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Emerging Viruses in Human Populations
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Zoonoses in the Emergence of Human Viral Diseases

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Viral zoonoses have represented a significant public health problem throughout history, affecting all continents. Furthermore, many viral zoonoses have emerged or reemerged in recent years, highlighting the importance of such diseases. Emerging viral zoonoses encompass a vast number of different viruses and many different transmission modes. There are many factors influencing the epidemiology of the various zoonoses, such as ecological changes, changes in agriculture and food production, the movement of pathogens, including via travel and trade, human behavior and demographical factors, and microbial changes and adaptation. Cost-effective prevention and control of emerging viral zoonoses necessitates an interdisciplinary and holistic approach and international cooperation. Surveillance, laboratory capability, research, training and education, and last but not least, information and communication are key elements.

Introduction

Throughout the history of mankind, animals have been an important source of infectious diseases transmissible to humans. Such diseases were formerly called anthropozoonoses (Greek "anthrópos" = man, "zoon" = animal, "nosos" = disease), whereas the diseases transmissible from humans to animals were called zooanthroponoses (Hubálek, 2003). Today, the term zoonoses is commonly used for infectious diseases that are naturally transmitted between vertebrate animals and man (WHO/FAO, 1959). The total number of zoonoses is unknown, but according to Taylor et al. (2001), who in 2001 cataloged 1415 known human pathogens, including 217 viruses and prions, 538 bacteria and rickettsia, 307 fungi, 66

protozoa, and 287 helminths, 61% were zoonotic. With time, more and more human pathogens are found to be of animal origin. Interestingly, wild animals seem to be involved in the epidemiology of most zoonoses and serve as significant reservoirs for transmission of zoonotic agents to domestic animals and man.

Many infectious diseases have emerged in the human population in recent years. According to Lederberg et al. (1992), emerging infectious diseases include those whose incidences in humans have increased within the past two decades or threaten to increase in the near future. Emerging infections also include those that have newly appeared in a population or that have been known for some time, but are rapidly increasing in incidence or geographic range.

Most emerging infectious diseases in humans are zoonoses. The WHO/FAO/OIE joint consultation on emerging zoonotic diseases held in Geneva in 2004 (whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.9.pdf) defined an emerging zoonosis as "a zoonosis that is newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range". At this consultation it was stated that emerging zoonotic diseases have potentially serious human health and economic impacts and that their current increasing incidences are likely to continue. Avian influenza was used as an example; events since that time have shown that these predictions were unfortunately correct.

Of the 1415 known human pathogens, 175 (12%) are associated with an emerging disease (Taylor et al., 2001), and can be designated emerging pathogens. Of these emerging pathogens, 75% are zoonotic. Overall, zoonotic pathogens are twice as likely to be associated with emerging diseases, compared to non-zoonotic pathogens. However, the result varies among taxa, with viruses and protozoa particularly likely to emerge, and helminths particularly unlikely to do so, regardless of their zoonotic status. Interestingly, no association between transmission route and emergence was found (Taylor et al., 2001).

Historical aspects of zoonoses

Throughout history, wild animals have always played a role in viral zoonoses. Rabies is one of the most feared viral zoonoses. It is an ancient disease; the origin of the word dates to 3000 BC from Sanskrit, meaning "to do violence". Rabies was described in hunting dogs in Mesopotamia as early as 2300 BC. Recognizable descriptions of rabies can also be found in early Chinese, Egyptian, Greek, and Roman records (Blancou, 2003). In medieval Europe, rabies occurred in both domestic and wild animals. Rabid foxes, wolves, badgers, and bears were described in literature as well as in figurative art. Although rabies is an ancient disease that is endemic in many areas, the zoonosis has also been emerging in some regions in recent years.

Ancient accounts and modern hypotheses suggest that Alexander the Great died of West Nile virus (WNV) encephalitis in Babylon 323 BC (Marr and Calisher, 2003). It was reported that "as he entered Babylon a flock of ravens exhibiting

unusual behavior died at his feet'' (Marr and Calisher, 2003). In 1999, WNV was introduced into the United States causing an epizootic in birds with spillover infections to man and equine animals.

A major human epidemic of influenza was recorded by Hippocrates in 412 BC. Influenza viruses have different hosts, both birds and different mammals including humans, and have a zoonotic potential. An antigenic shift in influenza A virus can cause the sudden emergence of a new subtype of the virus. Although this shift occurs only occasionally, large numbers of people, and sometimes the entire population, have no antibody protection against the new subtype of virus, resulting in a worldwide epidemic (''pandemic''). Three major influenza A pandemics emerged during the 20th century. Of these, the Spanish flu in 1918–1919 (subtype H1N1) was the most severe with an estimated 50 million deaths worldwide (Taubenberger and Morens, 2006). The Asian flu in 1957–1958 (H2N2) and the Hong Kong flu in 1968–1969 (H3N2) caused less serious pandemics. The latter two are known to be the result of a reassortment between an avian influenza strain from wild waterfowl and a human strain of influenza A, with the introduction of a new hemagglutinin protein in the human strain.

The avian influenza A subtype H5N1 epidemic that emerged in birds in Asia in 2002 has caused substantial death and economic losses in poultry. This strain can also infect humans, although rarely, but with a high degree of lethality. There is no evidence so far of human-to-human transmission of the H5N1 virus. The public health concern is that genetic reassortment of this avian strain with a human strain could cause the emergence of a new pandemic with the high degree of lethality seen in the sporadic zoonotic cases to date (http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans).

An epidemic of hantavirus infections emerged in the southwestern US in 1993. Healthy adults sickened and died suddenly of an unknown disease. Navajo leaders gave public health scientists clues; that year had seen a particularly bountiful harvest of piñon nuts accompanied by a large population of deer mice. The years 1918 and 1936 had also seen large harvests and large deer mouse populations as well as unexplained epidemics. Serological analyses of the blood of the victims revealed antibodies to the Haantan virus family, and as CDC scientists isolated and amplified viral DNA from victims' blood, trappers caught deer mice in the area, which proved to carry hantavirus.

Transmission modes

Zoonotic viruses replicate in the reservoir animal host and are usually transmitted to humans by direct contact (a bite by the infected reservoir animal or handling of the animal's tissues or materials contaminated by the animal's body fluids) or the bite of a hematophagous arthropod. For example, rabies virus is transmitted by the saliva from a bite of a rabid animal, and simian foamy virus (SFV) can be transmitted by bites from an infected monkey. Hantaviruses like Puumala and Sin Nombre viruses are typically spread from rodents to humans by aerosols of dust

containing rodent excreta. Transmission of simian immunodeficiency virus (SIV) and SFV can occur when hunters and butchers handle the meat of infected monkeys. Ebola virus transmission has been reported after preparation of dead chimpanzees and gorillas for food.

Most viral zoonoses require a blood-sucking arthropod for transmission to humans. Mosquitoes are the most important arthropod vectors (examples of viral zoonoses transmitted by mosquitoes are Rift Valley fever, WNV, and Japanese encephalitis), followed by ticks, sandflies, and midges. Arthropod vector-borne viruses are called arboviruses and are maintained in complex life cycles involving a non-human vertebrate primary host and a primary arthropod vector. The arthropod vector becomes infected when it ingests virus while feeding on the blood of a viremic animal. Virus replicates in the arthropod tissues, ultimately infecting the salivary glands. The arthropod then transmits the virus to a new host when it injects infectious salivary fluid while taking a blood meal. Arthropod-borne viruses generally remain undetected until the virus escapes the primary cycle via a secondary vector or secondary vertebrate host, such as when humans enter the enzootic cycle. Although humans may become ill as a result of these viruses, they are generally considered dead-end hosts for many of the viruses because they do not develop sufficient viremia to infect feeding vectors and thus do not contribute to the transmission cycle. Notable exceptions include dengue, yellow fever, chikungunya, and Ross River virus infections (www.acpmedicine.com/sample2/ch0731s.htm).

Zoonotic viruses may also be spread from wild animals to humans indirectly by contaminated food and water. An unusual and unexpected example of zoonotic transmission of this type has been suggested for hepatitis E virus (HEV) infection. In an outbreak of HEV infection among people who had eaten uncooked deer meat 6–7 weeks before, a leftover portion of the deer meat, kept frozen for a future meal, was positive for HEV RNA, and the nucleotide sequence was identical to sequences of virus from the patients. Patients' family members who ate little or none of the deer meat remained uninfected. These findings provide direct evidence that HEV infection may be a zoonosis (Tei et al., 2003).

Human noroviruses are a common cause of gastrointestinal infection and are spread between humans by contact, or indirectly via food and water. Other noroviruses can be found in animals. Although noroviruses are not considered zoonotic, new research raises questions of whether pigs may be reservoirs for emergence of new human noroviruses or if porcine/human genogroup II recombinants could emerge (Wang Q.-H. et al., 2005).

Factors influencing the epidemiology of viral zoonoses

Ecological changes

Ecological changes of natural or human origin can have a profound impact on the epidemiology and the emergence of viral zoonoses. These include, but are not limited to, human population expansion and encroachment, de-forestation and

reforestation, other habitat changes, pollution, and climatic changes. The opening of isolated ecosystems to human activity has contributed to the emergence of viral diseases. One classic example is the emergence of yellow fever when humans entered the Central American jungle to build the Panama Canal (Murphy, 1998).

Unprecedented population growth, mostly in developing countries, has resulted in major movements of people into urban centers. This unplanned and uncontrolled urbanization with inadequate housing, deteriorating water, sewage, and waste management systems, produces ideal conditions for increased transmission of mosquito- and rodent-borne diseases (Gubler, 1998). Meteorological factors such as temperature, rainfall, and humidity can influence the dynamics of vector-borne diseases. Climate changes with milder winters and early arrival of spring has been suggested as an explanation for the increased incidence of tick-borne encephalitis in Sweden (Lindgren and Gustafson, 2001). There are indications that warmer temperatures aid dengue virus transmission by accelerating development of the larvae of the mosquito vector, *Aedes egypti*, whose range is limited by cold weather. Yet another climate-related threat comes from the Asian tiger mosquito (*Aedes albopictus*), which transmits dengue virus and yellow fever virus and is able to tolerate cold weather (Ward and Burgess, 1993).

Hantavirus

Wild rodents constitute a reservoir of hantaviruses (virus family *Bunyaviridae*) (Schmaljohn and Hjelle, 1997). Each of the known hantaviruses appear to have one unique, natural, species-specific rodent reservoir. The rodents are chronically infected without any visible symptoms. The viruses are shed in urine, excretory droppings, and saliva, and humans are mainly infected by inhaling aerosols containing the virus. Human-to-human transmission of the viruses has not been reported.

A non-fatal form of hantavirus infection was described in Sweden in 1934 as nephropathia epidemica (NE), a hemorrhagic fever with renal disease syndrome (Niklasson and Le Duc, 1984). It is endemic in northern Sweden, Finland, western Russia, and some other areas in Europe. The causative agent, Puumala virus, is transmitted from excreta of the bank vole (*Clethrionomys glareolus*). Typically, infection occurs by inhalation of contaminated dust in relation to activities in forests or cleaning of sheds, barns, or huts.

Hantavirus infections first received serious attention in the western world when more than 3000 soldiers in the Korean War developed a disease with a fatality rate of approximately 10%, which became known as Korean hemorrhagic fever. The etiological agent, the Hantaan virus, is carried by the field mouse (*Apodemus agrarius*).

Critical environmental factors that can affect rodent population dynamics as well as viral transmission between animals, and from animals to humans, include the amount of precipitation, habitat structure, and food availability. In 1993, a previously unknown infectious disease was recognized in humans in New Mexico,

Colorado, and Nevada. The infection mainly affected the lungs, with a fatality rate of around 60%. The causative agent, a previously unknown hantavirus, subsequently was named Sin Nombre virus and the disease was named Hantavirus pulmonary syndrome (HPS). The principal animal host of Sin Nombre virus is the common deer mouse (*Peromyscus maniculatus),* which lives on pine kernels. The El Nino weather event of 1991–1992, with its unusually heavy summer rains, led to abundant crops that greatly increased the local mouse populations. The deer mouse population was 10–15 fold higher in that period than the seasonal average during the previous 20-year period (McMichael, 2004).

Arenaviruses

Deforestation with fragmentation of habitat increases the ''edge effect'', a phenomenon at the edge of a forest that promotes pathogen–vector–host interactions. The expansion of the world population, which perturbs ecosystems that were stable a few decades ago, has contributed in recent years to the emergence of hemorrhagic fevers in South America. These are caused by various members of the Arenavirus family, and wild rodents are their natural hosts. Human outbreaks have mostly occurred in rural populations. Clearing of forested land in Bolivia in the early 1960s was accompanied by blanket spraying of DDT to control malaria-bearing mosquitoes, and incidentally killed many village cats leading to decreased control of mice near human populations. Large areas with maize supported huge populations of *Calomys* mice carrying Machupo virus; this resulted in the appearance of the Bolivian hemorrhagic fever with a high fatality rate (McMichael, 2004). In addition, aerosols of mouse blood, urine, and feces were generated during harvests that infected the workers. A new outbreak occurred in the same place in 1994, killing seven members of one family.

Ebola virus

Ebola hemorrhagic fever is one of the most virulent and contagious viral diseases known, with a fatality rate of 50–90%. The virus belongs to the family *Filoviridae* and occurs in four distinct subtypes (Zaire, Sudan, Côte d'Ivoire, and Reston subtypes). Ebola virus was first identified in 1976 after significant epidemics in Yambuku, Zaire (now the Democratic Republic of Congo, DRC) and in Nzara, Sudan. Since its first discovery in 1976, there was a second Ebola outbreak in Nzara in 1979, then an outbreak 15 years later in Gabon in1994, and a major epidemic in Kikwit, DRC, in 1995 (with 315 cases and 250 deaths). Since then, new outbreaks have occurred almost each year. The largest outbreak ever occurred in Uganda in 2000–2001 with a total of 425 cases and a fatality rate of 53% (WHO, 2000).

The natural animal reservoir of the Ebola virus is unknown despite extensive studies. The reservoir animal seems to reside in the rain forests of Africa and the western Pacific. Humans as well as other primates are severely affected by Ebola virus, which is transmitted by direct contact with the blood, secretions, organs, or

other body fluids of infected individuals. Infection of humans has also been documented to have occurred as a result of handling infected chimpanzees and gorillas found dead in the rainforests, which suggests that they are not a reservoir since they die from the infection. Interestingly, bats experimentally infected with Ebola virus do not die. Furthermore, evidence of asymptomatic Ebola virus infection was found in three species of fruit bats collected during Ebola outbreaks in humans and great apes between 2001 and 2003 in Gabon and DRC. This evidence that fruit bats may be acting as reservoirs for Ebola virus supports previous evidence suggesting bats as candidate reservoirs for Ebola virus and the closely related Marburg virus (Leroy et al., 2005). If this is correct, humans coming into greater contact with bats because of encroaching agriculture may be at increasing risk for outbreaks of Ebola virus infection.

The Ebola-Reston subtype was detected in 1989 in Virginia, USA, in a colony of cynomolgus monkeys imported from the Philippines, illustrating the risk for spread of viral zoonoses through trade in animals. Several monkeys died and four people were infected, although none of the humans were symptomatic (WHO, 2000).

Changes in agriculture and food production

Over the past 50 years, changes in agricultural practices, including livestock handling and food production, directly or in combination with ecological factors, have influenced the emergence of viral zoonoses. Unprecedented human population growth has increased the demand for highly efficient and mechanized farming. Operators of agricultural machinery in some areas are likely to be exposed to hantaviruses. Combine harvesters suspend clouds of infective dust and create aerosols of infective blood when they accidentally crush the animals that are living among the crops.

Economic factors have resulted in dramatic changes in food animal production. Under such crowded animal conditions, rapid pathogen transmission can occur and lead to an epidemic situation. For instance, pig farms in many countries have grown recently from small family operations with fewer than 20 animals to huge facilities with thousands of animals.

Paramyxoviruses

During the 1990s three zoonotic paramyxoviruses, known to cross species barriers, have emerged from a wildlife reservoir. Hendravirus emerged in Australia in 1994 and was responsible for an outbreak of acute fatal respiratory disease that killed 14 racehorses and two humans (O'Sullivan et al., 1997). Menangle-virus was described in Australia in 1996, where it caused reproductive disorders in pigs and a flu-like disease in humans. Nipah virus emerged in Malaysia in 1998–1999 and caused a massive outbreak of a serious respiratory disease among pigs and spread to humans who were in close contact with pigs. Most patients presented with severe febrile

encephalitis with a fatality rate of 40% (Wong et al., 2002). The natural reservoirs for Hendra, Menangle, and Nipah viruses are bats, in particular large fruit bats, also called flying foxes (Daszak et al., 2004).

Bat Hendra virus isolates have shown a rather conservative genetic past, as shown by sequencing studies, not having undergone major mutational changes prior to their emergence. The concurrent appearance of several bat-associated viruses implies that changes in the ecology of fruit bats, as opposed to evolution of the pathogen itself, is the likely explanation for the spillover to new hosts (Daszak et al., 2004). The ecological trigger for the Nipah virus outbreak appears to have been a complex series of alterations to the fruit bat habitat caused by human activities including agriculture, in combination with a period of drought. The fruit bat's habitat was largely replaced in peninsular Malaysia by oil palm plantations. Deforestation in Sumatra, coupled with a serious drought and fires caused by a major El Nino-event in 1997, led to significant air-pollution haze that covered large areas in Malaysia and parts of Southeast Asia. This reduced the flowering of forest trees and caused a marked decline in forest fruit production, resulting in the encroachment of bats into fruit plantations where pig farms were also maintained (Chua et al., 2002). The culling of hundreds of thousands of pigs probably stopped the Nipah virus epidemic; human-to-human transmission has not been demonstrated.

Japanese encephalitis virus

Japanese encephalitis is a zoonosis caused by a flavivirus transmitted by Culex mosquitos that breed in wet rice fields. Intensification and expansion of irrigated rice production systems over the past 20 years in south Asia and Southeast Asia have had an important impact on the disease burden. The flooding of the fields by irrigation at the start of each cropping cycle leads to an explosive buildup of the mosquito population. The virus circulates in birds with pigs as amplifying hosts. Because of the critical role of pigs, its presence in Muslim countries is negligible. The distribution of Japanese encephalitis is significantly linked to irrigated rice production combined with pig farming (www.who.int/water_sanitation_health/diseases/encephalitis/).

Movements of pathogens; travel and trade

The movements of pathogens, vectors, and animal hosts are additional factors influencing the epidemiology of viral zoonoses. Such movements can occur via human travel and trade, by natural movement of wild animals including migratory birds, and by anthropogenic movements of animals. Wherever and whenever we travel and trade, unseen microbes accompany us. The speed, volume, and extent of today's travel and trade are unprecedented in human history and offer multiple potential routes for microbial spread around the globe. For instance, viruses harbored within insects, animals, or humans can travel halfway around the globe in

$<$24 h by plane; zoonotic viruses can be transported to the farthest land in less time than the incubation times of most diseases.

Rabies

Movement of infected wild and domestic animals is an important factor in the appearance of rabies in new locations. Rabies virus was introduced into North America by infected dogs in the early 18th century, with subsequent spillover to a variety of wild terrestrial mammals. Rabies became established in raccoons in the Mid-Atlantic States in the late 1970s due to translocation of raccoons from the southeastern United States, where rabies was endemic in this species (Smith et al., 1984). Finland experienced an outbreak of rabies linked to raccoon dogs in 1988. The raccoon dog had spread to Finland following the release of this species in western Russia for fur trade. Rabies most probably arrived in Finland with infected wolves migrating from Russia during winter along the ice-packed coast (Sihvonen, 2003). The movement of the arctic fox across ice "bridges" between continents, from the archipelago of Spitzbergen, Norway, to Novaja Zemlja in Siberia, and from Canada to Greenland has been described (Prestrud et al., 1992; Ballard et al., 2001).

West Nile virus

WNV was first isolated from a febrile patient in Uganda in 1937. In 1941, an outbreak occurred in Tel Aviv, Israel. Despite several outbreaks in Israel, WNV was considered a minor arbovirosis in the Old World and until the early 1990s; the virus was mainly confined to Africa and parts of Europe. Mosquitos of the *Culex pipiens* genus are the principal vectors for the virus; birds are amplifying hosts for the virus but were initially considered resistant to disease. However, the occurrence of an abnormal number of deaths in some bird species in Israel in 1998 indicated that a more virulent strain had emerged.

WNV was unknown in North America until it arrived in New York in 1999, via an infected mosquito in an airplane (McMichael, 2004). Apparently there were conditions in New York that were favorable for the virus, such as: (i) seasons of early rains and summer drought that provided ideal conditions for the *Culex* mosquitos; (ii) a high population of susceptible bird species, especially crows; and (iii) urban and suburban ecosystems that were conducive to close interactions of mosquitos, birds, and humans. In 2002, WNV had dramatically expanded its geographical range in the US and caused the largest recognized epidemic of arboviral diseases affecting the CNS (causing encephalitis and meningitis) in the Western Hemisphere.

Monkeypox

During the summer of 2003, an outbreak of monkeypox occurred in the United States with 37 confirmed human cases (Reed et al., 2004). Monkeypox is a rare zoonosis, caused by a poxvirus that typically occurs in Africa. It was first found in monkeys in 1958, and later in other animals, especially rodents. The African squirrel is probably the natural host. Transmission to humans occurs by contact with infected animals or body fluids. The cases in the United States, the first outside Africa, were associated with contact with infected prairie dogs. The outbreak was epidemiologically linked to an import of African rodents from Ghana. It is most likely that infected rodents imported into the United States transmitted the virus to prairie dogs. This illustrates the fact that non-native animal species can create serious public health problems when they introduce a viral disease to native animal and human populations. Thus, the transportation, sale, or distribution of animals, or the release of animals into the environment, can contribute to the spread of zoonoses.

Avian influenza (influenza A; H5N1)

In the fall of 2005, avian influenza subtype H5N1 emerged in Europe; there were outbreaks among poultry in Turkey, Romania, and Ukraine, and in wild migratory birds in Croatia and Romania. In January 2006, the first human cases of H5N1 infection in Europe were confirmed; fatal human cases occurred in Turkey, and were associated with contact with diseased poultry (www.who.int/csr/disease/avian_influenza/avianinfluenza_factsheetJan2006/en/index.html). It is believed that H5N1 reached Europe from Asia by means of migratory birds. Wild waterfowl are the natural reservoirs of influenza A viruses, but they usually do not get sick from them. H5N1 in its highly pathogenic form has been isolated from dead migratory birds (Liu et al., 2005). This finding may suggest a role for migratory waterfowl in the evolution and maintenance of highly pathogenic H5N1. The role of imported infected wild birds was demonstrated in October 2005, when two smuggled hawk eagles carried on a flight from Thailand to Belgium tested positive for H5N1 (WHO, 2005), and when a parrot imported from Surinam to the United Kingdom was found positive for H5N1 (www.defra.gov.uk/news/latest/2005/animal-1024.htm).

Human behavior and demographic factors

Aspects of human behavior and other demographic factors can influence the epidemiology of viral zoonoses. These include human recreational activities, such as hunting, camping, and hiking as well as eating habits and sexual habits.

Acquired immunodeficiency syndrome (AIDS)

The AIDS pandemic is probably the major example of a zoonosis that emerged in the 20th century; it entered the human population as a result of cross-species transmission of SIVs. Since the initial clinical description of AIDS 25 years ago (Gottlieb et al., 1981), about 30 million persons have died of AIDS worldwide and it is estimated that approximately 40 million people are living and infected with the etiologic agent of AIDS, Human Immunodeficiency Virus, type 1 (HIV-1). It is estimated that there are 6 million new infections per year, which means that an average of about 14,000 persons become infected per day, or 10 persons are newly infected every minute (www.WHO.int/hiv).

The two types of human HIV, HIV-1 and HIV-2, are members of the Retrovirus family and the genus *Lentivirus*. HIV-1 consists of three distinct groups (M, N, and O), with group M being responsible for the majority of HIV infections worldwide. HIV-2 is represented by six subtypes, A–F. Current molecular biological evidence indicates that the SIV counterparts of HIV-1 and HIV-2 have been transmitted into the human population on several occasions from two distinct primate sources: HIV-1 from the chimpanzee *Pan troglodytes troglodytes* (from the virus SIVcpz) and HIV-2 from the sooty mangabey monkey *Cercocebus atys* (virus SIVsm) (Gao et al., 1999; Hahn et al., 2000; Sharp et al., 2001). Since the three groups of HIV-1 (M, N, and O) genetically differ as much from each other as do different SIVcpz genomes, it is believed that they are each derived from a separate zoonotic transmission. Likewise, for HIV-2 there may have been six separate crossover events from sooty mangabeys to humans.

Although the simian lentiviruses are termed immunodeficiency viruses because of their genetic and structural similarities to the human AIDS viruses, the SIVs have not been linked to diseases in their natural hosts (Cichutek and Norley, 1993). SIV infections appear to be common and geographically widespread in African primates; in at least 31 different non-human primate species there has been evidence of SIV infection. In contrast, no Asian primate species has been reported to harbor SIV in the wild (Sharp et al., 2001); for instance, rhesus macaques do not seem to be naturally infected with SIV. However, cross-species transmission of the strain SIVsm from sooty mangabey to an "unnatural host", the macaque, results in immunosuppression and an AIDS-like disease in the macaque. SIVsm infection of macaques now serves as a valuable model for HIV disease in humans and has been used for vaccine development (Letvin, 1992) (Fig. 1).

The timing of SIVcpz cross-species transmission to humans, leading to the HIV-1 pandemic, has been evaluated using stored samples and molecular biological tools. A stored human serum sample from 1959 in Kinshasa, DRC contains the earliest laboratory-proven evidence of HIV-1 group M infection (Zhu et al., 1998). By use of the molecular clock approach, this particular chimpanzee-to-human transmission is estimated to most likely have occurred around 1930 (Korber et al., 2000).

Fig. 1 Non-human primates represent the origin of many important viral zoonoses (For colour version: see Colour Section on page 347).

Group O, was not identified until 1990 and has spread to a much lesser extent than group M. However, the genetic diversity points to an origin in time similar to that of group M. The earliest stored samples shown to contain HIV-1 group O are from a Norwegian sailor and his family, all of whom died in 1976 (Froland et al., 1988; Jonassen et al., 1997). The sailor probably was infected during a visit to Africa in the early 1960s and showed symptoms of AIDS by 1966. The daughter is the first recorded case of pediatric AIDS.

HIV-1 group N seems to have arisen more recently. This is most similar to SIVcpz. The scarcity of group N infections in humans may reflect a recent transmission event or, alternatively, lack of adaptation to the new host.

Sooty mangabey monkeys are the natural host for SIVsm and are infected in the wild at apparently high frequency (Hahn et al., 2000). Sooty mangabey monkeys inhabit forests in West Africa and are often hunted for food and are also kept as pets. HIV-2 is endemic among humans in West Africa and is frequently found in patients in, or originating from, that region. SIVsm and HIV-2 sequences from animals and humans from the same immediate geographic area are most closely related, consistent with the molecular biological evidence of cross-species transmission. Although HIV-2 also is associated with immunodeficiency and development of AIDS, the progression is slower than for HIV-1. HIV-2 also is appears less easily transmitted than HIV-1, with fewer cases of mother-to-child transmission and the lack of a pandemic such as seen with HIV-1 (Pepin et al., 1991; Lemey et al., 2003). HIV-1 group M viruses have spread globally, but HIV-2 subtypes are mainly restricted to West Africa and can be categorized as epidemic subtypes (A and B) and non-epidemic subtypes (C–G).

All primates that naturally carry SIV have been in contact with humans for thousands of years. Yet, despite centuries of opportunity to emerge as infections in humans, there is no evidence to suggest that HIV existed in Africa prior to the 20th century. Moreover, the chimpanzee and the sooty mangabey hosts are not found in

the same areas in Africa, but exist in widely separated, non-contiguous regions (Marx et al., 2001). To explain the almost simultaneous emergence of HIV-1 and HIV-2, occurring in different parts of Africa, Marx et al. (2001) suggested that a massive increase in unsterile medical injections may have served to increase the probability of serial transmission of partially adapted SIV infections in humans, particularly as a result of the general availability of penicillin beginning in the early 1950s. According to this theory, serial passage of partially adapted SIV between humans resulted in a cumulative series of mutations and the emergence of epidemic HIV strains.

The AIDS epidemic in Romania is a documented example of the role that unsterile injections can play in the serial transmission of HIV. Before December 1989, 13 AIDS cases were identified in Romania as reported to the WHO. By December 31, 1990, almost 1200 cases were reported, of which 94% occurred in children <13 years of age. Almost 60% of those children had acquired HIV infection from unsterilized medicinal use of needles and syringes (Hersh et al., 1991).

Human T-lymphotropic viruses

Human T-lymphotropic Virus, type 1 (HTLV-1) is associated with adult T-cell leukemia (ATL) and a variety of immune-mediated disorders, including the chronic neurological disease named HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Barmak et al., 2003; Proietti et al., 2005). ATL was originally described as a particular leukemia, with a striking cluster of cases in Kyushu island, Japan, in 1976, which suggested a unique etiology (Uchiyama et al., 1977). HTLV-1 was first isolated in 1979 (Poiesz et al., 1980). ATL or HAM/TSP occurs among only 1–5% of seropositive individuals. The vast majority of infected individuals remain asymptomatic virus carriers.

A few years later, a virus quite similar to HTLV-1, now called HTLV-2, was isolated from a person with T-cell "hairy cell leukemia". Despite being isolated from a patient with leukemia, there is no convincing role of HTLV-2 in human disease (Feuer and Green, 2005). HTLV-2 is endemic at a low level among the American Indian population in Brazil and among certain tribes in Africa, whereas in Europe and in the US it is mainly associated with intravenous drug abuse, still at a very low level (Alcantara et al., 2003). An interesting question is whether serial passage of this abuse, still at a very low level virus can result in cumulative mutations leading to emergence of a more pathogenic virus.

The simian counterpart of HTLV, STLV (simian T-lymphotropic virus) is endemic in many African and Asian monkeys; it can infect most Old World primate species (Watanabe et al., 1986; Slattery et al., 1999). In some instances, STLV-1 infection has been related to lymphomas and leukemias in monkeys (Sakakibara et al., 1986). STLV-1 sequences have been identified in a wild-caught gorilla and a chimpanzee in Cameroon (Nerrienet et al., 2004) that are similar to the sequence of HTLV-1 of central African subtype B, supporting the suggestion that HTLV-1

subtypes in humans have arisen from separate interspecies transmissions from STLV-1 infected monkeys (Vandamme et al., 1998).

Foamy viruses

Foamy viruses are widely distributed retroviruses and are endemic in most mammals except humans. Virtually all non-human primate species harbor distinct and species-specific clades of SFVs (Heneine et al., 2003). There is so far no clear role for foamy viruses in disease. They appear to be non-pathogenic viruses *in vivo,* in contrast to their strong cytopathic effects *in vitro* (Falcone et al., 2003). In the wild, these viruses are readily spread, most likely via biting. They can be found in all tissues as integrated DNA copies, but the replication has only been demonstrated in oral submucosal cells, which probably explains the natural route of transmission (Falcone et al., 1999).

Humans are susceptible to infection by SFV, as shown by a relatively high frequency of seropositivity (5.3%) among individuals working with primates at research centers and zoos (Switzer et al., 2004). However, all seropositive persons have been reported to be in good health even after longstanding infection (as long as 26 years, documented by an archival serum sample) and there has been no documented secondary transmission to spouses. Thus, these zoonotic infections may represent benign dead-end infections.

Bushmeat—a source for transmission of new viruses

Hunting of wildlife for food is associated with a substantial risk for cross-species transmission of new pathogens. The risk of zoonotic transmission and emergence of new zoonoses is increasing due to an increasing demand for food for the growing human population, and a globalized trade. In Africa, the forest is often referred to as ''the bush'', and thus, meat derived from it is often called ''bushmeat''. Non-human primates and other wildlife probably have been killed for food in parts of Africa for generations; it is estimated to account for 50–80% of the protein in the diet in some parts of Africa. Hunting, butchering, and eating bushmeat places people at increased risk of exposure to primate retroviruses and other zoonotic agents. Deforestation of tropical forests also contributes to increased contact with non-human primates and the consumption of bushmeat.

Since SFV is endemic in most non-human primates, the presence of SFV infection among bushmeat hunters can serve as a marker for the risk of acquiring potentially pathogenic simian retroviruses via zoonotic transmission. A study of 1099 individuals in Cameroon identified 10 persons (1%) with serologic evidence of SFV infection. Sequence analysis of samples from human lymphocytes revealed three viruses with known associations with three different non-human primates, associated with individual histories of contact with blood or body fluids from those primates, thus indicating separate zoonotic transmissions from gorilla, mandrill, and Brazza's guenon (Wolfe et al., 2004).

Two new unique HTLVs, designated HTLV-3 and HTLV-4, also have been associated with bushmeat preparation and/or consumption in rural villages in southern Cameroon (Calattini et al., 2005; Wolfe et al., 2005a). Serologic surveys of bushmeat hunters in southern Cameroon (Wolfe et al., 2005a) and among different tribes living in remote villages in the rainforest in Cameroon (Calattini et al., 2005) were performed with the aim of searching for infection of divergent HTLVs. The simian counterpart of HTLV-3, STLV-3, has been identified in wild-caught monkey species from several different ecosystems in Africa (Meertens and Gessain, 2003). So far, HTLV-3 infection has not been linked to disease and it is not known whether it is transmissible between humans. (HTLV-4 was identified in a Cameroonian bushmeat hunter (Wolfe et al., 2005a). The origin of HTLV-4 is unclear because so far no simian counterpart has been identified, although it most likely represents either an ancient or a recent transmission to humans from a non-human primate.)

The naming of HTLV-3 and HTLV-4 may need a word of caution. The strong phylogenetic relationship between the two HTLV-3 isolates and STLV-3 appears to justify calling them HTLV-3. However, the one isolate of HTLV-4 is the only known virus in a previously undescribed group; following the guidelines of the International Committee on Taxonomy of Viruses (Fauquet et al., 2004), it qualifies to be named HTLV-4. However, the term "HTLV-3" was used to refer to the virus now known as HIV-1 before the current nomenclature was agreed on (Gallo et al., 1984), and HIV-2 was referred to as "HTLV-4" during the early years after its discovery (Kanki et al., 1987; Kornfeld et al., 1987). There are thus a number of publications already describing an "HTLV-3" and an "HTLV-4" that have nothing to do with the newly discovered viruses. To avoid confusion and misunderstanding, renaming these new viruses should possibly be considered.

Microbial changes and adaptation

Cross-species infections probably occur quite frequently. However, most of them represent transient or abortive infections with no further human-to-human transmission and are thus deed-ends. Despite frequent exposure to SIV-infected monkeys in Africa only about a dozen known cross-species transmissions have occurred in the past 50 years that have resulted in significant human-to-human transmission of what are now known as HIV-1 and HIV-2. Several infections of humans by SFVs, which will not lead to further human-to-human transmission, have been documented. In the human host, the SFV remains mainly in its integrated proviral form and there is no detectable virus replication. Other zoonotic pathogens have also led to several small human epidemics with little or no evidence of human-to-human transmission. This phenomenon has been termed "viral chatter" and is probably an important mechanism in viral emergence (Wolfe et al., 2005b). High rates of viral chatter increase the diversity of virus sequence variants moving into humans and form a basis for accumulation of genetic changes that may result in adaptation to the new host.

The mechanisms that underlie cross-species transfer through host-range expansion and establishment of viruses in a new host species depend on the accumulation of genetic changes that may result in adaptation to the new host (Kilbourne, 1991). This process can occur by various mechanisms such as mutations, genetic drift, genetic shift, reassortment, and recombination. Most of the genetic changes do not result in altered proteins (silent mutations). Others may result in non-functional proteins or proteins with slightly altered properties that may allow the virus to adapt to a new milieu.

Mutations can occur in the genomes of both RNA and DNA viruses. However, because the genomes in RNA viruses are replicated by RNA polymerases that lack the proofreading function of many DNA polymerases, mistakes made by the polymerase during replication will not be corrected. Mutations can therefore occur much more frequently in RNA viruses than in DNA viruses. As a consequence, RNA viruses generally evolve more rapidly and lead to genetic heterogeneity, which can be seen as the presence of viral quasispecies. This means that, in the infected individual, the virus exists as a population of genetically related but divergent variants, of which the most common variant is a "master sequence". While the master sequence remains the dominant one, the spectrum of mutants may shift in response to selective pressure and any variant may be selectively expanded (Domingo and Holland, 1997). The importance of quasispecies was first recognized in infections with HIV-1 (Meyerhans et al., 1989).

Accumulation of point mutations is regarded as a major mechanism driving the adaptation of viruses to new hosts. However, evolution of the virus also can occur through recombination, leading to the exchange of parts of genomes. For recombination to take place, it is necessary that the cell be co-infected by two different virus variants.

Influenza A

Genetic changes typically influence the epidemiology of influenza viruses. Surveillance and characterization of the circulating strains are important in determining whether an available influenza vaccine will give protection or not. Influenza viruses are classified into types A, B, and C, of which types B and C are specific to humans, whereas type A viruses can have different hosts, both birds and different mammals including humans. There are only three A subtypes of influenza viruses (H1N1, H1N2, and H3N2) known to be currently circulating among humans as seasonal influenza. The seasonal influenza epidemics occur as a result of genetic drift, the accumulation of point mutations that occur due to lack of proofreading (Webster et al., 1992). Antigenic shift, an abrupt change in the hemagglutinin and/or the neuraminidase proteins of the virus, causes the sudden emergence of a new subtype of a type A virus that is antigenically distinct from former circulating influenza A viruses. The new virus is potentially capable of causing an epidemic in an immunologically naïve human population (Webster et al., 1992). Worldwide epidemics, called pandemics, occur only occasionally.

Avian influenza A viruses have caused occasional human infections since 1997. Most incidents have occurred in Asia (H5N1 yearly since 2003), in January 2006 in Turkey (H5N1), in the Netherlands in 2003 (H7N7), and a few instances in Canada in 2004 (H7N3), and in the US in 2002 (H7N2). To date, human infections with avian influenza A have not resulted in sustained human-to-human transmissions, although in certain instances transmission to family members cannot be ruled out (www.cdc.gov/flu/avian/gen-info/avian-flu-humans).

Of the avian influenza A variants infecting humans during the last decade, the 1997 Hong Kong H5N1 epidemic involved the most pathogenic variant. Analysis of the virus genome revealed that a reassorted virus entirely of avian origin had crossed the species barrier without adaptation to a mammalian host (Hatta and Kawaoka, 2002). There is evidence that H5N1 is now endemic in parts of Asia, having established a permanent ecological niche in poultry. As of January 2006, H5N1 has spread to Europe, with outbreaks among wild birds (Croatia and Romania), poultry (Turkey, Romania, and Ukraine), and humans (Turkey). Genomic analyses of H5N1 virus isolates from birds and humans show that the hemagglutinin has undergone significant antigenic drift since 1997 (Horimoto et al., 2004). Moreover, evidence further suggests that H5N1 is expanding its mammalian host range in that an outbreak was documented among captive tigers in Thailand (Keawcharoen et al., 2004).

SARS coronavirus

The severe acute respiratory syndrome coronavirus (SARS-CoV), the agent of SARS, emerged as a new cross-species transmission event in Guandong province, China, in 2002 and caused a serious epidemic in 2003, spreading to a number of other countries. Beijing experienced the largest SARS outbreak, with more than 2000 cases and a close to 10% fatality rate (Liu, 2005). Through a remarkable effort, the infectious agent was rapidly identified.

Coronaviruses closely related to SARS-CoV were discovered in several wild animal species and in live animal markets in Guandong. SARS-CoV isolated from patients during the 2002–2003 epidemic and from sporadic cases in 2003 and 2004 appears to be derived from a nearly identical virus in palm civets and raccoon dogs (Guan et al., 2003) (Fig. 2).

Sequencing of hundreds of SARS virus genomes from humans and animals have identified mutations in the receptor-binding domain (RBD) that distinguish the species-specific strains (Song et al., 2005). (The RBD of coronaviruses is located in the spike protein (S). Trimers of the S-protein bind to the specific cellular receptor, which for the SARS virus is angiotensin-converting enzyme 2 (ACE2); Prabakaran et al., 2004.) Only four amino acids differ between the human and the civet strains, but the human viral S-protein binds the human receptor 1000–10, 000 times more tightly than does its civet S-protein counterpart. The intimate interface between a loop of the S-protein of viruses from the SARS epidemic in 2002–2003 and human ACE2 mediates efficient binding and infection of the cell, which

Fig. 2 Animal markets represent a risk factor for transmission of various viral zoonoses, e.g. SARS. *Source*: Reuters/SCANPIX. (For colour version: see Colour Section on page 347).

probably is a key factor in determining the severity and possibly human-to-human transmission (Li F. et al., 2005). In contrast, S-protein from viruses of sporadic SARS cases in 2003 and 2004, each of which was an independent cross-species event with no further human-to-human transmission, had amino acids that more closely resembled the civet virus. The outcome was a reduced binding to human ACE2 and less efficient infection. Epidemiological investigation of the 2003 and 2004 SARS cases showed that SARS-CoV-positive palm civets, kept alive in cages close to the customers while waiting to be prepared as dinners in a restaurant, were the source for transmission to a waitress working in the restaurant and to a customer eating there (Wang M. et al., 2005).

In addition to mutations in the S-protein that resulted in high-affinity binding to the human receptor, molecular epidemiology and phylogenetic studies have identified a series of mutations in the so-called 5-locus motif (Liu, 2005). The mutations that occurred at different times in two geographically separate locations in China suggest a dominant process occurring during viral adaptation to the human host. The mutations observed in Beijing followed the same molecular path

as isolates from Guandong and from the epidemic outside China, i.e. an early GACTC motif was followed by transition to GGCTC motif before appearance of the stable TGTTT motif.

The SIVcpz recombination

The origin of the HIV-1 pandemic has been traced to the SIVcpz virus of chimpanzees (identified in two chimpanzee subspecies, *P. troglodytes troglodytes* and *P. troglodyte schweinfurthii,* but not in the third species, *P. troglodytes verus)*. Species-specific strains of SIV (like SIVsm and SIVagm) have been identified in more than 30 African primate species, but all except SIVcpz infect monkeys. SIVs seem to be non-pathogenic in the vast majority of natural hosts despite high levels of virus replication (Apetrei et al., 2004). This may be a consequence of the fact that the incubation period of the disease generally exceeds the life span of the host. SIVs also have a high propensity for cross-species transmission. SIV phylogeny is complex and analyses indicate recombination among viruses from different major lineages. Of the identified recombinants, SIVcpz so far represents the most important one, being the source of the HIV-1 pandemic. SIVrcm from red-capped mangabeys and SIVgsn from greater spot-nosed monkeys are most closely related to SIVcpz, but they are similar only in certain regions of the genome that do not overlap. Extensive phylogenetic analyses of subsets of SIV strains comparing the topologies among four regions of the proteome have provided evidence for a more recent origin of SIVcpz than of other strains, being a result of recombination between ancestors of SIVgsn and SIVrcm (Bailes et al., 2003). The geographic region of these two monkey species overlaps that of the chimpanzee and it is known that chimpanzees hunt smaller monkeys for food. The founder chimpanzee most likely was infected by one of the ancestor SIVs and thereafter became superinfected by the other ancestor virus, leading to recombination in a doubly infected cell.

The hybrid origin of SIVcpz, in contrast to SIVsm (from which HIV-2 is derived), has several important implications. First, it provides evidence that, in addition to humans, another primate species can acquire cross-species transmission under natural conditions. Second, the hybrid virus had adapted to the host and established substantial secondary spread within the species. Third, the chimpanzee virus was capable of spreading to humans. Moreover, the chimpanzee most likely acquired SIV-infection relatively recently, subsequent to the split of the chimpanzee into two subspecies, since SIVcpz has not been found in the third chimpanzee subspecies, *P. troglodytes verus*.

Retrovirus superinfection and recombination—potential emergence of new viruses

Two biological properties of retroviruses make them particularly likely candidates for the generation of new emerging viruses. One is the integration of the reversely transcribed provirus into the cellular genome, causing a life-long infection. Another

is the potential for superinfection, in which recombination may occur when a cell becomes infected with two genetically distinct viruses. During reverse transcription, the reverse transcriptase can switch from one RNA template to the other, thereby generating a progeny that is a mosaic of the parent viruses (Preston et al., 1988). HIV-1 genomes with this kind of mosaic structure are called circulating recombinant forms (CRFs). There are an increasing number of such CRFs identified; CRF 01_AE is mainly responsible for the HIV epidemic in Southeast Asia (Takebe et al., 2003; Watanaveeradej et al., 2003). These CRFs now constitute 10–20% of newly characterized circulating strains (Perrin et al., 2003).

The recent cross-species transmission of retroviruses like SFV and the recognition of two new HTLV retroviruses (HTLV-3 and HTLV-4) open wider possibilities of superinfection. Concomitant HIV-1 and HIV-2 infections have been documented in Africa, India, and Greece (Georgoulias et al., 1988; Rubsamen-Waigmann et al., 1994; Esteves et al., 2000). However, recombination between HIV-1 and HIV-2 has not been reported so far. Although recombination frequently takes place in HIV-1, certain genetic barriers may exist to recombination with HIV-2 or other retroviruses such as SFV, HTLV, etc.

Prevention and control

Efficient and cost-effective prevention and control of viral zoonoses necessitates an understanding of the nature of zoonoses and their ecology. The emergence of a new viral zoonosis and its further development into a pandemic can be conceptualized as a series of steps leading from initial contact to global spread and depends largely on three factors: (1) The prevalence of a potential zoonotic virus in animal populations and the frequency of human contact with these animal reservoirs. (2) Successful transmission of the zoonotic virus from the animal reservoir to humans, establishment of a productive infection in humans, and further direct transmission between humans. (3) The movement of the zoonotic virus into the global population.

The prevention and control of viral zoonoses share many common aspects, but in all cases the animal reservoir must be considered in the risk-analysis framework. It is thus important to integrate medical, veterinary, ecological, and other sciences in interdisciplinary teams (Daszak et al., 2004, FAO, WHO, and OIE, 2004). The role of bats in the etiology of many viral zoonoses illustrates the challenges of prevention and control (Dobson, 2005). Bats represent a reservoir of rabies, Hendra, Menangle, and Nipah viruses. Furthermore, there is strong evidence that bats may be the wildlife reservoir of Ebola virus and one of the reservoirs of SARS-CoV (Leroy et al., 2005; Li W. et al., 2005). Although SARS-CoV isolated from humans appeared to derive from a nearly identical virus circulating in masked palm civets and racoon dogs (Guan et al., 2003; Song et al., 2005), subsequent studies did not reveal widespread infection in wild or farmed civets, and experimental infection of civets with human SARS-CoV resulted in overt clinical symptoms suggesting that they are not the reservoir. A recent large study of different bat species from four

locations in China showed a high prevalence and wide distribution of SARS-CoV-seropositive bats (Lau et al., 2005; Li W. et al., 2005). Although horseshoe bats appear to be the natural reservoir of a SARS-like corona virus (SL-CoV), it is not clear how this virus could have got from the bat or another reservoir to humans. The human and civet isolates of SARS-CoV are phylogenetically located within the spectrum of these SL-CoVs. One possibility is that bats passed the virus to civets or to other animals in the wild or in the live animal markets of southern China.

In the wild, bats can transmit viruses to other species from the fruit they spit out after extracting the juice and sugars. This could explain how gorillas and chimpanzees might acquire Ebola virus during seasonal fruiting events when bats and primates feed among the same fruit-bearing trees. In the near future, zoonotic transmission of viruses from bats to humans must be given greater attention.

In order to increase the capability of recognizing viral zoonoses, there is a need for better national surveillance systems both in humans and animals, and better international sharing of information from such surveillance systems. Improved notification systems and screening programs for human infections, including the application of syndromic surveillance, are warranted in order to detect new and emerging zoonoses. Efficient surveillance is dependent upon a laboratory system that is capable of identifying and characterizing the pathogens in question. More research is needed to understand better the epidemiology and pathogenesis of various zoonoses, to improve diagnostic methods, and to develop cost-effective vaccines and drugs. Training and education are prerequisites in order to enable the personnel involved at the various stages, from field to laboratory personnel, to detect zoonoses. Information and communication are key components in any prevention and control strategy, and this should also involve the general public. The importance of public education and behavioral change are critical factors for successful intervention. The implementation of restrictions of animal movements caused by human activity is another important preventive measure. For vector-borne zoonoses, vector control should be an integral part of any intervention strategy.

Interdisciplinary and international collaboration are crucial for the rapid identification and effective management of viral zoonoses. The pivotal role of international organizations such as the World Health Organization, the Food and Agricultural Organization, and the Office International des Epizooties is exemplified by the response to the current avian influenza outbreak in Asia and Europe. Containment of viral zoonoses relies on efficient national, regional, and international cross-sectional networks to improve data sharing and enable a timely and effective response to disease outbreaks.

References

Alcantara LC, Shindo N, Van Dooren S, Salemi M, Costa MC, Kashima S, Covas DT, Vandamme AM, Galvao-Castro B. Brazilian HTLV type 2a strains from intravenous

drug users (IDUs) appear to have originated from two sources: Brazilian Amerindians and European/North American IDUs. AIDS Res Hum Retroviruses 2003; 19: 519.
Apetrei C, Robertson DL, Marx PA. The history of SIVS and AIDS: epidemiology, phylogeny and biology of isolates from naturally SIV infected non-human primates (NHP) in Africa. Front Biosci 2004; 9: 225.
Bailes E, Gao F, Bibollet-Ruche F, Courgnaud V, Peeters M, Marx PA, Hahn BH, Sharp PM. Hybrid origin of SIV in chimpanzees. Science 2003; 300: 1713.
Ballard WB, Follmann EH, Ritter DG, Robards MD, Cronin MA. Rabies and canine distemper in an arctic fox population in Alaska. J Wildl Dis 2001; 37: 133.
Barmak K, Harhaj E, Grant C, Alefantis T, Wigdahl B. Human T cell leukemia virus type I-induced disease: pathways to cancer and neurodegeneration. Virology 2003; 308: 1.
Blancou J. History of the Surveillance and Control of Transmissible Animal Diseases. Paris: Office International des Epizooties; 2003; p. 362.
Calattini S, Chevalier SA, Duprez R, Bassot S, Froment A, Mahieux R, Gessain A. Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa. Retrovirology 2005; 2: 30.
Chua KB, Chua BH, Wang CW. Anthropogenic deforestation, El Nino and the emergence of Nipah virus in Malaysia. Malays J Pathol 2002; 24: 15.
Cichutek K, Norley S. Lack of immune suppression in SIV-infected natural hosts. AIDS 1993(Suppl 1): S25.
Daszak P, Tabor GM, Kilpatrick AM, Epstein J, Plowright R. Conservation medicine and a new agenda for emerging diseases. Ann N Y Acad Sci 2004; 1026: 1.
Dobson AP. Virology. What links bats to emerging infectious diseases? Science 2005; 310: 628.
Domingo E, Holland JJ. RNA virus mutations and fitness for survival. Annu Rev Microbiol 1997; 51: 151.
Esteves A, Parreira R, Piedade J, Venenno T, Canas-Ferreira WF. Genetic characterization of HIV type 1 and type 2 from Bissau, Guinea-Bissau (West Africa). Virus Res 2000; 68: 51.
Falcone V, Leupold J, Clotten J, Urbanyi E, Herchenroder O, Spatz W, Volk B, Bohm N, Toniolo A, Neumann-Haefelin D, Schweizer M. Sites of simian foamy virus persistence in naturally infected African green monkeys: latent provirus is ubiquitous, whereas viral replication is restricted to the oral mucosa. Virology 1999; 257: 7.
Falcone V, Schweizer M, Neumann-Haefelin D. Replication of primate foamy viruses in natural and experimental hosts. Curr Top Microbiol Immunol 2003; 277: 161.
FAO, WHO, and OIE. Report of the FAO/WHO/OIE Joint Consultation on Emerging Zoonotic Diseases in Collaboration with the Health Council of the Netherlands. Geneva, Switzerland; 2004.
Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA. Virus Taxonomy, Seventh Report on the International Committee on Taxonomy of Viruses. London: Elsevier; 2004; p. 421.
Feuer G, Green PL. Comparative biology of human T-cell lymphotropic virus type 1 (HTLV-1) and HTLV-2. Oncogene 2005; 24: 5996.
Froland SS, Jenum P, Lindboe CF, Wefring KW, Linnestad PJ, Bohmer T. HIV-1 infection in Norwegian family before 1970. Lancet 1988; 1: 1344.
Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984; 224: 500.

Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH. Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. Nature 1999; 397: 436.

Georgoulias V, Fountouli D, Karvela-Agelakis A, Komis G, Malliarakis-Pinetidou E, Antoniadis G, Samakidis K, Kondakis X, Papapetropoulou M, Zoumbos N. HIV-1 and HIV-2 double infection in Greece. Ann Intern Med 1988; 108: 155.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981; 305: 1425.

Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, Butt KM, Wong KL, Chan KW, Lim W, Shortridge KF, Yuen KY, Peiris JS, Poon LL. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 2003; 302: 276.

Gubler DJ. Resurgent vector-borne diseases as a global health problem. Emerg Infect Dis 1998; 4: 442.

Hahn BH, Shaw GM, De Cock KM, Sharp PM. AIDS as a zoonosis: scientific and public health implications. Science 2000; 287: 607.

Hatta M, Kawaoka Y. The continued pandemic threat posed by avian influenza viruses in Hong Kong. Trends Microbiol 2002; 10: 340.

Heneine W, Schweizer M, Sandstrom P, Folks T. Human infection with foamy viruses. Curr Top Microbiol Immunol 2003; 277: 181.

Hersh BS, Popovici F, Apetrei RC, Zolotusca L, Beldescu N, Calomfirescu A, Jezek Z, Oxtoby MJ, Gromyko A, Heymann DL. Acquired immunodeficiency syndrome in Romania. Lancet 1991; 338: 645.

Horimoto T, Fukuda N, Iwatsuki-Horimoto K, Guan Y, Lim W, Peiris M, Sugii S, Odagiri T, Tashiro M, Kawaoka Y. Antigenic differences between H5N1 human influenza viruses isolated in 1997 and 2003. J Vet Med Sci 2004; 66: 303.

Hubálek Z. Emerging human infectious diseases: anthroponoses, zoonoses, and sapronoses. Emerg Infect Dis 2003; 9: 403.

Jonassen TO, Stene-Johansen K, Berg ES, Hungnes O, Lindboe CF, Froland SS, Grinde B. Sequence analysis of HIV-1 group O from Norwegian patients infected in the 1960s. Virology 1997; 231: 43.

Kanki PJ, Hopper JR, Essex M. The origins of HIV-1 and HTLV-4/HIV-2. Ann N Y Acad Sci 1987; 511: 370.

Keawcharoen J, Oraveerakul K, Kuiken T, Fouchier RA, Amonsin A, Payungporn S, Noppornpanth S, Wattanodorn S, Theambooniers A, Tantilertcharoen R, Pattanarangsan R, Arya N, Ratanakorn P, Osterhaus DM, Poovorawan Y. Avian influenza H5N1 in tigers and leopards. Emerg Infect Dis 2004; 10: 2189.

Kilbourne ED. New viruses and new disease: mutation, evolution and ecology. Curr Opin Immunol 1991; 3: 518.

Korber B, Muldoon M, Theiler J, Gao F, Gupta R, Lapedes A, Hahn BH, Wolinsky S, Bhattacharya T. Timing the ancestor of the HIV-1 pandemic strains. Science 2000; 288: 1789.

Kornfeld H, Riedel N, Viglianti GA, Hirsch V, Mullins JI. Cloning of HTLV-4 and its relation to simian and human immunodeficiency viruses. Nature 1987; 326: 610.

Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, Wong SS, Leung SY, Chan KH, Yuen KY. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci USA 2005; 102: 14040.

Lederberg J, Shope RE, Oaks SC, editors. Emerging Infections: Microbial Threats to Human Health in the United States. Washington, DC: National Academies Press; 1992.

Lemey P, Pybus OG, Wang B, Saksena NK, Salemi M, Vandamme AM. Tracing the origin and history of the HIV-2 epidemic. Proc Natl Acad Sci USA 2003; 100: 6588.

Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, Delicat A, Paweska JT, Gonzalez JP, Swanepoel R. Fruit bats as reservoirs of Ebola virus. Nature 2005; 438: 575.

Letvin NL. Animal models for the study of human immunodeficiency virus infections. Curr Opin Immunol 1992; 4: 481.

Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science 2005; 309: 1864.

Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005; 310: 676.

Lindgren E, Gustafson R. Tick-borne encephalitis in Sweden and climate change. Lancet 2001; 358: 16.

Liu J, Xiao H, Lei F, Zhu Q, Qin K, Zhang XW, Zhang XL, Zhao D, Wang G, Feng Y, Ma J, Liu W, Wang J, Gao GF. Highly pathogenic H5N1 influenza virus infection in migratory birds. Science 2005; 309: 1206.

Liu W, Tang F, Fontanet A, Zhan L, Wang TB, Zhang PH, Luan YH, Cao CY, Qiu-Min Zhao QM, Wu XM, Xin ZT, Zuo SQ, Baril L, Vabret A, Shao YM, Yang H, Cao WC. Molecular Epidemiology of SARS-associated Coronavirus. Beijing. Emerg. Infect. Dis. 2005; 11: 1420.

Marr JS, Calisher CH. Alexander the Great and West Nile Virus encephalitis. Emerg Infect Dis 2003; 9: 1599.

Marx PA, Alcabes PG, Drucker E. Serial human passage of simian immunodeficiency virus by unsterile injections and the emergence of epidemic human immunodeficiency virus in Africa. Philos Trans R Soc Lond B Biol Sci 2001; 356: 911.

McMichael AJ. Environmental and social influences on emerging infectious diseases: past, present and future. Philos Trans R Soc Lond B Biol Sci 2004; 359: 1049.

Meertens L, Gessain A. Divergent simian T-cell lymphotropic virus type 3 (STLV-3) in wild-caught *Papio hamadryas papio* from Senegal: widespread distribution of STLV-3 in Africa. J Virol 2003; 77: 782.

Meyerhans A, Cheynier R, Albert J, Seth M, Kwok S, Sninsky J, Morfeldt-Manson L, Asjo B, Wain-Hobson S. Temporal fluctuations in HIV quasispecies *in vivo* are not reflected by sequential HIV isolations. Cell 1989; 58: 901.

Murphy FA. Emerging zoonoses. Emerg Infect Dis 1998; 4: 429.

Nerrienet E, Meertens L, Kfutwah A, Foupouapouognigni Y, Ayouba A, Gessain A. Simian T cell leukaemia virus type I subtype B in a wild-caught gorilla (*Gorilla gorilla gorilla*) and chimpanzee (*Pan troglodytes vellerosus*) from Cameroon. J Gen Virol 2004; 85: 25.

Niklasson B, Le Duc J. Isolation of the nephropathia epidemica agent in Sweden. Lancet 1984; 1: 1012.

O'Sullivan JD, Allworth AM, Paterson DL, Snow TM, Boots R, Gleeson LJ, Gould AR, Hyatt AD, Bradfield J. Fatal encephalitis due to novel paramyxovirus transmitted from horses. Lancet 1997; 349: 93.

Pepin J, Morgan G, Dunn D, Gevao S, Mendy M, Gaye I, Scollen N, Tedder R, Whittle H. HIV-2-induced immunosuppression among asymptomatic West African prostitutes: evidence that HIV-2 is pathogenic, but less so than HIV-1. AIDS 1991; 5: 1165.

Perrin L, Kaiser L, Yerly S. Travel and the spread of HIV-1 genetic variants. Lancet Infect Dis 2003; 3: 22.

Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 1980; 77: 7415.

Prabakaran P, Xiao X, Dimitrov DS. A model of the ACE2 structure and function as a SARS-CoV receptor. Biochem Biophys Res Commun 2004; 314: 235.

Preston BD, Poiesz BJ, Loeb LA. Fidelity of HIV-1 reverse transcriptase. Science 1988; 242: 1168.

Prestrud P, Krogsrud J, Gjertz I. The occurrence of rabies in the Svalbard islands of Norway. J Wildl Dis 1992; 28: 57.

Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. Oncogene 2005; 24: 6058.

Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV, Kazmierczak JJ, Stratman EJ, Li Y, Fairley JA, Swain GR, Olson VA, Sargent EK, Kehl SC, Frace MA, Kline R, Foldy SL, Davis JP, Damon IK. The detection of monkeypox in humans in the western hemisphere. N Engl J Med 2004; 350: 342.

Rubsamen-Waigmann H, Maniar J, Gerte S, Brede HD, Dietrich U, Mahambre G, Pfutzner A. High proportion of HIV-2 and HIV-1/2 double-reactive sera in two Indian states, Maharashtra and Goa: first appearance of an HIV-2 epidemic along with an HIV-1 epidemic outside of Africa. Zentralbl Bakteriol 1994; 280: 398.

Sakakibara I, Sugimoto Y, Sasagawa A, Honjo S, Tsujimoto H, Nakamura H, Hayami M. Spontaneous malignant lymphoma in an African green monkey naturally infected with simian T-lymphotropic virus (STLV). J Med Primatol 1986; 15: 311.

Schmaljohn C, Hjelle B. Hantaviruses: a global disease problem. Epidemiol Infect 1997; 3: 95.

Sharp PM, Bailes E, Chaudhuri RR, Rodenburg CM, Santiago MO, Hahn BH. The origins of acquired immune deficiency syndrome viruses: where and when? Philos Trans R Soc Lond B Biol Sci 2001; 356: 867.

Sihvonen L. Documenting freedom from rabies and minimising the risk of rabies being reintroduced to Finland. Rabies Bull Eur 2003; 27: 5.

Slattery JP, Franchini G, Gessain A. Genomic evolution, patterns of global dissemination, and interspecies transmission of human and simian T-cell leukemia/lymphotropic viruses. Genome Res 1999; 9: 525.

Smith JS, Sumner JW, Roumillat LF, Baer GM, Winkler WG. Antigenic characteristics of isolates associated with a new epizootic of raccoon rabies in the U.S. J Infect Dis 1984; 149: 769.

Song HD, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, Zheng HJ, Chern SW, Cheng F, Pan CM, Xuan H, Chen SJ, Luo HM, Zhou DH, Liu YF, He JF, Qin PZ, Li LH, Ren YQ, Liang WJ, Yu YD, Anderson L, Wang M, Xu RH, Wu XW, Zheng HY, Chen JD, Liang G, Gao Y, Liao M, Fang L, Jiang LY, Li H, Chen F, Di B, He LJ, Lin JY, Tong S, Kong X, Du L, Hao P, Tang H, Bernini A, Yu XJ, Spiga O, Guo ZM, Pan HY, He WZ, Manuguerra JC, Fontanet A, Danchin A, Niccolai N, Li YX, Wu CI, Zhao GP. Cross-host evolution of severe acute

respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci USA 2005; 102: 2430.
Switzer WM, Bhullar V, Shanmugam V, Cong ME, Parekh B, Lerche NW, Yee JL, Ely JJ, Boneva R, Chapman LE, Folks TM, Heneine W. Frequent simian foamy virus infection in persons occupationally exposed to nonhuman primates. J Virol 2004; 78: 2780.
Takebe Y, Motomura K, Tatsumi M, Lwin HH, Zaw M, Kusagawa S. High prevalence of diverse forms of HIV-1 intersubtype recombinants in Central Myanmar: geographical hot spot of extensive recombination. AIDS 2003; 17(14): 2077.
Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerg Infect Dis 2006; 12: 15.
Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. Philos Trans R Soc Lond B Biol Sci 2001; 356: 983.
Tei S, Kitajima N, Takahashi K, Mishiro S. Zoonotic transmission of hepatitis E virus from deer to human beings. Lancet 2003; 362: 371.
Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977; 50: 481.
Vandamme AM, Salemi M, Desmyter J. The simian origins of the pathogenic human T-cell lymphotropic virus type I. Trends Microbiol 1998; 6: 477.
Wang M, Yan M, Xu H, Liang W, Kan B, Zheng B, Chen H, Zheng H, Xu Y, Zhang E, Wang H, Ye J, Li G, Li M, Cui Z, Liu YF, Guo RT, Liu XN, Zhan LH, Zhou DH, Zhao A, Hai R, Yu D, Guan Y, Xu J. SARS-CoV infection in a restaurant from Palm Civet. Emerg Infect Dis 2005; 11: 1860.
Wang Q-H, Han MG, Cheetham S, Souza M, Funk JA, Saif LJ. Porcine noroviruses related to human noroviruses. Emerg Infect Dis 2005; 11: 1874.
Ward MA, Burgess NR. *Aedes albopictus*—a new disease vector for Europe? J R Army Med Corps 1993; 139: 109.
Watanabe T, Seiki M, Hirayama Y, Yoshida M. Human T-cell leukemia virus type I is a member of the African subtype of simian viruses (STLV). Virology 1986; 148: 385.
Watanaveeradej V, DeSouza MS, Benenson MW, Sirisopana N, Nitayaphan S, Chanbancherd P, Brown AE, Sanders-Buell E, Birx DL, McCutchan FE, Carr JK. Subtype C/CRF01_AE recombinant HIV-1 found in Thailand. AIDS 2003; 17: 2138.
Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev 1992; 56: 152.
WHO. Ebola Haemorrhagic Fever. Fact Sheet No. 103. http://www.who.int//inf-fs/en/fact103.html2000.
WHO. Avian Influenza: Assessing the Pandemic Threat. http://www.who.int/entity/csr/disease/influenza/H5N1-9reduit.pdf2005.
WHO/FAO. Second Report of the Joint WHO/FAO Expert Committee on Zoonoses. WHO Technical Report Series No. 169. Geneva: WHO; 1959.
Wolfe ND, Daszak P, Kilpatrick AM, Burke DS. Bushmeat hunting, deforestation, and prediction of zoonotic disease. Emerg Infect Dis 2005b; 11: 1822.
Wolfe ND, Heneine W, Carr JK, Garcia AD, Shanmugam V, Tamoufe U, Torimiro JN, Prosser AT, Lebreton M, Mpoudi-Ngole E, McCutchan FE, Birx DL, Folks TM, Burke DS, Switzer WM. Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. Proc Natl Acad Sci USA 2005a; 102(22): 7994.
Wolfe ND, Switzer WM, Carr JK, Bhullar VB, Shanmugam V, Tamoufe U, Prosser AT, Torimiro JN, Wright A, Mpoudi-Ngole E, McCutchan FE, Birx DL, Folks TM, Burke

DS, Heneine W. Naturally acquired simian retrovirus infections in central African hunters. Lancet 2004; 363: 932.

Wong KT, Shieh WJ, Kumar S, Norain K, Abdullah W, Guarner J, Goldsmith CS, Chua KB, Lam SK, Tan CT, Goh KJ, Chong HT, Jusoh R, Rollin PE, Ksiazek TG, Zaki SR, Nipah Virus Pathology Working Group. Nipah virus infection: pathology and pathogenesis of an emerging paramyxoviral zoonosis. Am J Pathol 2002; 161: 2153.

Zhu T, Korber BT, Nahmias AJ, Hooper E, Sharp PM, Ho DD. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. Nature 1998; 391: 594.