates. In: Abee, C.R., Mansfield, K., Tardif, S.D., Morris, T. (Eds.), Nonhuman Primates in Biomedical Research: Biology and Management. Elsevier, pp. 1–104.
Wear, D.J., Margileth, A.M., Hadfield, T.L., Fischer, G.W., Schlagel, C.J., King, F.M., 1983. Cat stratch disease: a bacterial infection. Science 221, 1403–1405.
Weber, D.J., Hansen, A.R., 1991. Infections resulting from animal bites In: Weinber, A., Weber, D. (Eds.), Infectious Disease Clinics of North America, vol. 5. Saunders, Philadelphia, PA, pp. 663–677.
Webster, R.G., 1997. Influenza virus: transmission between species and relevance to the emergence of the next human pandemic. Arch. Virol. 13, 105–113.
Weigler, B.J., 1992. Biology of B virus in macaque and human hosts: a review. Clin. Infect. Dis. 14, 555–567.
Weigler, B.I., Hird, D.W., Hilliard, J.K., Lerche, N.W., Roberts, J.A., Scott, L.M., 1993. Epidemiology of *cercopithecine herpesvirus* 1 (B virus) infection and shedding in a large breeding cohort of rhesus macaques. J. Infect. Dis. 167, 257–267.
Weigler, B.J., Scinicareillo, F., Hilliard, J., 1995. Risk of venereal B virus (cercopithecine herpes virus 1) transmission on rhesus monkeys using molecular epidemiology. J. Infect. Dis. 171, 1139–1143.
Weigler, B.J., Di Giacomo, R.F., Alexander, S., 2005. A national survey of laboratory animal workers concerning occupational risks for zoonotic diseases. Comp. Med. 55, 183–191.
Weinstein, M.R., Litt, M., Kertesz, D.A., Wyper, P., Rose, D., Coulter, M., et al., 1997. Invasive infections due to a fish pathogen, *Streptococcus iniae*. N. Engl. J. Med. 337, 589–594.
Weir, E.C., Bhatt, P.N., Jacoby, R.O., Hilliard, J.K., Morgenstern, S., 1993. Infrequent shedding and transmission of *Herpesvirus simiae* from seropositive macaques. Lab. Anim. Sci. 43, 541–544.
Weisbroth, S.H., 1979. Bacterial and mycotic diseases In: Baker, H.J. Lindsey, J.R. Weisbroth, S.H. (Eds.), The Laboratory Rat, vol. 1. Academic Press, New York, pp. 194–230.
Wells, D.L., Lipper, S.L., Hilliard, J., 1989. *Herpesvirus simiae* contamination of primary rhesus monkey kidney cell cultures: CDC recommendations to minimize risks to laboratory personnel. Diagn. Microbiol. Infect. Dis. 12, 333–335.
Wentworth, D.E., McGregor, M.W., Macklin, M.D., Neumann, V., Hinshaw, V.S., 1997. Transmission of swine influenza virus to humans after exposure to experimentally infected pigs. J. Infect. Dis. 175, 7–15.
Whary, M.T., Fox, J.G., 2006. Detection, eradication and research implications of *Helicobacter* infections in laboratory rodents. Lab. Anim. 35, 25–36.
Wilkins, E.G.L., Millar, J.G.B., Cockcroft, P.M., Okubadejo, O.A., 1988. Rat-bite fever in a gerbil breeder. J. Infect. 16, 177.
Williams, S.G., Sacci Jr., J.B., Schreifer, M.E., Andersen, E.M., Fujioka, K.K., Sorvillo, F.J., et al., 1992. Typhus and typhus-like rickettsiae associated with opossums and their fleas in Los Angeles County, California. J. Clin. Microbiol. 30, 1758–1762.
Willy, E.M., Woodward, R.A., Thorton, V.B., Wolff, A.V., Flynn, B.M., Heath, J.L., et al., 1999. Management of a measles outbreak among Old World nonhuman primates. Lab. Anim. Sci. 49, 42–48.
Wilson, B.A., Ho, M., 2013. *Pasteurella multocida:* from Zoonosis to cellular microbiology. Clin. Microbiol. Rev. 26, 631–655.
Wilson, C.A., Wong, S., Muller, J., Davidson, C.E., Rose, T.M., Burd, P., 1998. Type C retrovirus released from porcine primary peripheral blood mononuclear cells infects human cells. J. Virol. 72, 3082–3087.
Winkler, W.G., Fashinell, T.R., Leffingwell, L., Howard, P., Conomy, P., 1973. Airborne rabies transmission in a laboratory worker. J. Am. Med. Assoc. 226, 1219–1221.
Wolf, R.H., Gibson, S.V., Watson, E.A., Baskin, G.B., 1988. Multidrug chemotherapy of tuberculosis in rhesus monkeys. Lab. Anim. Sci. 38, 25–33.
Wolfrom, E., Chene, G., Boisseau, H., Beylot, C., Geniaux, M., Taieb, A., 1995. Chronic urticaria and *Toxocara canis* [letter]. Lancet 345, 196.
Woodward, D.L., Khakhria, R., Johnson, W.M., 1997. Human salmonellosis associated with exotic pets. J. Clin. Microbiol. 35, 2786–2790.
Woolfrey, B.F., Moody, J.A., 1991. Human infections associated with *Bordetella bronchiseptica*. Clin. Microbiol. Rev. 4, 243–255.
Wright, W.H., 1985. Laboratory-acquired toxoplasmosis. Am. J. Clin. Pathol. 28, 1.
Wyers, M., Formenty, P., Cherel, Y., Guigand, L., Fernandez, B., Boesch, C., et al., 1999. Histopathological and immunohistochemical studies of lesions associated with Ebola virus in a naturally infected chimpanzee. J. Infect. Dis. 179, S54–S59.
Yanase, T., Muramatsu, Y., Inouye, I., Okabayashi, T., Ueno, H., Morita, C., 1998. Detection of *Coxiella burnetii* from dust in a barn housing dairy cattle. Microbiol. Immunol. 42, 51–53.
Yoder, J.S., Gargano, J.W., Wallace, R.M., Beach, M.J., 2012. Giardiasis surveillance – United States, 2009–2010. MMWR Surveill. Summ. 61, 13–23.
Yunker, C.E., 1964. Infections of laboratory animals potentially dangerous to man: ectoparasites and other arthropods, with emphasis on mites. Lab. Anim. Care 14, 455–465.

Zangwill, K.M., Hamilton, D.H., Perkins, B.A., Regnery, R.L., Plikaytis, B.D., Hadler, J., et al., 1993. Cat scratch disease in connecticut: epidemiology, risk factors, and evaluation of a new diagnostic test. N. Engl. J. Med. 329, 8–13.

Zeier, M., Handermann, M., Bahr, U., Rensch, B., Müller, S., Kehm, R., et al., 2005. New ecological aspects of hantavirus infection: a change of a paradigm and a challenge of prevention – a review. Virus Genes 30, 157–180.

Zhao, K., He, W., Gao, W., Lu, H., Han, T., Li, J., et al., 2011. Orf virus DNA vaccines expressing ORFV 011 and ORFV 059 chimeric protein enhances immunogenicity. Virol. J. 8, 562.

Zhou, X., de Man, R.A., de Knegt, R.J., Metselaar, H.J., Peppelenbosch, M.P., Pan, Q., 2013. Epidemiology and management of chronic hepatitis E infection in solid organ transplantation: a comprehensive literature review. Rev. Med. Virol. 23, 295–304.