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Emerging issues in occupationally relevant zoonoses

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Diseases that are transmitted from animals to humans are known as zoonoses. Humans can contract such diseases directly from animals, as in the case of rabies. They also can contract zoonoses after environmental contamination; this is the case with leptospirosis (Weil's disease), which results from infected urine-contaminated soil or water. Vectors also can transmit zoonoses to humans, as is the case with typhus.

Zoonoses not only cause human disease; they also play a critical role in the development of new human diseases [1]. Some of these diseases remain zoonotic, some develop the ability to be transferred between humans, and others specifically adapt to and persist within human populations. Bubonic plague, for example, persists in animal reservoirs but can cause human epidemics with human-to-human transmission. AIDS is a dramatic example in which an animal virus (simian immunodeficiency virus [SIV]) persists through infection in humans.

Workers are at risk when their occupation exposes them to zoonotic agents. The past decade has seen tremendous changes in the number of known zoonotic agents and the geographic range of some zoonoses. Each of these situations confers new issues for workers. This article examines some zoonotic agents that have been recently introduced into the United States, zoonotic agents diagnosed with increasing frequency in the Americas, newly identified zoonotic agents, and the zoonotic transmission of influenza virus. I intend to provide important examples of these situations and their impact on workers, but not to include all zoonotic agents present in each category. Each situation has important implications for worker protection.

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Zoonotic agents recently introduced into North America

Two important zoonotic diseases have been introduced into North America in the past 5 years. These are the arbovirus, West Nile virus (WNV) and the protozoal parasite, *Leishmania donovani*. Both are usually transmitted by insect or arthropod vectors.

WNV has been reviewed recently [2–4]. It first was recognized in the United States in 1999 as the cause of death of humans and birds in New York [5]. By July 30, 2002, WNV had been detected in 31 states [6].

In some North American birds, particularly crows, WNV produces high virus titers and is fatal. Birds can serve as reservoirs for WNV and mosquitoes feeding on these birds ingest large numbers of virions. Recent studies also suggest that infected crows can transmit the disease directly to uninfected crows [7]. Other recent studies confirm the recovery of West Nile virus from cloacal and oral swabs of dead jays and crows [8]. The role of direct transmission in the rapid spread of the virus within North American avian populations is not known.

Humans and horses are incidental hosts. They become infected with WNV after being bitten by an infected mosquito. Viral numbers are low in horses, which do not appear to play a significant role in disease transmission [9,10]. Asymptomatic infections are common in both horses and humans, but some individuals develop clinical disease that can be fatal [3,11]. In humans, increasing age confers increased risk of serious or fatal disease [12–14].

As WNV becomes established in the United States, several occupational issues are emerging. First, in areas with WNV and mosquito vectors, outdoor occupations confer an occupational risk for WNV. Second, some agricultural activities may confer additional risk. For example, domestic geese are highly susceptible to WNV [12,15]. In the 1999 to 2000 WNV outbreak in Israel, people working closely with sick geese had a WNV seroprevalence rate of 86%, which is much higher than that of the general population or those living in the path of avian migrations [12]. In an experimental study involving four WNV inoculated goslings and two uninoculated in-contact goslings, three of the four inoculated geese had WNV present in oral swabs and one of the in-contact goslings developed a transient viremia [15]. These studies strongly suggest that those working directly with WNV-infected birds have an increased risk of acquiring WNV. The potential role of direct transmission of WNV between birds and from birds to humans has been incompletely investigated. The potential role of occupational exposures to agents that affect WNV virulence also is incompletely investigated. For example, recent experiments demonstrate that mice exposed to the inhalation anesthetics halothane and nitrous oxide have increased mortality and neuroinvasion from an attenuated strain of WNV [16]. Thus, a number of occupational, demographic, and social factors may influence WNV infection rate and severity in workers in the United States.

L donovani is a very different disease from WNV. Like WNV, however, *L donovani* is a well-described cause of human zoonotic disease in many other countries that is newly established in parts of the United States The disease

affects several different species including humans and dogs. Both humans and animals can serve as reservoirs. The disease is caused by a dimorphic protozoan parasite and the described vectors are sand flies which are not found in the northeastern United States. In mammals, *L donovani* lives in the lysosomes of macrophages. In the sand fly, *L donovani* is extracellular and principally localized within the midgut where it replicates [17] The disease caused by *Leishmania* spp is known as leishmaniasis [18]. Three different clinical presentations are seen in both dogs and humans. These are cutaneous, mucosal, and visceral leishmaniasis. The most serious form is visceral leishmaniasis and, worldwide, about 500,000 cases of visceral leishmaniasis occur each year [19]. Leishmaniasis recently has been reviewed [18,19].

In 2000, several cases of leishmaniasis were recognized in foxhound dogs in the United States. One foxhound kennel in New York had a 36% prevalence of *L donovani* infection detected by polymerase chain reaction [20]. Because the original cases were described in foxhounds used for fox hunting, direct transmission has been proposed as a potential transmission mechanism in the northeastern United States [21]. The recent description of cases in other parts of the country, however, has lead others to suggest the possibility of a new vector functioning within this country [20]. The subspecies causing the canine cases is *L donovani infantum* [20], which previously had a geographic distribution principally involving South America and the Mediterranean region [22]. No acquired human cases in the United States have yet been described in association with the canine outbreak. Because United States vectors are not identified, it is difficult to predict occupations at increased risk.

Zoonotic agents diagnosed with increasing frequency in the Americas

Some nematode parasites of domestic and wild animals have larval forms that migrate through the tissues of their hosts. Tissues may be damaged directly during larval migration and indirectly from inflammation directed against the parasite. The conditions produced by nematode larval migration are named for the damaged tissues and include cutaneous larval migrans, visceral larval migrans, neural larval migrans, and ocular larval migrans [23]. Larval migrans can occur in animals as well as humans [24]. In humans, the condition can be caused by zoonotic spread of nematode parasites common in domestic and wild animals [23,25]. Zoonotic nematode parasites that commonly produce human disease include the roundworms of dogs and cats (*Toxocara canis* and *Toxocara cati*), hookworms of dogs and cats (*Ancylostoma brasilense* and *Ancylostoma caninum*), and the roundworm of raccoons (*Baylisascaris procyonis*). Early worming of puppies and kittens can reduce environmental contamination by parasite eggs markedly [25]. Obviously, worming wild raccoons is problematic. Zoonotic larval migrans recently have been reviewed [23,25,26].

As human populations expand into areas occupied by wildlife, some established animal diseases have crossed the species barrier and now cause human

disease. The raccoon adapts particularly well to human presence [26]. Raccoons are frequently infected with their common roundworm, *B procyonis* [27]. In addition, *B procyonis* eggs remain viable in the environment for years, and the larval stage of *B procyonis* migrates aggressively in tissue. *B procyonis* larvae are also larger than most nematode larvae. The heavy shedding of *B procyonis* eggs in raccoon feces, as well as the large, aggressively migrating larval stage, can result in severe tissue damage in affected humans. Children are at the greatest risk. During play, children can transfer large numbers of *B procyonis* eggs into their mouths. The severity of the resulting infection generally is increased when more eggs are ingested and when larval migration involves the eye or the brain. Adult human activities are less likely to cause transfer of *B procyonis* eggs into the mouth, but adults are susceptible to disease when this occurs.

B procyonis has been recognized as a cause of larval migrans for nearly 20 years [28,29]. In the past decade, the frequency of larval migrans caused by *B procyonis* has increased so that 7 of the 11 cases reported up until 1999 were reported from 1992 to 1999 [26]. An additional 4 cases were reported in 2000 and 2001 [30–32]. Emerging issues regarding larval migrans include the recent discovery that dogs can harbor patent infections with *B procyonis* [33]. Thus, *B procyonis* larval migrans can occur by direct contamination of the human environment with raccoon feces or indirectly through dogs that bring patent *B procyonis* infections home with them.

Larval migrans generally is not an occupational disease. For example, vacation travelers can be at increased risk. Some workers do have increased risk, however. For example, a recent study revealed that 27% of a group of Austrian veterinarians had antibodies to *Toxocara canis/cati*, a 20 fold higher prevelance than seen in the general Austrian population [34]. Potential occupational exposures to *B procyonis* were recognized more than a decade ago when Kazacos and Boyce suggested an increased risk for wildlife rehabilitators [35]. As suburban and rural life increase in popularity with small businesses moving to these locations to support residents, and as raccoons adjust to populated areas, increased cases of occupational and avocational larval migrans are predictable. This form of larval migrans increasingly is reported, and it is a potential cause of occupational outbreaks for any work involving potential ingestion of material contaminated by raccoon feces. Examples of those with potential risk include wildlife veterinarians, their technicians, and those working in home construction in rural areas frequented by raccoons.

Lyme disease is another disease that is associated with increased outdoor activity and increased habitation of areas occupied by wildlife. Lyme disease was first recognized in North America in the mid-1970s [36]. Subsequently, ticks were implicated in its transmission [37,38]. Lyme disease is now known to be caused by the tick-transmitted infection of the bacterial spirochete *Borrelia burgdorferi* [37,39]. It is currently the most frequently diagnosed vector-borne disease in the United States [40]. The specific spirochete associated with disease in the United States is *B burgdorferi* senso stricto, which is part of a larger group of organisms classified as *B burgdorferi* senso lato complex [41]. In Eurasia, Lyme borreliosis

can be caused by three separate members of the *B burgdorferi* senso lato complex: *B burgdorferi* senso stricto, *Borrelia afzelii,* and *Borrelia garinii* [42–44]. Most species of *B burgdorferi* senso lato complex are not known to cause human disease, however [42]. Recently described North American members of this complex include *Borrelia andersonii* and *Borrelia bissettii* [43,45].

In one of the important North American reservoirs of Lyme disease, the white-footed mouse, *Peromyscus leucopus*, *B burgdorferi* organisms infect multiple tissues and can circulate in the blood but cause little disease in the mouse [46–48]. Immature forms of *Ixodes* spp ticks become infected when they feed on reservoir species [47–49]. *Ixodes* spp ticks transmit *B burgdorferi* to humans and dogs when they subsequently feed on these species, often at a more mature stage of the tick life cycle. Transmission of *B burgdorferi* usually takes a day or more of feeding in the new host. Therefore, rapid removal of ticks can decrease Lyme disease transmission [50]. Clinical disease results when *B burgdorferi* migrate from the site of tick attachment through tissue [51].

Ixodes spp ticks, *B burgdorferi*, a suitable wildlife reservoir, and susceptible humans must all be present to produce human Lyme disease. A museum specimen study has demonstrated *B burgdorferi* DNA in *Peromyscus leucopus* mice collected in Massachusetts in 1894 [52]. This suggests that *B burgdorferi* has been endemic in the United States for more than a century, but other changes caused the human disease to be first recognized in this country in the mid-1970s. Reported cases of Lyme disease continue to increase. The number of cases reported in 1992 was 19 fold greater than in 1982 [53]. Cases continued to rise in the following decade and, by 1998, were 1.7 times the number reported in 1992 [40]. The number of reported cases had slightly increased by 2000 [54]. Genetic studies on *B burgdorferi* and its major United States vector, *Ixodes scapularis,* suggest that both of these species have recently expanded from a genetic bottleneck [55]. This spread may be associated with the expansion of areas in the northeastern United States suitable for *I scapularis*, the principal vector of that region [56,57]. Heavy deer populations, though not a major reservoir of *B burgdorferi*, contribute to large numbers of tick vectors and the spread of *Ixodes* spp ticks into new geographic areas [58]. Thus, as humans enter into areas occupied by *Ixodes* spp ticks, the geographic expansion of Lyme disease continues.

The white-footed deer mouse of the southwestern United States, *Peromyscus maniculatus*, is associated with another emerging zoonosis, Hantavirus pulmonary syndrome, which has recently been reviewed [59]. In 1993, a cluster of cases of acute respiratory disease with high case mortality appeared in the southwestern United States. The respiratory cases were caused by a hantavirus [60–62]. The new syndrome was called Hantavirus pulmonary syndrome, and the new hantavirus was named Sin Nombre virus. Clinically, the original cases presented as adult respiratory distress syndrome with pathologic features of interstitial pneumonia or diffuse alveolar damage [63]. The genomic sequence of Sin Nombre virus isolated from an autopsied patient had high sequence homology with the genomic sequence of Sin Nombre virus isolated from *P maniculatus* [64]. Subsequently, several additional related hantaviruses with different sigmo-

dontine rodent reservoirs were found also to cause Hantavirus pulmonary syndrome in man [65–67]. Rodent hantaviruses are distributed widely in the Americas and have numerous rodent reservoirs [68,69].

The original 1993 outbreak of Hantavirus pulmonary syndrome was associated with a weather change that produced more moisture, more abundant food for mice, and more *P maniculatus*. Similar climatic conditions recurred in 1998 and were associated with an increased number of human cases [70]. Several recent studies have identified factors associated with seropositivity for Sin Nombre virus in *P maniculatus*. *P maniculatus* living in peridomestic environments have a higher seroprevalence of the virus than mice living in sylvan environments [71]. Additional risk factors for mice are being adult, male, and having a scar [72]. *P maniculatus* appears well adapted to Sin Nombre virus, and experimental infection produces persistent virus without consistent histopathologic alterations [73].

The spectrum of viruses, reservoirs and clinical presentations associated with hantavirus pulmonary syndrome is evolving but exposure of humans to a sigmodontine rodent reservoir remains a common feature [59]. Sigmodontine rodents are found only in the New World and include rats and mice that are widespread in the Americas. Although hantaviruses are found in Europe and Asia, the Old World hantaviruses are carried by different rodents and tend to cause hemorrhagic diseases with renal manifestations [74]. Recent phylogenetic studies suggest that hantaviruses genetic relationships are determined by the host species [75]. Since the hantaviruses and their natural rodent hosts have apparently coevolved, the persistent viral infection and carrier status of these rodents is not surprising. However, as incidental hosts of the hantaviruses, humans can develop severe and fatal disease when infected.

Recommendations recently have been developed for reducing the risk of Hantavirus pulmonary syndrome [76]. In terms of occupational risk, an increased risk is conferred by any job involving handling of wild sigmodontine rodents or working in an indoor rodent-infested environment. Examples of specific occupations at increased risk include pest-control workers, building inspectors, agricultural workers, domestic workers, and mammalogists [76].

Emerging issues in regards to New World hantaviral infections are an expanding spectrum of clinical presentations seen with hantaviral infections [66,77]. In addition, the number of South American cases of Hantaviral pulmonary syndrome is rapidly increasing [78]. Consistent with the coevolution of hantaviruses and rodents, as the geographic distribution of cases increases, so do the number of identifed hantaviruses that cause Hantaviral pulmonary syndrome [68,79].

Newly identified occupational zoonotic agents

The emergence of new zoonotic agents recently has been reviewed [80]. Three newly identified paramyxoviruses—Hendra virus, Menangle virus, and Nipah virus—were first identified because of simultaneous morbidity or mortality in

animals and humans working with those animals. Hendra and Nipah viruses both caused human deaths, whereas Menangle virus caused influenza-like illness in swine workers. Each of these related paramyxoviruses originated in Old World fruit bats (*Pteropus* spp) as did another emerging zoonotic virus, Australian bat lyssavirus [81,82]. These zoonotic viruses were first identified in the past decade in Southeast Asia and Australia, and the emergence of new viral diseases in Southeast Asia and the Western Pacific recently has been reviewed [83]. Emerging paramyxoviruses as well as Hendra and Nipah also have been reviewed [84,85].

In Queensland, Australia, a pregnant mare became ill and died from a severe respiratory infection in 1994. Two weeks later, the trainer and a stable hand who cared for her and additional horses became ill. The trainer and 14 horses died. This was a systemic viral infection with pulmonary changes characterized by necrotizing alveolitis, inclusion bodies, and syncytia [86]. The etiologic agent was identical in the trainer and horses and was identified as a previously undescribed member of the virus family Paramyxoviridae [87]. Experimentally, the etiologic paramyxovirus could infect horses, cats, guinea pigs, and fruit bats [87–89]. The new virus, Hendra virus, originally was described as a morbillivirus but is now believed to be the first recognized member of a new genus within the subfamily Paramyxovirinae [90].

Another case of Hendra virus infection was contracted by a worker at another horse farm within a month of the first described cases and resulted in the death of that patient from encephalitis in 1995 [91]. As with the first case, this patient had contact with a dying pregnant mare. This patient assisted in care and necropsy of two dying horses. By comparing the wildlife species present at both affected farms, Young et al hypothesized that fruit bats were a potential wildlife reservoir and documented seropositivity in several fruit bats of the genus *Pteropus* [92]. Hendra virus subsequently was isolated from uterine fluid and fetal tissues of pregnant *Pteropus* spp fruit bats [93]. Experimentally infected fruit bats did not develop clinical disease, but some fruit bats had foci of vascular lesions including fibrinoid degeneration in the vasculature, lymphocytic vasculitis, and lymphocytic perivasculitis [88,89]. Thus, fruit bats appear well adapted to Hendra virus. Hendra virus, however, can cause severe disease when it is transmitted to a diverse group of other species including humans, horses, cats, and guinea pigs.

While fruit bats were being examined as a potential reservoir for Hendra virus, a lyssavirus closely related to the rabies virus was identified as a cause of encephalitis in Australian fruit bats and also produced neurologic signs in some mice exposed by intracerebral inoculation [94]. Later in 1996, Australian bat lyssavirus produced fatal encephalitis in an animal caretaker who was exposed when scratched by fruit bats [82]. A second case of Australian bat lyssavirus caused the 1998 death of a woman bitten by a yellow-bellied sheathtail bat in 1996 [81]. The Australian bat lyssavirus was a separate genotype from classical rabies virus but with antigenic similarities [95]. These cases confirmed that a rabies-like zoonosis was endemic in Australia.

In 1997, a paramyxovirus named Menangle virus was isolated from stillborn pigs with congenital malformations in a swine breeding and production facility in

Australia [96]. A total of 2 out of 251 exposed workers were seropositive and were apparently previously infected by the virus. Both of these workers had developed a flu-like condition with a rash after heavy exposure to affected stillborn pigs [97]. Fruit bats near the affected swine operation frequently were seropositive for Menangle virus and were the apparent reservoir. The disease was eliminated from the pigs by the use of serologic testing and husbandry practices that restricted naive pigs from exposure to actively infected pigs [98].

Lessons learned from the previous bat-transmitted virus were used rapidly in an outbreak of severe encephalitis in Malaysia that lasted from the fall of 1998 until the spring of 1999. The encephalitis was frequently fatal and principally affected adult men occupationally exposed to pigs [99]. The etiologic paramyxovirus previously was undescribed, closely related to Hendra virus, but transmitted from pigs to humans [100,101]. At least 265 cases of encephalitis cases occurred with an initial fatality rate of 40% [102]. More than 20% of the Nipah infection survivors had residual neurologic deficits [103]. In addition, an estimated 7.5% of the initial encephalitis survivors and 3.4% of Nipah-infected individuals without initial encephalitis developed encephalitis in the 2 years after the initial outbreak. The late-onset and recurrent cases were associated with an 18% mortality rate and appeared to result from persistent Nipah virus [104]. For confirmed cases, 86% had direct contact with pigs and 64% had contact with pigs that appeared ill [105]. Approximately 1.1 million pigs were destroyed in controlling the outbreak [106]. Nipah virus infections also occurred in March 1999 in workers in a Singapore abbattoir that slaughtered Malaysian pigs [107]. In humans, Nipah virus infections usually presented as encephalitis. In autopsy cases, Nipah virus was present in the brain in multiple cell types, including neurons and endothelial cells. Intracytoplasmic inclusions, intranuclear inclusions, and syncytia were seen in the central nervous system and were consistent with a paramyxovirus. Vasculitis was a characteristic finding in human cases and sometimes caused secondary vascular thrombosis [100,108]. In naturally infected pigs, Nipah virus caused pneumonia, meningitis, meningoencephalitis, or a combination of these conditions.

Nipah virus infection of pigs and cats (but not humans, horses, or dogs) localizes to the tracheobronchial epithelium [108]. The presence of viral antigen in tracheobronchial epithelium is consistent with the potential for the virus to be aerosolized from the respiratory tract of pigs and cats. Nipah virus can be cultured from the nose and oropharynx of experimentally infected pigs and from the oropharynx and urine of experimentally infected cats [109]. The potential for Nipah virus to produce infectious aerosols may well be responsible for the much more rapid spread of Nipah virus when compared with the closely related Hendra virus. Protective equipment, including masks, gloves, and boots, appears to greatly decrease the risk of contracting Nipah virus. Use of this protective equipment may have been responsible for the very low rate of infection (0.4% with no reported fatalities) in the military personnel responsible for the culling and disposal of pigs to control the Nipah virus outbreak in Malaysia [110].

Seropositivity for Nipah virus was demonstrated in 5 of 14 species of Malaysian bats, with the highest prevalence in species of flying foxes, which

are types of fruit bats. *Pteropus hypomelanus* (island flying foxes) and *Pteropus vampyrus* (Malaysian flying foxes) had seroprevalence rates of 31% and 17%, respectively [106]. Nipah virus was isolated from the urine of *Pteropus hypomelanus* and from fruit partially consumed by this species of fruit bat [111].

Thus, it appears that both Nipah and Hendra are viruses that cause few signs of disease in the fruit bats that commonly carry them. Human disease resulted when the paramyxovirus spreads from the fruit bats into domestic animals. For Hendra virus, the domestic animal was the horse; for Nipah, principally pigs. Both viruses were pathogenic for a broad spectrum of mammalian species. The first human cases appeared in those persons occupationally exposed to the affected domestic animals. Fortunately, neither Hendra nor Nipah virus was highly contagious among infected humans. The epidemic associated with Nipah was associated largely with its rapid spread among pigs and from pigs to humans. Containment of Hendra virus by quarantine and Nipah virus by destroying approximately 1.1 million pigs limited human Hendra cases to a few farms and human Nipah cases to two countries. These viruses persist in their reservoir hosts, and their control depends on understanding the potential role of domestic animals that spread the virus to those who work with animals.

Zoonotic transmission of influenza viruses

In general, influenza viruses cause respiratory diseases spread by aerosol between members of the same species. Influenza occurs in three types. Influenza B and influenza C generally cause limited disease and are usually restricted to humans; however, influenza A can cause serious disease and periodically causes pandemic influenza. Some influenza A viruses spread from humans to animals and from animals to humans. Human-to-animal spread can affect the efficiency of animal protein production. Increasing evidence suggests that animal to human transmission can play an important role in the development of human influenza A pandemics. The role of the zoonotic transfer is the exposure of humans to pathogenic influenza that is antigenically not recognized by the immune system. Zoonotic transmission of influenza A has been reviewed recently [112–115].

Influenza A viruses are orthomyxoviruses that have two envelope glycoproteins, hemaglutinin and neuraminidase. Major types of influenza A are named for these two antigens. The 1918 Spanish flu epidemic, for example, was caused by an H1N1 influenza virus—one with hemaglutinin 1 and neuraminadase 1. Known influenza viruses have 1 of 15 hemaglutinin subtypes and one of 9 neuraminadase subtypes. All of these subtypes occur in aquatic birds [112]. As with many classical reservoirs of zoonoses, aquatic birds generally show no signs of infection with influenza A viruses.

Domestic chickens, however, can develop infections from some subtypes of influenza A, usually developing a disease known as "mildly pathogenic avian influenza." Periodically, influenza A outbreaks cause high mortality in poultry, and this disease is known as "fowl plague" or "highly pathogenic avian

influenza" [116]. Highly pathogenic avian influenza viruses have hemaglutinin envelope glycoproteins H5 or H7 and arise from point mutations in mildly pathogenic avian influenzas [116,117].

A limited number of influenza A subtypes occur in humans, pigs, horses, whales, seals, and mink [114]. Until 1996, human influenza A was of types H1N1 (from 1918–1957 and 1977–present), H2N2 (1957–1968), and H3N2 (1968–present) [112]. Point mutations occur within subtypes and contribute to persistence in humans. The appearance of new subtypes historically has been associated with influenza A pandemics. As will be discussed below, three new subtypes have infected limited numbers of humans since 1996, each of apparent avian origin.

Influenza A is an RNA virus and the genome is comprised of eight separate RNA segments that are incorporated into the virus particle. When more than one type of influenza A infection occurs in the same cell, RNA segments from the different viruses can become incorporated together to form new viruses [118]. The mixing of different viruses has been hypothesized to occur in pigs because they are susceptible to infection with both avian and human influenza A subtypes. Phylogenetic studies support the reassortment of human and avian viruses in pigs [119]. Recent studies also support the transmission of influenza virus with potential avian genes from pigs to swine workers [120–122].

Recent events clearly establish the ability of some avian influenza A strains to infect humans directly, however. In 1996, an H7N7 avian influenza virus was isolated from the inflamed conjunctiva of a woman who kept ducks [123]. The infection was limited but showed that avian influenza could be transmitted directly from birds to man. In spring 1997, highly pathogenic avian H5N1 influenza virus appeared in chicken farms in Hong Kong [124]. Chicks and ducklings were noted to be ill at a school in the spring of 1997 [113,125]. That May, a 3-year-old boy from the school died from acute respiratory distress syndrome, influenza, and Reye's syndrome. An H5N1 influenza A virus was isolated from this child [126,127]. Viral RNA sequence analysis of the HA1 portion of the H5 gene demonstrated only three amino acid changes between this human isolate and the isolates from chickens [128]. The human isolate was also highly pathogenic in experimentally infected chickens [127]. In the fall of 1997, 17 other human influenza cases in Hong Kong were attributed to H5N1 influenza A virus of avian origin [128]. These cases were very severe, with five additional deaths (overall mortality rate of 33%). Clinical presentations in some cases included pneumonia, renal failure, gastrointestinal signs, and elevated hepatic enzymes [129]. Postmortem examination of two of the six fatal cases indicated that the pneumonia was viral without secondary bacterial involvement. Morphologic changes corresponding to the renal failure and elevated liver enzymes included acute, renal tubular necrosis and centrolobular hepatic necrosis [130]. Epidemiologic studies demonstrated that cases were more likely than controls to have been exposed to poultry through the retail sale of live birds [131]. In the poultry markets of Hong Kong, H5N1 influenza was isolated from the feces of 20% of the chickens and from 2% of the geese and ducks [124].

The scientific evidence strongly suggested that lethal H5N1 influenza A was spreading from the live birds in the poultry markets to the people in those markets.

In addition, if humans became coinfected with both the existing human influenza A and the new H5N1 subtype, genes from existing human H3N2 subtype potentially could be incorporated into the H5N1 subtype so that it spread from person to person [125]. In the face of this evidence, in December 1997, the approximately 1.5 million birds comprising the chicken population of Hong Kong and their avian contacts were destroyed. Thereafter, poultry imports were controlled, and aquatic birds were separated from chickens in the poultry markets. Human cases of influenza A H5N1 stopped. Many believe a human influenza pandemic was prevented [125].

This incident greatly increased the understanding of zoonotic influenza A. Humans who became sick with H5N1 influenza acquired the infection from poultry, but poultry workers did not get sick. A follow-up study suggested, however, that workers occupationally exposed to poultry were infected. Antibodies to H5 were present in 3% of 293 government workers who helped destroy the infected birds and in 10% of 1525 poultry workers [132]. Among poultry workers, exposure to sick birds and butchering birds was associated with seropositivity [132]. Epidemiologic studies associated with the first human case revealed that 17% or 5 of 29 poultry workers had antibodies to H5N1 influenza A, whereas 4 (0.9%) of 451 people otherwise associated with the index case had antibodies to H5N1 influenza A. Two of these individuals also were exposed to the same group of birds believed to be the source of the child's exposure [133].

A major impact of the 1997 Hong Kong H5N1 influenza outbreak was acceptance of the transmission of avian influenzas directly to humans in whom genetic reassortment with established human influenza viruses was possible [134]. The H5N1 virus that caused the 1997 Hong Kong outbreak appears to have evolved quickly within the poultry markets [135]. An H9N2 influenza A virus also infected the chickens in the poultry markets in 1997. The 1997 H9N2 chicken virus contained unusual internal genetic segments shared with, and possibly derived from, quail influenza A viruses. These internal genetic segments appear to have been incorporated by reassortment into the H5N1 viruses that spread to humans [136].

The importance of the internal influenza A genes in zoonotic potential is supported by the recent discovery that H9N2 influenza viruses with these same internal genes have spread from birds to humans in Hong Kong [137]. No fatalities have been reported with this subtype, and there is no evidence of human-to-human transmission [138]. Recent evidence suggests that pigs in southeastern China have antibodies to H1, H3, H4, H5, and H9 of influenza A—suggesting the potential for reassortment of these avian and human influenza viruses in pigs [139]. As a whole, the recent influenza cases in China support the importance of genetic reassortment of influenza A genes in the creation of new human and animal pathogens and transmission of influenza A between species.

Summary

The past decade has seen a continuing increase in the number of potential zoonotic agents in the workplace. For workers in the United States who work outdoors,

two new agents, WNV and leishmaniasis, may be transmitted from animals to man by a vector. For WNV, mosquitoes are the vectors; the North American vector of *Leishmania donovani* is not known. For agricultural workers, we now know that in Israel, working with geese sickened by WNV confers increased risk of contracting WNV. We do not know if that risk is associated with mosquitoes or direct transmission. As raccoons adapt to a suburban lifestyle, we now know that cases of *B procyonis* larval migrans are increasing and that this risk is associated with oral exposure to surfaces contaminated by raccoon feces. This certainly is an issue affecting selection of eating areas for outdoor workers and vacationers. The number of cases and geographic range of Lyme disease and its *Ixodes* spp tick vector continue to expand as ticks increasingly become transmitters of zoonotic disease.

In the past decade, we have recognized many new zoonotic diseases that exist in relative harmony with their wildlife reservoirs but can cause severe disease in humans. In the Americas, excellent examples include increasing numbers of described hantaviruses that are carried by sigmodontine rodents. In Australia and China, three zoonotic paramyxoviruses and one lyssavirus exist in wild bats. Each of these agents has been transmitted to animal workers, and several have killed workers. Hendra virus, Menangle virus, and Nipah virus spread from the bat reservoir to domestic animals and from domestic animals to humans.

Nipah virus is an excellent example of how occupational practices, particularly in domestic animal husbandry, can affect zoonotic disease propagation. Nipah virus was not transmitted between humans; pigs were the primary source of human exposure. Widespread contact of pigs from different sources permitted the virus to spread between farms. Closed farming operations not only reduce the introduction of swine pathogens that reduce feed efficiency, they should also prevent the widespread propagation of Nipah virus or similar viruses transmitted among pigs.

Avian H5N1 influenza was an equally impressive example of how animal husbandry practices appear to have affected zoonotic disease development as well as transmission. The housing of multiple bird species in crowded poultry markets appears to have produced new influenza A viruses with genes derived from other avian species. The result was an avian influenza that spread to humans and had high lethality.

As human populations have increased, occupationally relevant zoonoses have expanded their geographic range, are being diagnosed more frequently, and are now known to include additional agents. Control of these agents involves understanding the natural ecology of the etiologic agents in their natural hosts. It also involves understanding how the disease can leave the natural hosts and cause significant disease in workers.

References

[1] Weiss RA. The Leeuwenhoek lecture 2001. Animal origins of human infectious disease. Phil Trans R Soc Lond B 2001;356:957–77.

[2] Hayes CG. West Nile virus: Uganda, 1937, to New York City, 1999. Ann N Y Acad Sci 2001; 951:25–37.
[3] McLean RG, Ubico SR, Bourne D, Komar N. West Nile virus in livestock and wildlife. Curr Top Microbiol Immunol 2002;267:271–308.
[4] Meek J. West Nile virus in the United States. Curr Opin Pediatr 2002;14:72–7.
[5] Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. Science 1999;286:2333–7.
[6] US Centers for Disease Control and Prevention. Weekly Update: West Nile virus activity—United States, July 24–30, 2002. MMWR 2002a;51:668–79.
[7] McLean RG, Ubico SR, Docherty DE, Hansen WR, Sileo L, McNamara TS. West Nile virus transmission and ecology in birds. Ann N Y Acad Sci 2001;951:54–7.
[8] Komar N, Lanciotti R, Bowen R, Langevin S, Bunning M. Detection of West Nile virus in oral and cloacal swabs collected from bird carcasses. Emerg Infect Dis 2002;8:741–2.
[9] Bunning ML, Bowen RA, Cropp B, Sullivan K, Davis B, Komar N, et al. Experimental infection of horses with West Nile virus and their potential to infect mosquitoes and serve as amplifying hosts. Ann N Y Acad Sci 2001;951:338–9.
[10] Bunning ML, Bowen RA, Cropp CB, Sullivan KG, Davis BS, Komar N, et al. Experimental infection of horses with West Nile virus. Emerg Infect Dis 2002;8:380–6.
[11] US Centers for Disease Control and Prevention. Serosurveys for West Nile virus infection—New York and Connecticut counties, 2000. MMWR 2001;50:37–9.
[12] Bin H, Grossman Z, Pokamunski S, Malkinson M, Weiss L, Duvdevani P, et al. West Nile fever in Israel 1999–2000: from geese to human. Ann N Y Acad Sci 2001;251:127–42.
[13] Weinberger M, Pitlik SD, Gandacu D, Lang R, Nassar F, Ben David D, et al. West Nile fever outbreak, Israel, 2000: epidemiologic aspects. Emerg Infect Dis 2001;7:686–91.
[14] Weiss D, Carr D, Kellachan J, Tan C, Phillips M, Bresnitz E, et al. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. Emerg Infect Dis 2001;7:654–8.
[15] Swayne DE, Beck JR, Smith CS, Shieh WJ, Zaki SR. Fatal encephalitis and myocarditis in young domestic geese (Anser anser domesticus) caused by West Nile virus. Emerg Infect Dis 2001;7:751–3.
[16] Katz Y, Lustig S, Ben-Shlomo I, Kobiler D, Ben-Nathan D. Inhalation anesthetic-induced neuroinvasion by an attenuated strain of West Nile virus in mice. J Med Virol 2002;66:576–80.
[17] Sacks DL, Modi G, Rowton E, Spath G, Epstein L, Turco SJ, et al. The role of phosphoglycans in *Leishmania*-sand fly interactions. Proc Natl Acad Sci USA 2000;97:406–11.
[18] Herwaldt BL. Leishmaniasis. Lancet 1999;354:1191–9.
[19] Boelaert M, Criel B, Leeuwenburg J, Van Damme W, Le Ray D, Van der Stuyft V. Visceral leishmaniasis control: a public health perspective. Trans R Soc Trop Med Hyg 2000;94:465–71.
[20] Breitschwerdt EB. Leishmaniasis in North America. Compendium Cont Ed Pract Vet 2002; 24(1A):3–6.
[21] Monti DJ. Hunters hounded as leishmaniasis is diagnosed in foxhounds. J Am Vet Med Assoc 2000;216:1887–90.
[22] Salotra P, Sreenivas G, Pogue GP, Lee N, Nakasi HL, Ramesh V, et al. Development of a species-specific PCR assay for detection of Leshmania donovani in clinical samples form patient with kala-azar and post-kala-azar dermal leishmaniasis. JCM 2001;39:849–54.
[23] Kazacos KR. Larval migrans from pets and wildlife. Compendium Cont Ed Pract Vet 2002; 24(1A):41–6.
[24] Anderson BC. Congenital Baylisascaris sp. larval migrans in a newborn lamb. J Parasitol 1999;85:128–9.
[25] Schantz PM. Zoonotic ascarids and hookworms: the role for veterinarians in preventing human disease. Compendium Cont Ed Pract Vet 2002;24(1A):47–52.
[26] Sorvillo F, Ash LR, Berlin OG, Yatabe J, Degiorgio C, Morse SA. Balisascaris procyonis: an emerging helminthic zoonosis. Emerg Infect Dis 2002;8:355–9.

[27] Kerr CL, Henke SE, Pence DB. Baylisascariasis in raccoons from southern coastal Texas. J Wildl Dis 1997;33:653–5.
[28] Fox AS, Kazacos KR, Gould NS, Heydemann PT, Thomas C, Boyer KM. Fatal eosinophilic meningoencephalitis and visceral larval migrans caused by the raccoon ascarid Baylisascaris procyonis. N Engl J Med 1985;312:1619–23.
[29] Huff DS, Neafie RC, Binder MJ, De Leon GA, Brown LW, Kazacos KR. Case 4. The first fatal Baylisascaris infection in humans: an infant with eosinophilic meningoencephalitis. Pediatr Pathol 1984;2:345–52.
[30] Moertel CL, Kazacos KR, Butterfield JH, Kita H, Watterson J, Gleich GJ. Eosinophil-associated inflammation and elaboration of eosinophil-derived proteins in 2 children with racoon roundworm (Baylisascaris procyonis) encephalitis. Pediatrics 2001;108:E93.
[31] Park SY, Glaser C, Murray WJ, Kazacos KR, Rowley HA, Frederick DR, et al. Raccoon roundworm (Baylisascaris procyonis) encephalitis: case report and field investigation. Pediatrics 2000;106:E56.
[32] Rowley HA, Uht RM, Kazacos KR, Sakanari J, Wheaton WV, Barkovich AJ, et al. Radiologic-pathologic findings in raccoon roundworm (Baylisascaris procyonis) encephalitis. An J Neuroradiol 2000;21:415–20.
[33] Kazacos KR. Baylisascaris procyonis and related species. In: Samuel WM, Pybus MJ, Kocan AA, editors. Parasitic diseases of wild mammals. 2nd edition. Ames, IA: Iowa University Press; 2001. p. 301–41.
[34] Nowotny N, Deutz A, Fuchs K, Schuller W, Hinterdorfer F, Auer H, et al. Prevalence of swine influenza and other viral, bacterial and parasitic zoonoses in veterinarians. J Inf Dis 1997;176: 1414–5.
[35] Kazacos KR, Boyce WM. Baylisascaris larva migrans. J Am Vet Med Assoc 1989;195:894–903.
[36] Steere AC, Malawista SE, Snyderman DR, Shope RE, Andiman WA, Ross MR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthris Rheum 1977;20:7–17.
[37] Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP. Lyme disease-a tick borne spirochetosis? Science 1982;216:1317–9.
[38] Steere AC, Broderick TF, Malawista SE. Erythema chronicum migrans and Lyme arthritis: epidemiologic evidence for a tick vector. Am J Epidemiol 1978;108:312–21.
[39] Johnson RC, Hyde FW, Schmid GP, Brenner DJ. Borrelia burgdorferi sp. nov.: etiologic agent of Lyme disease. Int J Syst Bacteriol 1984;34:496–7.
[40] Orloski KA, Hayes EB, Campbell GL, Dennis DT. Suveillance for Lyme disease—United States, 1992–1998. MMWR CDC Surveill Summ 2000;49:1–11.
[41] Lin T, Oliver Jr JH, Gao L, Kollars Jr TM, Clark KL. Genetic heterogeneity of Borrelia burdorferi sensu lato in the southern United States based on restriction fragment length polymorphism and sequence analysis. J Clin Microbiol 2001;39:2500–7.
[42] Baranton G, Marti Ras N, Postic D. Borrelia burgdorferi, taxonomy, pathogenicity and spread [in French]. Ann Med Interne [Fr] 1998;149:455–8.
[43] Postic D, Ras NM, Lane RS, Humair P-F, Wittenbrink MM, Baranton G. Common ancestry of Borrelia burgdorferi senso lato strains from North America and Europe. J Clin Microbiol 1999; 37:3010–2.
[44] Lebech AM. Polymerase chain reaction in diagnosis of Borrelia burdorferi infections and studies on taxonomic classification. APMIS Suppl 2002;105:1–40.
[45] Marconi RT, Liveris D, Schwartz I. Identification of novel insertion elements, restriction fragment length polymorphism patterns, and discontinuous 23S rRNA in Lyme disease spirochetes: phylogenetic analyses of rRNA genes and their intergenic spacers in Borrelia japonica sp. nov. and genomic group 21038 (Borrelia andersonii sp. nov.) isolates. J Clin Microbiol 1995;33:2427–34.
[46] Anderson JF, Johnson RC, Magnarelli LA. Seasonal prevalence of Borrelia burgdorferi in natural populations of white-footed mice, Peromyscus leucopus. J Clin Microbiol 1987;25:1564–6.
[47] Donahue JG, Piesman J, Spielman A. Reservoir competence of white-footed mice for Lyme disease spirochetes. Am J Trop Hyg 1987;36:92–6.

[48] Wright SD, Nielsen SW. Experimental infection of the white-footed mouse with *Borrelia burgdorferi*. Am J Vet Res 1990;51:1980–7.
[49] Mather TN, Wilson ML, Moore SI, Ribeiro JM, Spielman A. Comparing the relative potential of rodents as reservoirs of the Lyme disease spirochete (Borrelia burgdorferi). Am J Epidemiol 1989;13:143–50.
[50] Piesman J, Dolan MC. Protection against Lyme disease spirochete transmission provided by prompt removal of nymphal Ixodes scapularis (Acari: Ixodidae). J Med Entomol 2002;39: 509–12.
[51] Appel MJG. Lyme disease in dogs. Compendium Cont Ed Pract Vet 2002;24(1A):19–23.
[52] Marshall WF, Elford SR, Rys PN, Rutledge BJ, Mathiesen D, Malawista SE, et al. Detection of Borelia burgdorferi DNA in museum specimens of Peromyscus leucopus. J Infect Dis 1994; 170:1027–32.
[53] Steere AC. Lyme disease: a growing threat to urban populations. Proc Natl Acad Sci USA 1994;91:2378–83.
[54] US Centers for Disease Control and Prevention. Lyme disease—United States, 2000. MMWR 2002b;51:29–31.
[55] Qiu WG, Dykhuizen DE, Acosta MS, Luft BJ. Geographic uniformity of the Lyme disease spirochete (Borrelia burgdorferi) and its shared history with tick vector (Ixodes scapularis) in the northeastern US. Genetics 2002;160:833–49.
[56] Estrada-Pena A. Increasing habitat suitability in the United States for the tick that transmits Lyme disease: a remote sensing approach. Environ Health Perspect 2002;11:635–40.
[57] Guerra M, Walker E, Jones C, Paskewitz S, Cortinas MR, Stancil A, et al. Predicting the risk of Lyme disease: habitat suitability for Ixodes scapularis in the north central United States. Emerg Infect Dis 2002;8:289–97.
[58] Wilson ML, Ducey AM, Litwin TS, Gavin TA, Spielman A. Microgeographic distribution of immature *Ixodes dammini* ticks correlated with that of deer. Med Vet Entomol 1990;4:151–9.
[59] Peters CJ, Khan AS. Hantavirus pulmonary syndrome: the new American hemorrhagic fever. Clin Infect Dis 2002;34:1224–31.
[60] US Centers for Disease Control and Prevention. Outbreak of acute illness–southwestern United States, 1993. MMWR 1993;42:421–4.
[61] Chapman LE, Khabbaz RF. Etiology and epidemioloy of the four corners hantavirus outbreak. Infect Agents Dis 1994;3:234–44.
[62] Nichol ST, Spiropoulou CF, Morsunov S, Rollin PE, Ksiazek TG, Feldmann H, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:832–6.
[63] Zaki SR, Greer PW, Coffield LM, Goldmith CS, Nolte KB, Foucar K, et al. Hantavirus pulmonary syndrome:pathogenesis of an emerging infectious disease. Am J Pathol 1995;146: 552–79.
[64] Chizhikov VE, Spiropoulou CF, Morzunov SP, Monroe MC, Peters CJ, Nichol ST. Complete genetic characterization and analysis of isolation of Sin Nombre virus. J Virol 1995;69:8132–6.
[65] Khan AS, Gaviria M, Rollin PE, Hlady WG, Ksiazek TG, Armstrong LR, et al. Hantavirus pulmonary syndrome in Florida: association with the newly identified Black Creek Canal Virus. Am J Med 1996;100:46–8.
[66] Rhodes III LV, Huang C, Sanchez AJ, Nichol ST, Zaki SR, Ksiazek TG, et al. Hantavirus pulmonary syndrome associated with Monogahela virus. Pennsylvania. Emerg Infect Dis 2000; 6:616–21.
[67] Song JW, Baek LJ, Gavrilovskaya IN, Mackow ER, Hjelle B, Yanagihara R. Sequence analysis of the complete S genomic segment of a newly identified hantavirus isolated from the white-footed mouse (Peromyscus leucopus): phylogenetic relationship with other sigmodontine rodent-borne hantaviruses. Virus Genes 1996;12:249–56.
[68] Bohlman MC, Morzunov SP, Meissner J, Taylor MB, Ishibashi K, Rowe J, et al. Analysis of hantavirus genetic diversity in Argentina: S segment-derived phylogeny. J Virol 2002;76: 3765–73.

[69] Drebot MA, Gavrilovskaya I, Mackow ER, Chen Z, Lindsay R, Sanchez AJ, et al. Genetic and serotypic characterization of sin nombre-like viruses in Canadian *Peromyscus maniculatus* mice. Virus Res 2001;75:75–86.

[70] Hjella B, Glass GE. Outbreak of hantavirus infection in the Four Corners region of the United States in the wake of the 1997–1998 El Nino-southern oscillation. J Infec Dis 2000;181:1569–73.

[71] Kuenzi AJ, Douglass RJ, White Jr D, Bond CW, Mills JN. Antibody to Sin Nombre virus in rodents associated with peridomestic habitats in west central Montana. Am J Trop Med Hyg 2001;64:137–46.

[72] Douglass RJ, Wilson T, Semmens WJ, Zanto SN, Bond CW, Van Horn RC, et al. Longitudinal studies of Sin Nombre virus in deer mouse-dominated ecosystems of Montana. Am J Trop Med Hyg 2001;65:33–41.

[73] Botten J, Mirowsky K, Kusewitt D, Bharadwaj M, Yee J, Ricci R, et al. Experimental infection model for Sin Nombre hantavirus in the deer mouse (Peromyscus maniculatus). Proc Natl Acad Sci USA 2000;97:10578–83.

[74] Khan AS, Young JC. Hantavirus pulmonary syndrome: at the crossroads. Curr Opin Infect Dis 2001;14:205–9.

[75] Hughes AL, Friedman R. Evolutionary diversification of protein-coding genes of hantaviruses. Mol Biol Evol 2000;17:1558–68.

[76] Mills JN, Corneli A, Young JC, Garrison LE, Khan AS, Ksiazek TG. Hantavirus pulmonary syndrome—United States: updated recommendations for risk reduction. MMWR 2002;51: 1–12.

[77] Kitsutani PT, Denton RW, Fritz CL, Muraay RA, Todd RL, Pape WJ, et al. Acute Sin Nombre hantavirus infection without pulmonary syndrome. United States. Emerg Infect Dis 1999;5: 701–5.

[78] US Centers for Disease Control and Prevention. Hantavirus pulmonary syndrome: Panama, 1999–2000. MMWR 2000;49:205–7.

[79] Padula PJ, Colavecchia SB, Matinez VP, Gonzalez MO, Valle D, Edelstein A, et al. Genetic diversity, distribution, and serological features of hantavirus infections in five countries in South America. J Clin Microbiol 2000;38:3029–35.

[80] Mahy BW, Brown CC. Emerging zoonoses: crossing the species barrier. Rev Sci Tech 2000; 19:33–40.

[81] Hanna JN, Carney IK, Smith GA, Tannenberg AEG, Deverill JE, Botha JA, et al. Australian bat lyssavirus infection: a second human case, with a long incubation period. Med J Aust 2000; 172:597–9.

[82] Samartunga H, Searle JW, Hudson N. Non-rabies lyssavirus human encephalitis from fruit bats: Australian bat Lyssavirus (pteropid Lyssavirus) infection. Neuropathol Appl Neurobiol 1998; 24:331–5.

[83] Mackenzie JS, Chua KB, Daniels PW, Eaton BT, Field HE, Hall RA, et al. Emerging viral diseases of Southeaster Asia and the western Pacific. Emerg Infect Dis 2001;7:497–504.

[84] Hooper PT, Williamson MM. Hendra and Nipah virus infections. Vet Clin North Am Equine Pract 2000;16:597–603.

[85] Wang L-F, Eaton BT. Emerging paramyxoviruses. Infect Dis Rev 2001;3:52–69.

[86] Paterson DL, Murray PK, McCormack JG. Zoonotic disease in Australia caused by a novel member of the Paramyxoviridae. Clin Infect Dis 1998;27:112–8.

[87] Murray K, Selleck P, Hooper P, Hyatt A, Gould A, Gleeson L, et al. A morbillivirus that caused fatal disease in horses and humans. Science 1995;268:94–7.

[88] Williamson MM, Hooper PT, Selleck PW, Gleeson LJ, Daniels PW, Westbury HA, et al. Transmission studies of Hendra virus (equine morbillivirus) in fruit bats, horses and cats. Aaust Vet J 1998;12:813–8.

[89] Williamson MM, Hooper PT, Selleck PW, Westbury HA, Slocombe RF. Experimental Hendra virus infection in pregnant guinea-pigs and fruit bats (Pteropus poliocephalus). J Comp Path 2000;122:201–7.

[90] Wang LF, Harcourt BH, Yu M, Tamin A, Rota PA, Bellini WJ, et al. Molecular biology of Hendra and Nipah viruses. Microbes Infect 2001;3:279–87.
[91] O'Sullivan JD, Allworth AM, Paterson DL, Snow TM, Boots R, Gleeson LJ, et al. Fatal encephalitis due to novel paramyxovirus transmitted from horses. Lancet 1997;349:93–5.
[92] Young PL, Halpin K, Selleck PW, Field H, Gravel JL, Kelly MA, et al. Serologic evidence for the presence in Pteropus bats of a paramyxovirus related to equine mobillivirus. Emerg Infect Dis 1996;2:239–40.
[93] Halpin K, Young PL, Field HE, Mackenzie JS. Isolation of Hendra virus from pteropid bats: a natural reservoir of Hendra virus. J Gen Virol 2000;81:1927–32.
[94] Fraser GC, Hooper PT, Lunt RA, Gould AR, Gleeson LJ, Hyatt AD, et al. Encephalitis caused by a lyssavirus in fruit bats in Australia. Emerg Infect Dis 1996;2:327–31.
[95] Gould AR, Hyatt AD, Lunt R, Kattenbelt JA, Hengstberger S, Blacksell SD. Characterization of a novel lyssavirus isolated from Pteroptid bats in Australia. Virus Res 1998;54:165–87.
[96] Philbey AW, Kirkland PD, Ross AD, Davis RJ, Gleeson AB, Love RJ, et al. An apparently new virus (Family Paramyxovirdiae) infectious for pigs, humans, and fruit bats. Emerg Infect Dis 1998;4:269–71.
[97] Chant K, Chan R, Smith M, Dweyer DE, Kirland P, and the NSW Expert Group. Probable human infection with a newly described virus in the family paramyxoviridae. Emerg Infect Dis 1998;4:273–5.
[98] Kirkland PD, Love RJ, Philbey AW, Ross AD, Davis RJ, Hart KG. Epidemiology of Menangle virus in pigs. Aust Vet J 2001;79:199–206.
[99] Enserink M. New virus fingered in Malaysian epidemic. Science 1999;284:407–10.
[100] Chua KB, Bellini WJ, Rota PA, Harcourt BH, Tamin A, Lam SK, et al. Nipah virus: a recently emergent deadly paramyxovirus. Science 2000;288:1432–5.
[101] Chua KB, Goh KJ, Wong KT, Kamarulzaman A, Tan PSK, Ksiazek TG, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. Lancet 1999;354:1257–9.
[102] Parashar UD, Sunn LM, Ong F, Mounts AW, Arif MT, Ksiazek TG, et al. Case-control study of risk factors for human infection with a new zoonotic paramyxovirus, Nipah virus, during a 1998–1999 outbreak of severe encephalitis in Malaysia. J Infect Dis 2000;181: 1755–9.
[103] Goh KJ, Tan CT, Chew NK, Tan PSK, Kamarulzaman A, Sarji SA, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. N Engl J Med 2000;342:1229–35.
[104] Tan CT, Goh KJ, Wong KT, Sarji SA, Chua KB, Chew NK, et al. Relapsed and late-onset Nipah encephalitits. Ann Neurol 2002;51:703–8.
[105] US Centers for Disease Control and Prevention. Update: outbreak of Nipah virus—Malaysia and Singapore, 1999. MMWR 1999;48:335–7.
[106] Yob JM, Field H, Rashdi AM, Morrissy C, Van Der Heide B, Rota P, et al. Nipah virus infection in bats (order Chiroptera) in peninsular Malaysia. Emerg Infect Dis 2001;7:439–41.
[107] Chew MHL, Arguin PM, Shay DK, Goh KT, Rollin PE, Shieh W-J, et al. Risk factors for Nipah virus infection among abattoir workers in Singapore. J Infect Dis 2000;181:1760–3.
[108] Hooper PT, Zaki S, Daniel P, Middleton D. Comparative pathology of the diseases caused by Hendra and Nipah viruses. Microbes Infect 2001;3:315–22.
[109] Middleton DJ, Westbury HA, Morrissy CJ, Van Der Heide BM, Russell GM, Braun MA, et al. Experimental Nipah virus infection in pigs and cats. J Comp Path 2002;126:124–36.
[110] Ali R, Mounts AW, Parashar UD, Sahani M, Lye MS, Isa MM, et al. Nipah virus infection among military personnel involved in pig culling during an outbreak of encephalitis in Malaysia, 1998–1999. Emerg Infect Dis 2001;7:759–61.
[111] Chua KB, Koh CL, Hooi PS, Wee KF, Khong JH, Chua BH, et al. Isolation of Nipah virus from Malaysian island flying-foxes. Microbes Infect 2002;4:145–51.
[112] Alexander DJ, Brown IH. Recent zoonoses caused by influenza A viruses. Rev Sci Tech Off Int Epiz 2000;19:197–225.
[113] Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. Annu Rev Med 2000; 51:407–21.

[114] Webby RJ, Webster RG. Emergence of influenza A viruses. Phil Trans R Soc Lond B 2001; 356:1817–28.
[115] Webster RG. The importance of animal influenza for human disease. Vaccine 2002;20:S16–20.
[116] Swayne DE, Suarez DL. Highly pathogenic avian influenza. Rev Sci Tech 2000;19:463–82.
[117] Alexander DJ. A review of avian influenza in different bird species. Vet Microbiol 2000;74: 3–13.
[118] Webster RG, Campbell CH, Granoff A. The "in vivo" production of "new" influenza viruses. 3. Isolation of recombinant influenza viruses under simulated conditions of natural transmission. Virology 1973;51:149–62.
[119] Castrucci MR, Donatelli I, Sidoli L, Barigazzi G, Kawaoka Y, Webster RG. Genetic reassortment between avian and human A viruses in Italian pigs. Virology 1993;193:503–6.
[120] Campitelli L, Donatelli I, Foni E, Castrucci MR, Fabiani C, Kawaoka Y, et al. Continued evolution of H1N1 and H3N2 influenza viruses in pigs in Italy. Virology 1997;232:310–8.
[121] Olsen CW, Brammer L, Easterday BC, Arden N, Belay E, Baker I, et al. Serologic evidence of h1 swine influenza virus infection in swine farm residents and employees. Emerg Infect Dis 2002;8:814–9.
[122] Wentworth DE, McGregor MW, Macklin MD, Neumann V, Hinshaw VS. Transmission of swine influenza virus to humans after exposure to experimentally infected pigs. J Infect Dis 1997;175:7–15.
[123] Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet 1996;348:901–2.
[124] Shortridge KF, Zhou NN, Guan Y, Gau P, Ito T, Kawaoka Y, et al. Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. Virology 1998;252:331–42.
[125] Shortridge KF, Gao P, Guan Y, Ito T, Kawaoka Y, Markwell D, et al. Interspecies transmission of influenza viruses: H5N1 virus and a Hong Kong SAR perspective. Vet Microbiol 2000;74: 141–7.
[126] De Jong JC, Claas ECJ, Osterhaus ADME, Webster RG, Lim WL. A pandemic warning. Nature 1997;389:554.
[127] Subbarao K, Klimov A, Katz J, Regnery H, Lim W, Hall H, et al. Characterization of an avian influenza A (H5N1) virus isolated form a child with a fatal respiratory illness. Science 1998;279:393–6.
[128] Claas ECJ, Osterhaus ADME, van Beek R, De Jong JC, Rimmelzwaan GF, Senne DA, et al. Human influenza a H5N1 virus related to a highly pathogenic avian influenza virus. Lancet 1998;351:472–7.
[129] Yuen KY, Chan PKS, Peiris M, Tsang DNC, Que TL, Shortridge KF, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998;351:467–71.
[130] To K-F, Chan PKS, Chan K-F, Lee WK, Lam W-Y, Wong K-F, et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J Med Virol 2001;63:242–6.
[131] Mounts AW, Kwong H, Izurieta HS, Ho Y, Au T, Lee M, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999;180:505–8.
[132] Bridges CB, Lim W, Hu-Primmer J, Sims L, Fukuda K, Mak KH, et al. Risk of Influenza A (H5N1) infection among poultry workers, Hong Kong, 1997–1998. J Infect Dis 2002;185: 1005–10.
[133] US Centers for Disease Control and Prevention. Update: Isolation of avian influenza A(H5N1) viruses from humans–Hong Kong, 1997–1998. MMWR 1998;46:1245–7.
[134] Osterhaus ADME, de Jong JC, Rimmelzwaan GF, Claas ECJ. H5N1 influenza in Hong Kong: virus characterizations. Vaccine 2002;20:S82–3.
[135] Zhou NN, Shortridge KF, Claas ECJ, Krauss S, Webster RG. Rapid evolution of H5NI influenza viruses in chickens in Hong Kong. J Virol 1999;73:3366–74.
[136] Guan Y, Shortridge KF, Krauss S, Webster RG. Molecular characterization of H9N2 influenza viruses: Were they the donors of the "internal" genes of H5N1 viruses in Hong Kong? Proc Natl Acad Sci USA 1999;96:9363–7.

[137] Lin YP, Shaw M, Gregory V, Cameron K, Lim W, Klimov A, et al. Avian-to-human transmission of H9N2 subtype influenza A viruses: relationship between H9N2 and H5N1 human isolates. Proc Natl Acad Sci USA 2000;97:9654–8.

[138] Uyeki TM, Chong Y, Katz JM, Lim W, Ho Y, Wang SS, et al. Lack of evidence for human-to-human transmission of avian influenza A (H9N2) viruses in Hong Kong, China, 1999. Emerg Infect Dis 2002;8:154–9.

[139] Ninomiya A, Takada A, Okazaki K, Shortridge KF, Kida H. Seroepidemiological evidence of avian H4, H5, and H9 influenza A virus transmission to pigs in southeastern China. Vet Microbiol 2002;88:107–14.