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CHAPTER

8

Emerging and Reemerging Viral Diseases

The litany of the viruses described in the previous chapters of this volume makes clear that humans have been subjected to a large number of viral diseases throughout our history. Some of these viruses evolved along with humans and have been present since the earliest human walked the earth. Such viruses include the various herpesviruses, for example, which were present as human pathogens at the time that humans first appeared. Others have been acquired from zoonotic sources. These are animal viruses that have acquired the ability to infect humans. Upon jumping from their animal sources to humans, some of these viruses became human viruses that infect only humans, and humans became the vertebrate reservoir of this new virus. Such viruses include measles, described in Chapter 4, and the dengue viruses, described in Chapter 3 and in this chapter. Many of these viruses entered the human population long ago. Arguments were presented in Chapter 4 that measles virus could not have existed as a human virus until perhaps 5000 years ago when the human population first reached the numbers required to sustain the virus in the population, and that this virus probably jumped from cattle to humans after humans domesticated these animals. Others have entered the human population more recently. The four serotypes of dengue virus, for example, appeared to have jumped independently from monkeys to humans between 200 and 1000 years ago, and HIV was established as a human virus within the last 50–100 years. Other zoonotic viruses that infect humans do so only peripherally and humans do not serve as the vertebrate reservoir of these viruses. Examples are West Nile virus, Eastern equine encephalitis virus, Ebola virus, and rabies virus.

As the human population expands it impinges on wildlife more and more, and changes in habitat caused by humans lead to closer interactions between humans and wildlife, with the result that an increasing number of zoonotic viruses are causing epidemics of serious human disease. Some, like HIV, became human viruses while others, like influenza virus, remain zoonotic viruses. There is growing concern that viruses to date have caused small epidemics in humans but may acquire the ability to cause very large epidemics. In this chapter we will consider a number of viruses that are known to have caused epidemics in humans only within the last century, or that have the potential to cause wide-ranging epidemics in the future, or that are undergoing dramatic range expansion at present.

BAT-ASSOCIATED VIRUSES

A number of emerging viruses are bat viruses that have recently entered the human population and caused small or large epidemics of disease. Although these viruses can cause serious illnesses in humans, they usually cause little or no illness in bats. The recent emergence of bat viruses as human pathogens may seem strange because so many viruses are now known to come from bats, but in fact bats form a sizable proportion of the diversity of mammals. More than 900 species are currently recognized and these constitute more than 20% of all mammalian species. Furthermore, bats are intensely social creatures that are ideally suited to pass viruses back and forth among large populations. Humans impinge more and more into the habitats of bats, and this, as well as disruptions of bat colonies caused by humans, has led to more contact between bats and humans or their domestic animals. Furthermore, in many areas of the world bats are used as food or for medicinal purposes, resulting in human–bat contacts.

Almost all bats are nocturnal. They are classified in the order *Chiroptera*, which has two major divisions or suborders. *Megachiroptera* are mostly large, fruit-eating bats that are classified in a single family, *Pteropodidae*. There are about 170 species distributed throughout the tropics of

the Old World. They find their food, consisting of fruits, flowers, and pollen, using eyesight and an excellent sense of smell. Of these, more than a third, 65, belong to the genus *Pteropus* and are called flying foxes. The *Pteropus* flying foxes are found from Australia across southern Asia and India to Madagascar (Fig. 8.1). They weigh from 300 grams to more than a kilogram and have a wingspan of 0.6 to 1.7 meters. *Microchiroptera* are in general smaller and most eat insects. They are virtually worldwide in distribution. They have evolved echolocation to navigate and find their prey in the dark. Bats play an important role in the ecology of the planet, dispersing seeds, pollinating plants, and reducing the number of night flying insects such as mosquitoes.

Rabies Virus

Rabies virus is an example of a virus for which bats are an important reservoir. Although we think of rabies as being primarily associated with canines such as dogs and other mammals such as skunks and raccoons, and these animals do serve as important reservoirs for rabies that enter the human population, bats are also an important reservoir. In fact, in the United States over the last few years the majority of human cases of rabies have been bat-associated rabies. In some of these cases of bat rabies in humans, exposure to bats is documented and the bite of infected bats is known to have transmitted the virus, but in other cases there is no known contact with bats, leading to the suggestion that inhaling aspirated droplets containing rabies may be the cause of the infection.

In South America, vampire bats, which feed on the blood of mammals after biting them with their sharp incisors, have been an important vector in the spread of rabies to livestock and humans. This has resulted in campaigns to indiscriminately slaughter bats using a variety of methods, including poison and the destruction of roosts and caves with explosives. Although these campaigns have resulted in enormous numbers of bats being killed, these campaigns have had no effect on the spread of rabies. Thus, reduction of bat numbers is not effective in the control of rabies but does destroy ecologically important animals.

The various bat lyssaviruses, which can also cause rabies in humans, were described in Chapter 4. Although only a few human cases are known that arose from infection by these viruses, they have the potential to spread more widely. Further, bites or scratches from bats need to be treated as potential

FIGURE 8.1 Illustration of the distribution of the genus *Pteropus* in the Old World. These large bats, called flying foxes, are present from Madagascar across the Indian subcontinent and throughout the tropical and subtropical regions of Indonesia, Australia, and the Philippines, and as far east as the Cook Islands. Adapted from Figure 1B in Eaton *et al.* (2006).

exposure to rabies and treated accordingly. This is expensive and in effect only available in developed countries.

Henipaviruses

In September of 1994, a number of cases of severe respiratory illness occurred in racehorses near Brisbane, Australia. The first horse to become ill was a pregnant mare that was pastured in a field, which was then moved into a stable with 23 other thoroughbreds. The disease spread among the horses in this stable and to an adjoining stable and ultimately 17 horses became ill, of which 13 died. Of the four horses that survived, two were left with mild neurological sequelae. Three other horses were infected but did not suffer symptoms. Two humans that nursed the horses became ill with a severe respiratory disease, of whom one died of respiratory and kidney failure. Spread of the disease required close contact, and imposition of quarantine measures contained the outbreak. A previously unknown virus was isolated from the sick animals that was found to be a paramyxovirus and it was initially named equine morbillivirus. Sequencing of the genome showed that it was not closely related to the morbilliviruses; however, and the virus was assigned to a new genus called *Megamyxovirus* because of the large size of the genome. Subsequent studies established that the virus was a bat virus and widespread in flying foxes in eastern Australia. The virus was renamed Hendra virus after the Brisbane suburb where the outbreak occurred and the genus was renamed *Henipavirus*. Analysis of sera from healthy humans and horses in the area failed to detect the presence of antibody, and analysis of more than 5000 sera from a variety of wild animals trapped in the areas also failed to detect antibody in any animal other than flying foxes. Flying foxes can be readily infected experimentally with the virus but do not suffer illness upon infection.

A second outbreak of Hendra virus began in August 1994 about 1000 km north of Brisbane. Two horses died and the owner of the horses became mildly ill with neurological symptoms from which he appeared to recover. However, in October of 1995 the owner suffered a relapse and died of encephalitis. At this point an investigation showed that Hendra virus was to blame for the illness of the horses and the death of the owner. In January 1999, a fatal case of Hendra infection occurred in a horse near Cairns, Australia, and in 2004 a horse died of Hendra infection in Townsville. In the 2004 incident the veterinarian who attended the horse was infected but recovered after a mild illness.

Extensive studies of flying foxes have shown that Hendra virus is present in all four species of flying fox that occur in Australia. Almost half of flying foxes have been found to have antibodies to the virus, so it is widespread and common. It is only rarely transmitted to other animals, however, at least to date, as shown by the extensive serological studies and the limited occurrence of clinical illness caused by the virus in humans and their horses.

A related virus, 83% identical to Hendra virus at the amino acid level, emerged in 1998 that represents a much more serious threat to human health. From September 1998 to April 1999, an outbreak of 258 cases of human encephalitis occurred in Malaysia and Singapore that had a 40% mortality rate. Clinical symptoms included fever, headache, myalgia (muscle aches), drowsiness, and disorientation that sometimes progressed to coma within 48 hours. The disease was associated with an outbreak of respiratory disease in pigs with or without neurological symptoms, and humans infected with the disease were pig farmers or others closely associated with pig farming. It was first thought that the outbreak was due to infection by Japanese encephalitis (JE) virus (see Chapter 3 on the importance of pigs as amplifying hosts for this virus) and the Malaysian government vaccinated 2.4 million pigs against JE virus. When this did not slow the epidemic, 1.1 million pigs were culled in an attempt to reduce the incidence of disease. In March 1999, with the assistance of the Centers for Disease Control and Prevention, the virus responsible for the epidemic was identified as a Hendra-like virus, a virus related to but distinct from Hendra virus. Retrospective studies suggested that the virus had been responsible for disease in pigs in Malaysia for several years and it seems clear that the human cases were contracted from pigs. There is no evidence for human-to-human transmission in this outbreak. The virus responsible has been called Nipah virus, after the village in Malaysia where the disease first appeared, and it is classified as a second member of the genus *Henipavirus* (which gets its name from Hendra and Nipah viruses).

Like Hendra virus, the reservoir of Nipah virus is flying foxes and the virus has been isolated from flying foxes in the area. It has been suggested that the outbreak occurred in part because the destruction of the natural habitat of the flying foxes caused by deforestation and consequent food shortage led the bats to forage in nearby orchards located very near piggeries. There, half-eaten fruit or regurgitated fruit that was contaminated with virus-containing saliva from the bats could be eaten by pigs, causing them to become infected.

More recent epidemics of Nipah virus encephalitis have occurred in southern Asia. Epidemics in Bangladesh occurred in 2001, 2003, 2004, and 2005. No evidence for the intermediate infection of an animal, as occurred in the Malaysian epidemic, has been seen in these epidemics. Furthermore, in the 2004 epidemic evidence was obtained that person-to-person transmission of the virus had occurred. It is likely that the disease was transmitted directly from bats to humans, possibly by human consumption of partially eaten fruit that was contaminated with bat saliva containing the virus, followed by person-to-person transmission. It is known in Bangladesh, for example, that during the fruiting season young boys climb trees to pick fruit. If this fruit was partially eaten by bats, the fruit could be contaminated with the virus from the bat. The fatality rate in these

epidemics was as high as 75%. In nearby India, an epidemic of Nipah occurred in 2001. Flying foxes are widely distributed throughout this area (Fig. 8.1) and Nipah virus has been isolated from them in both Malaysia and Bangladash. The virus has also been isolated from flying foxes in Cambodia although human infection has not been documented to date.

The very wide distribution of Hendra and Nipah viruses, the possibility of person-to-person transmission, and the increasing contacts between humans and their domestic animals with fruit bats carrying the virus, suggests that epidemics will continue to occur. As indicated for rabies, eradication of the bats is neither desirable nor feasible. However, simple solutions exist to reduce the contacts of humans and their animals with the bats, such as not locating fruit orchards near piggeries.

SARS Coronavirus

SARS virus (***s***evere ***a***cute ***r***espiratory ***s***yndrome virus) occurs in a number of cave-dwelling species of horseshoe bats in China belonging to the genus *Rhinolophus*. Field studies have found that 30–70% of bats belonging to this genus have been infected by the virus. In the autumn of 2002 an epidemic of SARS in humans began in Guangdong Province in China. The disease is an atypical pneumonia characterized by high fever, myalgia, and lymphopenia (smaller numbers of lymphocytes). By February of 2003 there were 305 cases with five deaths. The infection was then spread to other areas by a Chinese doctor who had been treating patients in Guangdong. He traveled to Hong Kong on 21 February 2003 and while staying in a hotel he developed symptoms of SARS and died shortly thereafter. Ten guests at the hotel who were housed on the same floor or nearby floors became infected and before developing symptoms traveled to Singapore, Vietnam, Canada, and the United States, spreading the epidemic. The epidemic also spread independently to Beijing in April of 2003. The epidemic finally waned in the summer of 2003 when the World Health Organization reported the cumulative total of 8098 probable cases of SARS with 774 deaths worldwide in 29 countries (Fig. 8.2). The death rate from the disease was thus about 10% although it is age related. Children either do not contract the virus or show little reaction to it, whereas the death rate in people over 65 can be as high as 50%.

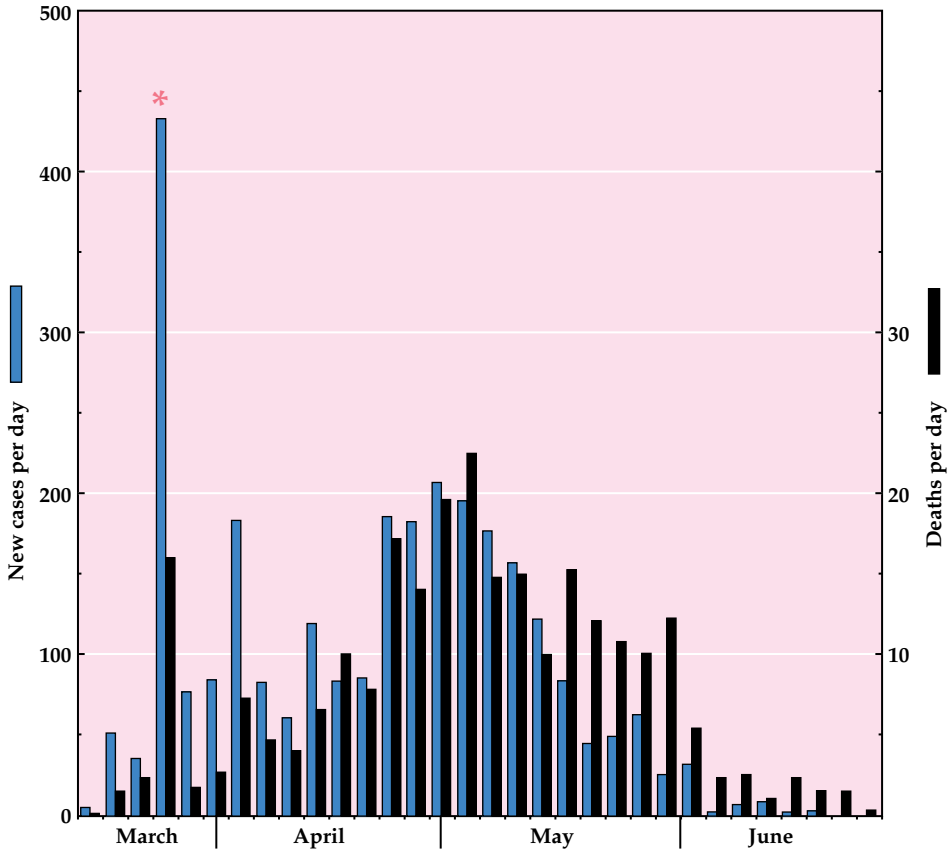


FIGURE 8.2 SARS epidemic of 2003. Cases and deaths reported between March 17 and June 23 are plotted. The data for this graph were reported in the outbreak updates from the World Health Organization, and can be found at: http://www.who.int/csr/don/archive/disease/severe_acute_respiratory_syndrome/en/. Cases and deaths have been normalized for the length of the reporting interval, which varied from 2 to 4 days. The asterisk marks the date on which cumulative totals were first released by China.

The disease probably started in markets in China in which a number of exotic animals including bats, masked palm civets (*Paguma larvata*), and raccoon dogs (*Nyctereuctes procyonoides*) are sold for food. Civets and raccoon dogs from the markets were found to be infected by the virus and it is believed that either these animals or bats being consumed as food spread the disease to humans, followed by human-to-human spread of the virus. It is almost certain that the civets in the markets contracted the virus there from bats because civets on farms were largely free from the SARS virus. In addition, 13% of tested merchants in the markets in Guangdong had SARS antibodies (showing they had been infected by the virus).

Adaptation of SARS Virus to a Human Receptor

Recent studies have shown that the SARS virus, a coronavirus, had to adapt to human receptors in order to cause severe illness. Infection by the bat virus or the civet virus appears to cause only mild illness. As stated before, merchants who were infected did not develop illness, and some persons who work with wildlife were found to be seropositive for SARS but suffered no illness. However, several changes are present in the virulent SARS virus isolated from humans. There is a deletion of 29 nucleotides upstream of the start codon for the N protein and there are four amino acid changes in the spike protein. It is believed that the crucial changes are two amino acid changes in the spike protein that allow the virus to bind to the human receptor called ACE2 (angiotensin-converting enzyme 2) 1000-fold more avidly than does the civet strain or the bat strain. This is perhaps the reason why the virus has not to date reappeared in the human population, together with extensive culling of animals in the food markets in China. If occasional human cases occur they are likely to be mild unless the virus has the opportunity to mutate in humans to form the virulent strain of the virus. However, this did happen in 2002 and may happen again in the future. There is need to develop vaccines or antiviral treatments for the virus, as well as to maintain the Chinese food markets in a way that does not encourage the spread of the virus.

The ACE2 protein is highly conserved among mammals and it is perhaps surprising that one of the few amino acid differences in the human form of this protein occurs in the virus-binding site and causes such a change in the ability of SARS to utilize ACE2 as a receptor. In view of the fact that to become virulent the virus must mutate to bind more strongly to the human form of the ACE2 protein, it is interesting that there is a second receptor for SARS virus, the protein called CD209L or L-SIGN. Why this second receptor cannot compensate for the failure of unmodified SARS to infect humans efficiently is unknown. It may be significant that another human coronavirus, NL63, only recently discovered, also uses ACE2 as its receptor. Other coronaviruses use different receptors, including aminopeptidase N (also called CD13) by the human coronavirus 229E, transmissible gastroenteritus virus of swine, and feline infectious peritonitis virus, and carcinoembryonic antigens by mouse hepatitis virus.

A Second Bat Coronavirus

It is noteworthy that at least one other coronavirus, as yet unnamed, circulates in bats belonging to the genus *Miniopterus*. In *Miniopterus pusillus* more than 60% of the bats were found to be positive for this virus. This virus is distinct from the SARS virus. It belongs to group 1 coronaviruses whereas SARS belongs to group 2 coronaviruses. This new virus is not known to infect humans or to cause disease.

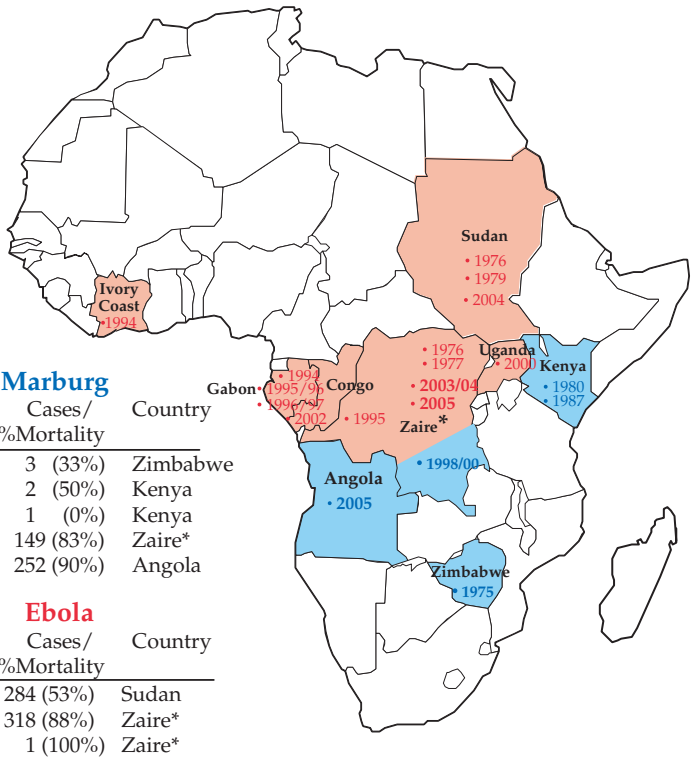
The Zoonotic Origin of a Human Coronavirus

SARS is a zoonotic disease of humans caused by a coronavirus. It is of interest that human coronavirus HCoV OC43 also appears to have a zoonotic source. It is very similar to a virus of cattle, bovine coronavirus (BCoV). From studies of the rate that mutations have been fixed in these viruses, it has been estimated that the virus entered the human population around 1890.

Filoviruses

Marburg Virus

The filoviruses first came to the attention of science in 1967 when outbreaks of hemorrhagic fever occurred in Marburg and Frankfurt, Germany, and in Belgrade, Yugoslavia. The cause was a virus subsequently named Marburg that was present in African green monkeys imported from Uganda whose kidneys were being processed for cell culture production (for use in preparing poliovirus vaccine). Twenty-five laboratory workers were infected and six secondary cases resulted; of these 31 infected people, 7 died. The monkeys in the shipment, which originated in Uganda, also died. Subsequent studies with the virus isolated during the outbreak showed that it caused lethal illness in African green monkeys following experimental infection. There were 3 cases of Marburg in South Africa in 1975 (the source of infection was probably Zimbabwe) with one death, 2 cases in Kenya in 1980 (infection probably in Uganda), 1 case in Kenya in 1987, an outbreak of 149 cases with 123 deaths in Zaire (now the Democratic Republic of Congo) in 1998–2000, and an outbreak of 374 cases with 329 deaths in northern Angola in 2005. The number of cases is surely underreported since many people in remote areas do not seek medical assistance when ill, and counting of new graves in such locations indicates that the death toll is higher than officially reported. The locations of these outbreaks are shown on the map in Fig. 8.3. The reported fatality rate in the larger outbreaks was 80–90%.



Marburg

Year	Cases/ %Mortality	Country
1975	3 (33%)	Zimbabwe
1980	2 (50%)	Kenya
1987	1 (0%)	Kenya
1998/00	149 (83%)	Zaire*
2005	252 (90%)	Angola

Ebola

Year	Cases/ %Mortality	Country
1976	284 (53%)	Sudan
1976	318 (88%)	Zaire*
1977	1 (100%)	Zaire*
1979	34 (65%)	Sudan
1994	44 (64%)	Gabon
1994	1 (0%)	Ivory Coast
1995	315 (77%)	Zaire* (Kikwit)
1995/96	37 (57%)	Gabon
1996/97	60 (75%)	Gabon
2000	425 (53%)	Uganda
2002	122 (81%)	Gabon/Congo
2003/04	178 (89%)	Zaire*
2004	17 (41%)	Sudan
2005	12 (75%)	Zaire*

*Now called Democratic Republic of Congo

FIGURE 8.3 Map of Africa showing the different filovirus outbreaks. Data from Porterfield (1995) p. 320, and later data from Georges-Courbot *et al*. (1997); Peters and Khan (1999), and news bulletins from the World Health Organization (2005) at: http://www.who.int/disease-outbreak-news/. Note that in recent years, outbreaks of Ebola disease have occurred almost annually in the center of the range, particularly in Gabon and the Democratic Republic of Congo. On the contrary, the recent epidemic of Marburg in Angola was the first in 5 years.

African Ebola Virus

Ebola virus was first isolated during a 1976 epidemic of severe hemorrhagic fever in Zaire and Sudan and named for a river in the region. During this epidemic, the more than 600 cases resulted in 430 deaths and asymptomatic infection appeared to be rare. One case of Ebola occurred in 1977, and in 1979 there were 34 cases with 22 deaths in the Sudan. In this latter epidemic, an index case was brought to the hospital and the virus spread to four people there, who then spread it to their families. After this, Ebola disease in Africa disappeared until 1994. In late 1994, a Swiss ethologist working in the Ivory Coast performed necropsies on chimps. She contracted Ebola but survived, and a new strain of Ebola was isolated from her blood. Then, in May 1995, there was an epidemic in Kikwit, Zaire, that resulted in at least 315 cases with >75% mortality. This was followed by several deaths in western Africa that resulted from consumption of a monkey that had died of Ebola. Then there was a prolonged series of smaller outbreaks in Gabon from 1995 through 1997. In 2000, Ebola appeared in Uganda for the first time and caused an epidemic of more than 425 cases. There have been further outbreaks in 2002, 2003, 2004, and 2005 in various countries including Gabon, the Democratic Republic of Congo, and Sudan. A map showing these various filoviral outbreaks is shown in Fig. 8.3. Three strains or species of African Ebola viruses are now recognized which differ in their virulence. Zaire ebolavirus is the most virulent with a case fatality rate approaching 90%, Sudan

ebolavirus is less virulent, and Ivory Coast ebolavirus is the least virulent.

The natural reservoir of Ebola virus in Africa has recently been shown to be bats. Three species of fruit bats collected in Gabon and the Democratic Republic of Congo, close to areas where an epidemic of Ebola had devastated local gorilla and chimpanzee populations, showed evidence of infection. Significant numbers of *Hypsignathus monstrosus* (4 of 17 tested), *Epomops franqueti* (8 of 117), and *Myonycteris torquata* (4 of 58) were found to have antibodies to Ebola virus, and viral nucleic acid was detected in liver or spleen of other bats of these three species (4 of 21, 5 of 117, and 4 of 41, respectively). No viral RNA was found in any other animal species tested, which included 222 birds and 129 small vertebrates, among others. The infection of the bats appears to be asymptomatic, consistent with the hypothesis that the fruit bat is the reservoir of Ebola virus. It is probable that bats are also the reservoir of Marburg virus.

It is clear that monkeys can be infected by the virus and spread it to humans, but how the monkeys contract it is not known. Perhaps the monkeys eat fruit that has been partially eaten by the bats. There have been serious die-offs of gorillas and chimpanzees in the last decade or so that have severely impacted the populations of these animals in some areas. Some human epidemics get started when monkeys dying of the disease are butchered for food, but in other epidemics monkeys are not implicated and how the epidemic starts is not known. Again, perhaps consumption of partially eaten fruit is to blame. The recent large die-offs of apes and chimpanzees in some areas together with the increasing frequency of human infection indicates that the virus is spreading more widely. Whether this is due to a new strain of virus that is more easily spread to humans and nonhuman primates, or to the recent introduction of the virus from a source outside the areas now experiencing epidemics, or to human alterations of the environment leading to more contact between humans and nonhuman primates with the bats that carry the virus is not known.

Reston Ebola Virus

A fourth strain of Ebola virus originating from the Philippines (or, perhaps, another region of Asia) first appeared as the causative agent of an epidemic of hemorrhagic fever in monkeys imported from the Philippines. This epidemic occurred in Reston, Virginia, near Washington, D.C., in 1989. The deaths were at first attributed to simian hemorrhagic fever virus (SHFV), but investigation by the U.S. Army Medical Research Institute for Infectious Diseases and the Centers for Disease Control and Prevention found that both SHFV and Ebola virus were present in the monkeys. Believing that the community was at risk for Ebola, made even the more alarming because the epidemic was occurring in the neighborhood of the central government of the United States, the army team quickly decided to euthanize the monkeys and decontaminate the facility. Follow-up studies showed that four animal handlers at the facility had been infected by the virus but had suffered no illness. Thus the strain of Ebola present in the Reston monkeys, called Reston ebolavirus, seems to be nonpathogenic for humans although it remains pathogenic for monkeys. The story of the Reston incident was recounted in a book called *The Hot Zone* by Richard Preston. Since this first epidemic of Reston ebolavirus, a new outbreak has occurred in Reston, two outbreaks have occurred in an animal facility in Alice, Texas, and an outbreak took place in Sienna, Italy. All outbreaks occurred in monkeys imported from the Philippines and it seems probable that the virus is native to the Philippines. No serious illness in humans has occurred in any of these outbreaks. Nucleotide sequencing has shown that Reston ebolavirus is closely related to the African ebolaviruses. The reason it is attenuated in humans is still unexplained, and high containment is used for studies of Reston ebolavirus in the laboratory.

Are Filoviruses a Major Threat?

To date, the filoviruses have caused only a limited number of human infections. However, if a filovirus were to adapt to humans such that human-to-human transmission occurred readily, it could become a major problem. The probability of such an event is unknown.

VIRUSES ASSOCIATED WITH BIRDS

Many viruses are known for which birds are the vertebrate reservoir but which can also infect humans, causing outbreaks of serious illness. Because many species of birds travel large distances during their annual migration, viruses associated with such species are spread rapidly over a wide geographic area. Here we consider the rapid spread of West Nile virus in the Americas and the alarming appearance of new strains of influenza virus that have the potential to cause very large epidemics of very serious influenza in human populations.

West Nile Virus in the Americas

Appearance and Spread of West Nile in the New World

In the summer of 1999, West Nile virus, a mosquito-borne flavivirus (Chapter 3), appeared in North America for the first time. There were 62 human cases of West Nile disease in the New York City area, of whom 7 died of encephalitis. Numerous birds also died, including exotics in zoos as well as native birds. With the end of the mosquito season the epidemic died out, but the virus had become established. Over

the next 6 years the virus rapidly spread across the United States and north into Canada as well as south into Central America, northern South America, and the Caribbean. The march of the virus across the United States is illustrated in Figs. 8.4 and 8.5. The rapid spread of this virus into a new ecological area requiring adaptation to new mosquito vectors as well as new vertebrate hosts is extraordinary. In the process, more than 20,000 Americans became ill from WN virus infection and more than 800 died of neurological complications (Fig. 8.6). Figures 8.5 and 8.6 illustrate an interesting and not well understood phenomenon. After the front passes through an area, there are many fewer human cases of disease in the following years. Yet only a minority of humans in any area had been infected and are therefore immune to the virus, and the virus continues to be present. In some way the transmission cycle has been interrupted, perhaps by the die-off of the birds that serve as the primary amplifying hosts.

WN virus strains from the United States are 99.7% identical to strains from Israel, and the U.S. strain certainly originated in the Middle East. It presumably arrived in New York on a jet aircraft, and there are three possible vectors that could have carried the virus. It is conceivable that a viremic human introduced the virus, although this seems unlikely because humans are poorly able to pass on the virus as described in Chapter 3. A second possibility is that the virus arrived in a viremic bird being imported legally or illegally, although there is no evidence for such an event. It seems highly unlikely that a migratory bird that was off course introduced the virus because West Nile first appeared near a major international airport. The favored hypothesis is that the virus arrived in an infected mosquito that came along for the ride in a jet aircraft. Introduction of the virus was almost certainly a singular event.

Effects of West Nile on Wildlife

West Nile virus has had profound and well documented effects on horses and wildlife as it moved across North America. Many horses died of WN disease, and a vaccine has now been introduced in order to protect horses. The effect upon bird populations has been particularly dramatic. Crows, jays, and raptors (hawks and owls) are particularly sensitive to the virus. Almost all crows die after infection, for example, and in many parts of the country the crow population crashed with the arrival of the virus, although there are recent signs that the population is at least partially recovering. Many raptors prey upon small rodents and are

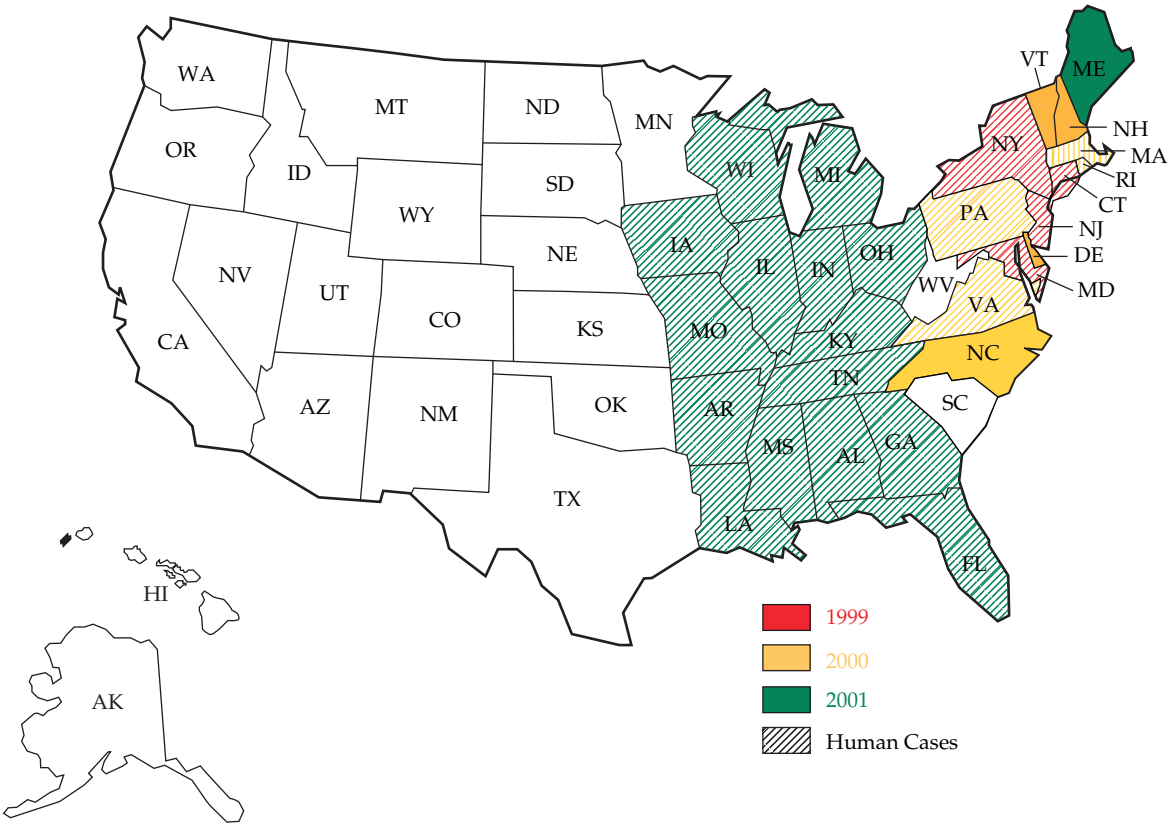


FIGURE 8.4 The early spread of West Nile virus across the United States from 1999 to 2001. Data are from the archives of the West Nile Virus Surveillance site from the Centers for Disease Control and Prevention at: http://www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm.

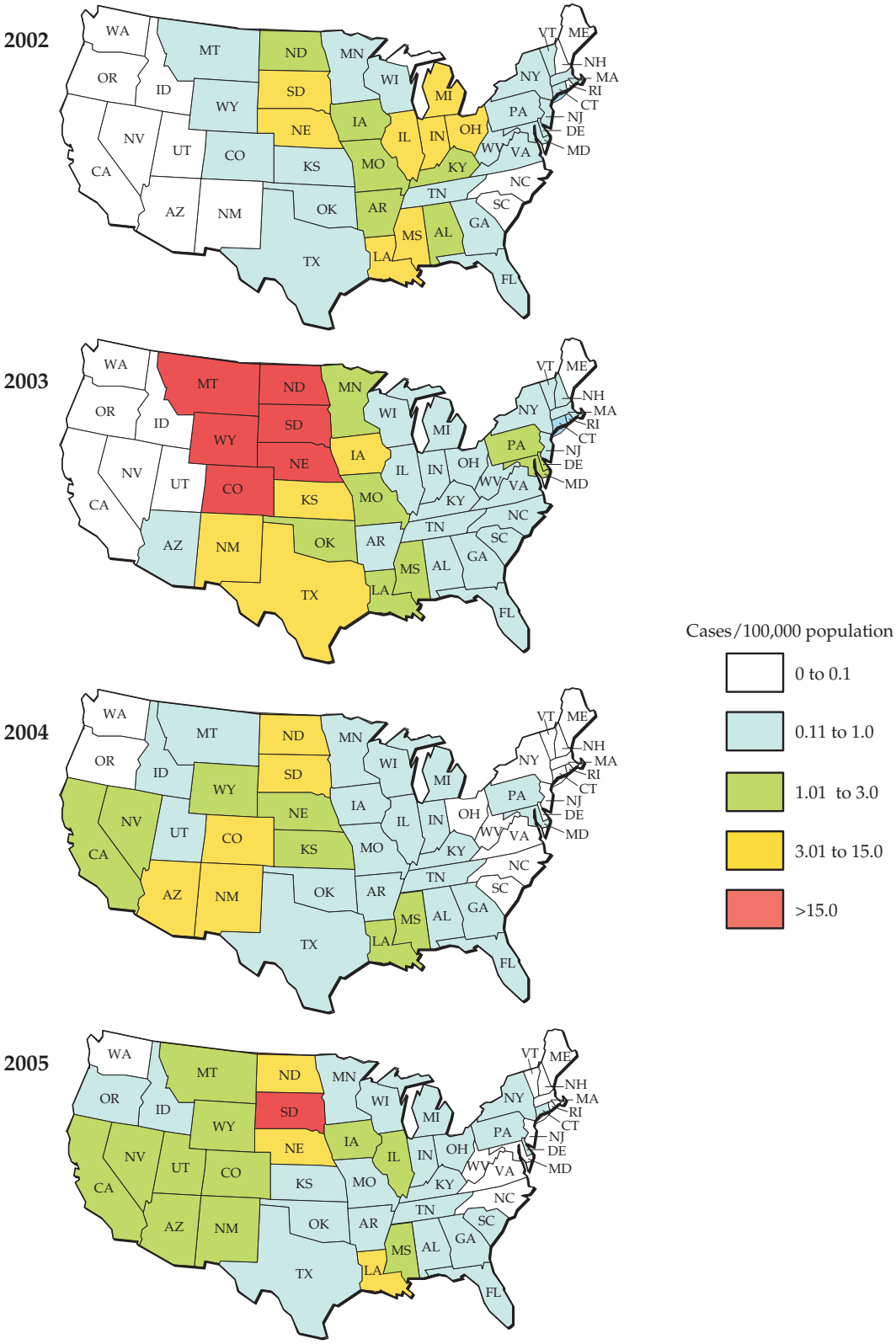


FIGURE 8.5 The spread of West Nile virus across the United States from 2002 to 2005. Data are from the archives of the West Nile Virus Surveillance site from the Centers for Disease Control and Prevention at: http://www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm.

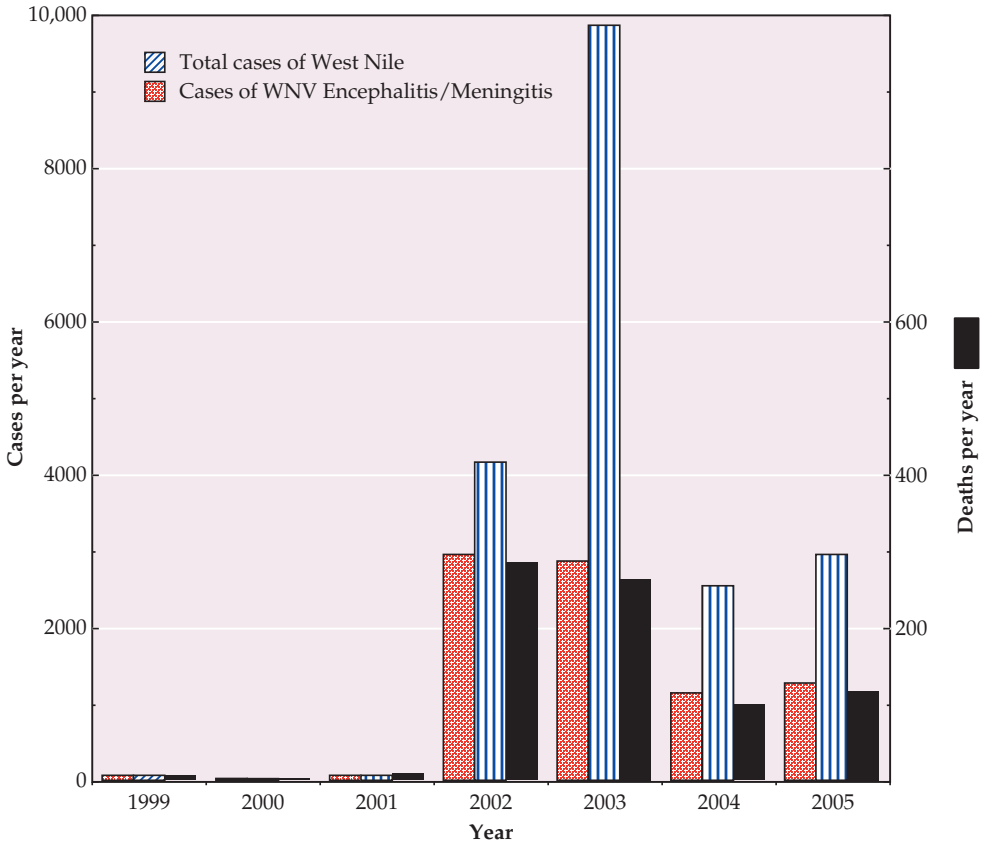


FIGURE 8.6 Total number of cases of West Nile fever, cases of encephalitis and meningitis due to WN virus, and deaths from WN virus are shown for 1999 through 2005. Data are from the archives of the West Nile Virus Surveillance site from the Centers for Disease Control and Prevention at: http://www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm.

important in controlling their numbers, and a crash in their numbers results in an increase in rodent populations. As an example of the sensitivity of some owls to WN virus, there was an outbreak of WN disease in North American owls in a rehabilitation facility in Ontario in 2002, associated with the die-off of corvids in the area. Large owls with a northern breeding range were particularly susceptible. Snowy owls, northern hawk owls, great gray owls, and boreal owls experienced 100% mortality, and northern saw-whet owls experienced 92% mortality.

The Future of West Nile in the Americas

WN virus is now well established in the Americas and will surely continue to cause sporadic cases of human illness, if not sporadic epidemics, and sporadic die-offs of birds. It is possible that the interruption of its transmission cycle described above is due to extensive die-off of susceptible species of birds that serve as its major amplifying vectors. If so, the resurgence of the crow population and the populations of other amplifying species could lead to renewed outbreaks similar to those that occurred with the first appearance and spread of the virus. One encouraging finding relating to the potential of the virus to cause future epidemics of disease is the appearance of an attenuated variant of WN virus in Texas in 2003. In a mouse model, this variant is attenuated in neurovirulence. The emergence of WN virus was associated with the appearance in Europe and the Middle East of a more virulent strain of virus, perhaps enabling it to spread more easily. It seems possible that once the virus becomes endemic, attenuated strains may become dominant.

Avian Influenza

Influenza A virus caused three pandemics of severe influenza in the twentieth century. The pandemic of 1918 was especially severe, infecting perhaps 30% of the world's population and causing up to 100 million deaths. These pandemics were associated with the appearance of new subtypes of HA and NA, the surface glycoproteins of the virus, in human adapted viruses. The reservoir of influenza A is birds and the bird viruses must ordinarily undergo adaptation in some way to humans in order to infect and cause epidemic spread. In part this adaptation involves reassortment of flu segments to

incorporate human adapted segments. It had been thought that virus circulating in birds will not infect humans and cause disease without prior adaptation, and that only HA subtypes H1, H2, and H3 were compatible with spread in humans. Recently, however, there have been numerous cases of direct human infection by several strains of avian influenza resulting in serious, even fatal, illness involving new subtypes of HA. Three such viruses, H5N1, H7N7, and H9N2 will be considered here.

H5N1 Influenza

H5N1 virus was first detected in China in 1996 where it caused the death of a number of geese. After undergoing reassortment to obtain new genes, it surfaced in Hong Kong in 1997 where it became widespread in live poultry markets. Eighteen people were infected by the virus and six died. The virus was eradicated by culling all domestic chickens in Hong Kong. Different reassortants of H5N1 continued to arise and in 2002 an epidemic of influenza killed most birds, domestic and wild, in Hong Kong nature parks. Two people were infected and one died. The virus then spread widely over eastern Asia. The virus killed wild as well as domestic waterfowl and chickens, and together with repeated efforts to stop the spread of the virus by culling of birds, the death of more than 140 million birds occurred. The virus has a high mortality rate in humans, about 50%, and as of early 2007 more than 150 people have died as a result of H5N1 infection. There is no evidence for human-to-human transmission at the current time. All human infections appear to have originated from close contact with infected birds.

The virus has continued to spread westward. It has now reached many countries in Europe and established a beachhead in Africa. It is thought that the virus will soon reach North America, brought by migratory birds. The mechanism of its rapid spread is not completely clear. It is thought that transport of domestic birds may be responsible in part for the spread, but there is reason to believe that wild waterfowl, ducks, geese, and swans, are also spreading the virus. These birds undergo seasonal migrations over large distances, and episodes of dead and dying migratory birds have been associated with the appearance of the virus in new areas. The virus is continuing to evolve. Unlike most avian influenza viruses, it is highly pathogenic in chickens and many strains are also pathogenic in ducks, both domestic and wild. Virulence in wild ducks seems to be moderating, as some recent isolates do not kill wild ducks, but virulence in chickens continues. All isolates contain the multibasic cleavage site in HA that is recognized by furin, which is correlated with increased virulence.

Studies of H5N1 virus in mice and ferrets have shown that many virus isolates are highly virulent for these mammals. In one study with ferrets, isolates from humans caused a fatal infection characterized by broad tissue tropism, including infection of the brain. In this same study, isolates from birds caused nonlethal infection with virus replication restricted to the upper respiratory tract.

There have been three or four pandemics of influenza every century for as long as can be ascertained from historical studies and there is every reason to believe that pandemics will come again in the twenty-first century. If H5N1 virus should acquire the ability to spread readily from person to person, and if its high lethality for humans should continue unabated, it could cause a devastating pandemic. Efforts are being made to prepare defenses against this virus, including vaccines and antiviral drugs, supported by the U.S. government and other governments. Promising vaccines are being developed and tested in clinical trials, and plans are to stockpile such a vaccine for possible use if an epidemic of this virus arises. This effort is complicated by the fact that H5N1 influenza, like all influenzas, continues to evolve, and stockpiled vaccine might not be completely effective against the strain that ultimately might emerge as a pandemic strain. Nevertheless, there is hope that at least partial immunity might be effected by such a vaccine that could ameliorate the symptoms of the disease and protect against the extreme virulence of the virus. As described in Chapter 4, new approaches to flu vaccine development are being tried, including development of a universal flu vaccine that would work against any influenza A strain, but such an approach will clearly require many more years of research before a licensed vaccine for general use could be produced. Efforts are also being directed toward producing and stockpiling antiviral compounds directed against influenza. Unfortunately, most H5N1 isolates tested are resistant to amantadine and related compounds, antiflu agents that have been in use for years and that are readily available. It is thought that this is the result of the wide use of amantadine by Chinese farmers to protect their chicken flocks from influenza, thereby selecting for amantadine-resistant variants of the viruses. This effect may be moderating, however, as some recent isolates are sensitive to amantadine. Inhibitors of the influenza neuraminidase such as oseltamivir (Tamiflu) and zanamivir appear to be reasonably effective against H5N1 virus, but these drugs must be used early in infection if they are to be effective. Production of these compounds is limiting at present, but production is being accelerated in order to stockpile them for possible use if or when a pandemic erupts.

H7N7 Influenza

An epidemic of H7N7 influenza A erupted in The Netherlands in 2003. A total of 89 human infections was recorded, of whom 86 were directly involved in handling poultry. Human-to-human transmission occurred and three family members were also affected. The primary disease syndrome was conjunctivitis but there were two cases

characterized by mild influenza-like symptoms only and one fatal case characterized by pneumonia followed by respiratory distress syndrome. The virus was eradicated by culling of poultry in the country.

H9N2 Influenza

In 1999, two cases of human infection by H9N2 influenza A occurred in Hong Kong and five cases in Guangdong Province, China. Then in 2003 another case occurred in Hong Kong. The disease was characterized by mild influenza-like symptoms and recovery was uneventful.

VIRUSES ASSOCIATED WITH PRIMATES

Dengue Virus

The Origin of Dengue Viruses

Dengue viruses are mosquito-borne flaviviruses that cause widespread epidemics in humans (Chapter 3). Forest cycles of dengue have been documented in Africa and Southeast Asia in which the vertebrate reservoir is monkeys and various species of *Aedes* mosquitoes maintain the virus. Recent sequencing studies have now shown that the sylvatic monkey viruses evolved in monkeys into four serotypes. This evolution from a common ancestor occurred in the African/Southeast Asian region at some time in the distant past. These different dengue viruses then jumped independently into humans to become human dengue viruses. A dendrogram of dengue viruses of monkeys (sylvatic strains) and humans (endemic/epidemic strains) is shown in Fig. 8.7. Notice, for example, that the monkey dengue-4 virus groups with human dengue-4 but forms a distinct lineage from that of the other dengue viruses. Similarly, monkey dengue-1 and dengue-2 group with the respective human viruses but form distinct lineages. Sequencing of sylvatic dengue-3 has not yet been done but it will presumably group in the same way. From the extent of the divergence in sequences between the monkey viruses and the human viruses, it is estimated that the jump to humans occurred on the order of 200 years ago for DEN-1, 600 years ago for DEN-4, and 1000 years ago for DEN-2. It is further estimated that the African and Malaysian sylvatic viruses diverged about 800 years ago. Such estimates are subject to considerable uncertainty but are probably valid to within a factor of two. Since human dengue virus is an exclusively human virus that is epidemic in nature and induces lifelong immunity, it could not have existed until human populations were large enough to support the continued existence of such a virus. This topic is covered in more detail in Chapter 4 when discussing measles virus, but sufficiently large human populations arose only within the last thousand years or so in the regions in which dengue viruses first arose and flourished.

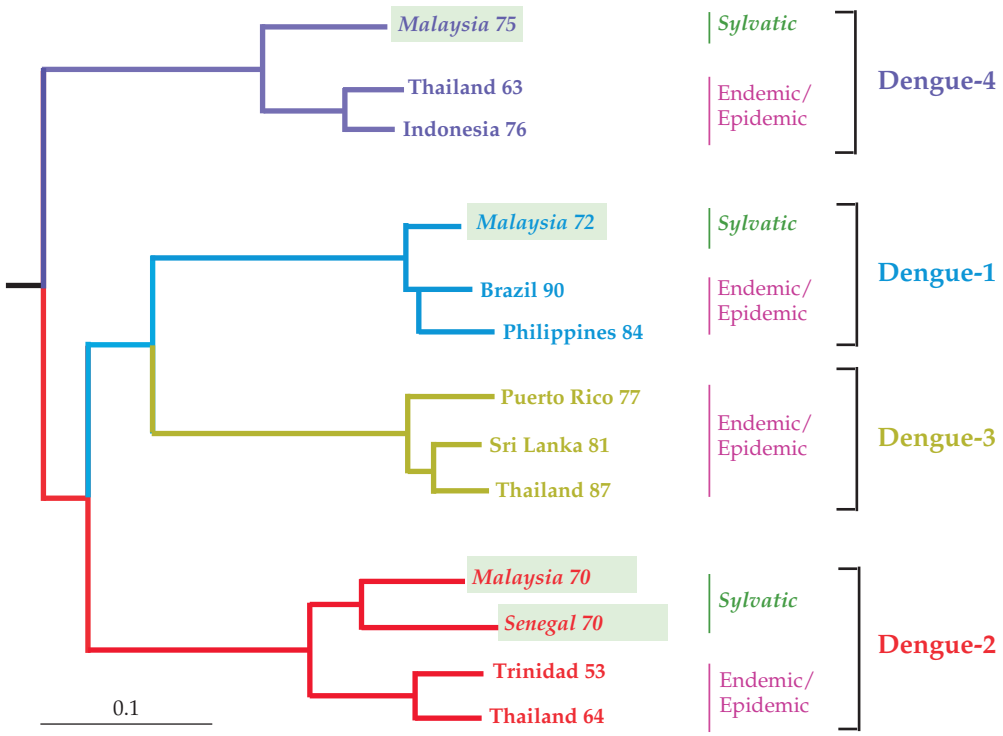


FIGURE 8.7 Phylogenetic tree of the four dengue virus types derived from E protein gene nucleotide sequences of sylvatic (in monkeys) and representative endemic/epidemic (in humans) DEN strains using maximum parsimony. The scale shows a genetic distance of 0.1 or 10% nucleotide sequence divergence. Adapted from Wang *et al*. (2000).

Dengue in the Americas

Dengue viruses have been continuously active over large areas of Asia and the Pacific region for many years. They have recently dramatically expanded their range in the Americas. The viruses may have caused large epidemics in the Americas, including the United States, in the 1800s and into the early 1900s. However, it is impossible to determine with certainty from descriptions of the disease written at the time whether dengue was the causative agent of these epidemics or whether other viruses that cause similar illnesses might have been responsible. In any event, dengue almost died out in the Americas following World War II because of efforts to control *Aedes aegypti*, the urban vector of the virus. With the discovery of DDT in the mid 1900s, a serious effort was made in the Americas to eradicate *Ae. aegypti* from large regions, in order to control viral diseases spread by these mosquitoes, which include not only dengue but also yellow fever and other arboviruses. These efforts succeeded in eliminating the mosquito from large areas of Central and South America, as illustrated in Fig. 8.8A. However, in 1970 these efforts were abandoned because of the expense involved and the detrimental effects of DDT on the environment, and by 2000 the mosquito had reestablished itself over most of the region (Fig. 8.8A). The reintroduction of multiple dengue strains into the Americas from foci in Asia after the reestablishment of *Ae. aegypti* resulted in the outbreak of dengue hemorrhagic fever associated with huge epidemics of dengue fever (Fig. 8.8B). The history of the increasing infection rate is illustrated in Fig. 8.9 by data from Brazil. Before 1993, epidemics of dengue were sporadic, occurring

FIGURE 8.8 Changing distribution of dengue hemorrhagic fever (DHF), and the vector for dengue virus in the New World. (A) Distribution of the vector mosquito *Aedes aegypti* in the Americas in 1970 and 2000. *Aedes aegypti* spread rapidly during this period due to the collapse of mosquito control programs and urbanization. (B) Increase and spread of dengue hemorrhagic fever, from 1981 to 2003. Data for these graphs came from the dengue fever information sheets from the Centers for Disease Control and Prevention Web site at: html://www.cdc.gov.

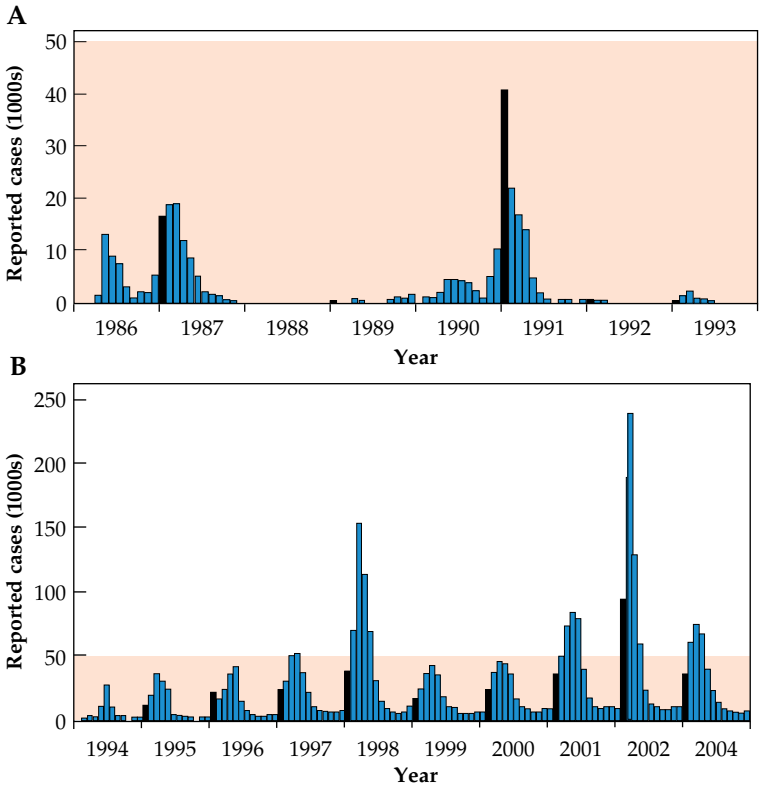


FIGURE 8.9 Number of dengue fever cases reported per month in Brazil (A) between 1986 and 1993 and (B) between 1994 and 2004. Note that the areas shaded in pink in the two graphs represent the same number of cases (50,000). Bars for January cases are filled in black. Adapted from Siquiera *et al*. (2005).

every few years and then dying out. After this, however, epidemics have occurred every year and the total number of cases has increased dramatically (notice the difference in scales).

Prior to the 1980s, a "native American" strain of DEN-2 circulated and there was very little dengue hemorrhagic fever (DHF) in the Americas. A strain of DEN-3 circulated in the 1960s and 1970s but it then disappeared. DEN-1 was introduced into the Americas in 1977 and DEN-4 in 1981 and these viruses then radiated throughout large regions of the Caribbean and northern South America. The first epidemic of DHF occurred in 1981, but interestingly, it was due to the introduction of a new strain of DEN-2 from Asia. This DEN-2 strain grows more vigorously than the native American strain, which is not associated with DHF, and led to the DHF epidemic. Then in 1994 the Southeast Asian strain of DEN-3 responsible for the DHF epidemic in Sri Lanka described in Chapter 3 reached the Americas. The result of all these introductions has been a dramatic increase in the incidence of DHF and dengue shock syndrome (DSS) in the Americas. Whereas in the 1970s there were very few cases of DHF in the Americas, there were more than 10,000 cases in the 1980s and more than 60,000 cases in the 1990s. Cases have continued to increase in number. In the last 5 years (2001–2005 inclusive), more than 50,000 cases have been reported that resulted in about 700 deaths.

The evolution of DEN-1 in the Americas after its introduction in 1977 is illustrated in Fig. 8.10. Sequencing of strains isolated in various years after 1977 show that silent nucleotide substitutions (i.e., synonymous substitutions that do not result in a coding change) have been fixed at the rate of 0.2% per year. However, essentially no coding changes have occurred. Thus, coding changes are not acceptable and viruses containing such changes do not persist.

Human Immunodeficiency Virus

HIVs are human viruses that have become established in the human population within the last century. The two human viruses HIV-1 and HIV-2 derive from different simian immunodeficiency viruses (SIVs), HIV-1 from SIVcpz and HIV-2 from SIVsmm. Further, HIV-1 has become established at least three times by independent entry of SIVcpz into humans. A phylogenetic tree of the primate lentiviruses is shown in Fig. 8.11. There are three lineages of HIV-1, all of which are related to SIV isolated from chimpanzees (SIVcpz). Of these three lineages, the M lineage is found worldwide and is responsible for the majority of human infections. The O lineage is found only in western Africa and in France. The N lineage represents a third introduction of SIVcpz into humans. The structure of the dendrogram makes clear that these three viruses independently entered the human population.

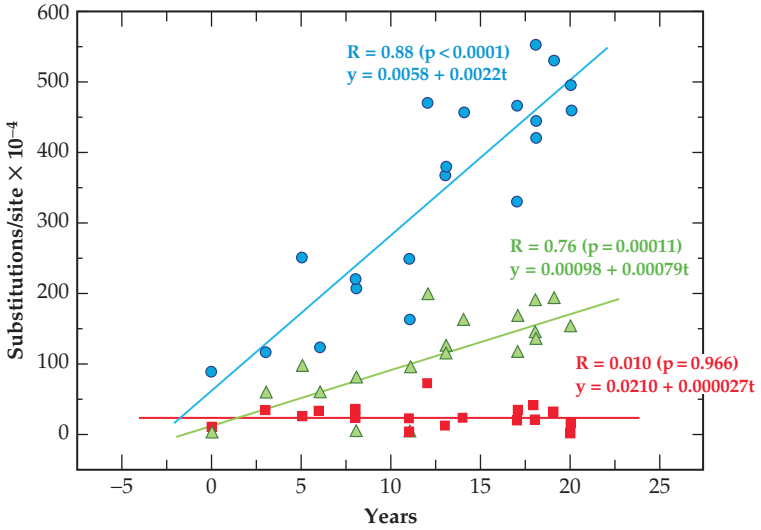


FIGURE 8.10 Relationship between the number of total (▲), synonymous (●), and nonsynonymous (■) nucleotide substitutions per site and the number of years since the introduction of dengue 1 into the Americas in 1977. R is the regression constant. Adapted from Figure 2 in Goncalvez *et al.* (2002).

Epidemiology of SIVcpz

Until recently, the extent of SIVcpz infection of chimpanzees was not known. The chimp is an endangered species, limited in numbers, difficult to study, and only a few isolations of SIV from chimps had been made. In recent studies to examine the extent of SIV infection of wild chimps, 1300 stool samples from wild chimps were collected in the field and laboriously tested for the presence of anti-SIV antibodies and for SIV RNA by RT–PCR. The individual responsible for the stools was identified by examining the host DNA in the sample using highly polymorphic microsatellite loci. Several different chimp populations were included in these studies.

There are four different subspecies of chimpanzee. The type subspecies, *Pan troglodytes troglodytes*, is found in West Africa in southern Cameroon, Gabon, and Congo (Fig. 8.12). *Pan t. schweinfurthii* is further east, primarily in the Democratic Republic of Congo but penetrating northward into the Central African Republic and eastward into a swath from southern Sudan down to Tanzania. *Pan t. vellerosus* is north of the range of *troglodytes*, in northern and western Cameroon. Finally, *Pan t. verus* is west of the range of *vellerosus*, in a broad zone from Senegal to Ghana. Subspeciation has resulted in part because chimps do not swim and large rivers fragment the various populations. Of these four subspecies only two, *troglodytes* and *schweinfurthii*, are naturally infected by SIV. Rates of infection vary in different populations but average about 20%, with some populations exhibiting almost 50% infected individuals. Thus, SIVcpz is a naturally occurring, widespread virus for which two subspecies of chimps are the reservoir. The virus does not appear to cause disease in chimps, similar to the case for other SIVs that infect African monkeys.

Surprisingly, SIVcpz is itself a recombinant virus. The 5′ half of the genome is derived from SIV infecting red-capped mangabeys, whereas the 3′ half is derived from SIV infecting greater spot-nosed or mustached or mona monkeys (Fig. 8.13). The recombination probably occurred in a chimp that had been infected by the two SIVs. Chimps eat other monkeys and could have become infected in this process in the same way that humans probably became infected with SIVcpz upon slaughtering and eating chimps. The fact that only two of the four subspecies of chimps are infected with SIVcpz argues that this virus arose after subspeciation of the chimps had taken place. The spread of this virus in chimps might in fact be a fairly recent occurrence.

Establishment and Spread of HIV

After infection of humans by SIVcpz, the virus had to adapt to humans and become a human virus in order to be transmitted from person to person and to spread widely. It seems probable that humans have become infected with SIVcpz repeatedly but in most cases the virus failed to adapt to humans or failed to become epidemic because of the low transmissibility of the virus. Following a human infection, it may have smoldered in a small number of people but then died out. When the viruses crossed the species barrier and became firmly established in the human population as HIV-1 is not clear. HIV-1 has been isolated from serum collected in 1959 in Zaire and antibodies to HIV have been found in serum collected in 1963 in Burkina Faso, so

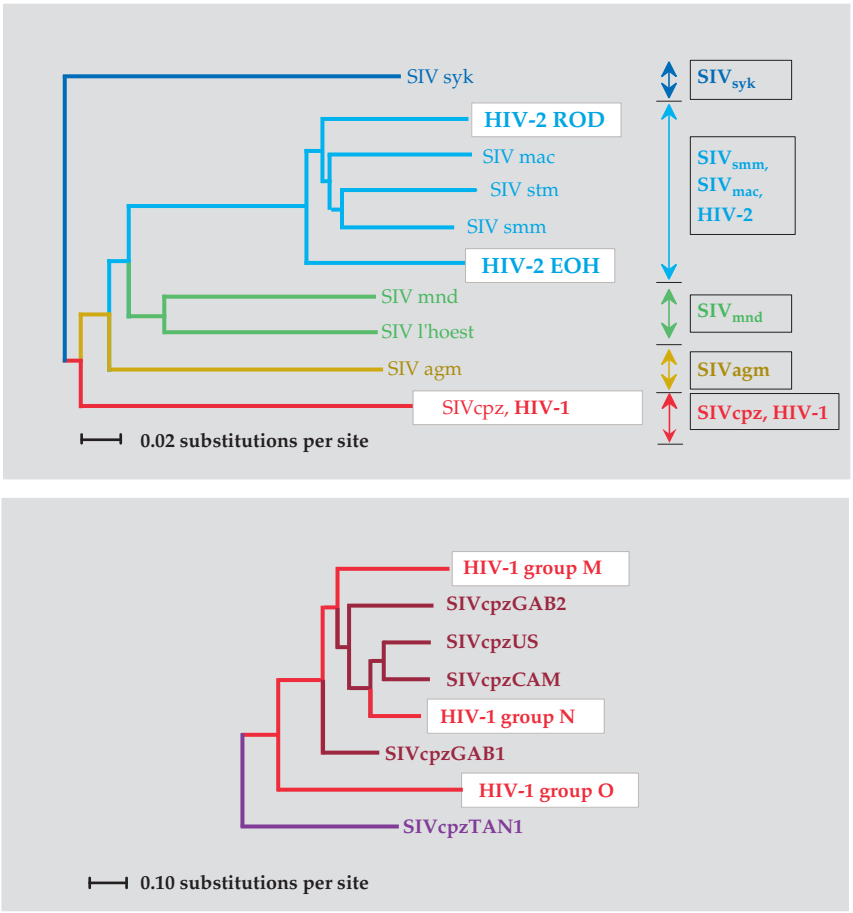


FIGURE 8.11 Phylogenetic trees of the primate lentiviruses. Upper panel: a tree constructed using the neighbor-joining method on selected SIV and HIV *pol* sequences. Horizontal branch lengths are to the scale shown below. HIV strain names are arbitrary. SIV names include the name of the host from which they were obtained: syk, Sykes monkey; smm, sooty mangabey; mac, rhesus macaque; mnd, mandrill; l'hoest, l'hoest monkey; agm, African green monkey; cpz, chimpanzee. The boxes at the right give the names of the five major lineages of primate lentiviruses identified to date. Redrawn from Whetter *et al*. (1999), Figure 1. Lower panel: a tree constructed from maximum-likelihood analysis of full-length *env* sequences from HIV-1 isolates of groups M, N, and O and a number of SIV strains from chimpanzees, corresponding to the box on the lowest branch in panel (A). Human viruses are in red (within a white box), viruses from *Pan troglodytes troglodytes* are in dark red, and the strain from *P. t. schweinfurthii* is in purple. Note the difference in scale. Redrawn from Sharp *et al*. (2005).

HIV-1 has been in the human population at least that long. From sequencing studies of the glycoprotein gene and examination of the rate of divergence, one estimate is that the virus might have entered the human population about 70 years ago, although estimates of divergence rates are controversial. Recent changes in human behavior, including more extensive travel by truck, bus, and plane, changes in sexual practices, and the use of injectable drugs, as well as the increase in the human population, could have allowed the virus to reach major population centers and spread more extensively than in the past, becoming epidemic worldwide. The spread of the virus could also have been aided by the appearance of mutants that were more easily transmissible from person to person. The large increase in population during the last century has certainly resulted in more opportunities for the introduction and spread of the virus in humans, and therefore for the selection of such transmissible mutants.

HIV-2 represents a distinct lineage that is closely related to SIV of sooty mangabey monkeys (smm) and of macaques (mac). SIV of African green monkeys (agm) and of mandrills (mnd) form other lineages that are more closely related to HIV-2 than to HIV-1. It is clear that SIVsmm and SIVagm are naturally occurring infectious agents that are widespread in Africa and have coevolved with their monkey hosts. Sequence comparisons have shown that different isolates of SIV group with their hosts rather than by geography, and they are therefore adapted to their hosts. They cause no disease in their natural host, but SIVsmm does cause AIDS when transferred to Asian macaques in captivity. HIV-2 is found primarily in western central Africa, where its distribution is almost coincident with that of mangabey monkeys. It

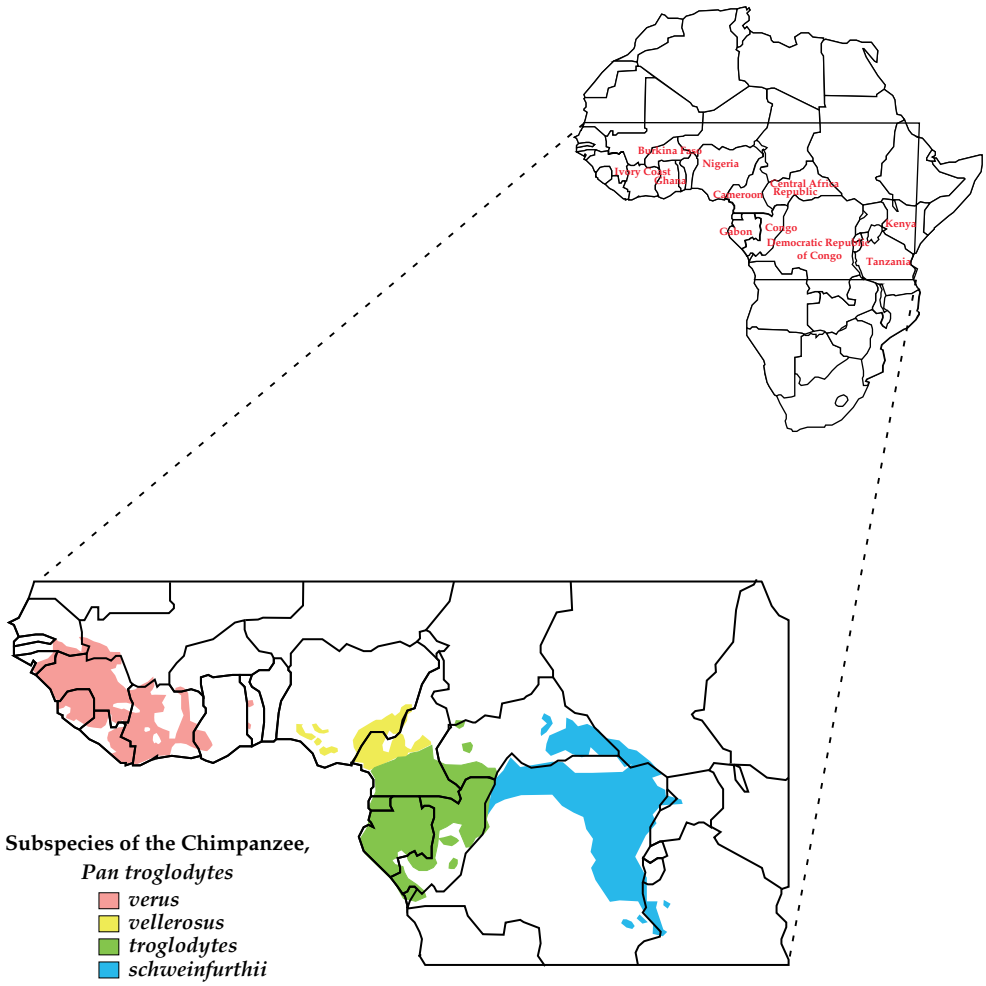


FIGURE 8.12 Natural ranges of four chimpanzee subspecies. Note that only chimpanzees belonging to the subspecies *trogodytes* and *schweinfurthii* have been found naturally infected with SIVcpz. The strains of SIVcpz that have been found cluster into two divergent lineages corresponding to the chimp subspecies lineages, and the strain of SIVcpz found in *troglodytes* was the source of HIV-1. Figure has been adapted from Figure 1 in Sharp *et al*. (2005).

seems clear that HIV-2 represents a separate introduction of SIVsmm into humans.

Repetitive Introductions of Monkey Retroviruses into Humans

It has been found recently that the multiple introductions of SIV into humans that became HIV-1 and -2 do not represent the only human infections by monkey retroviruses. Studies of bush meat hunters in Cameroon showed that at least six retroviruses have crossed from monkeys into humans who were exposed to fresh bush meat. These include two previously unknown retroviruses, HTLV-3 (PTLV-3) and HTLV-4 (PTLV-4). Thus, infection of humans by simian retroviruses has not been a rare event. A book called *The River* by Edward Hooper claimed that the HIV epidemic started because an early version of polio vaccine was contaminated by HIV (or its progenitor). No evidence for such contamination exists, and recent analysis of lots of this vaccine that had been stored for 40 years by three different laboratories failed to find any trace of SIV/HIV in the vaccine. Further, given that monkey viruses have repeatedly entered the human population, it is unnecessary to postulate human vaccine activity for the origin of HIV. Rumors based upon this claim, however, have led to suspension of vaccination for polio in some African nations, resulting in a resurgence of poliomyelitis in Africa that has spread to other areas previously free of polio (see Chapter 3).

VIRUSES ASSOCIATED WITH RODENTS

Hantaviruses

Hantaviruses are associated with rodents and infect humans through aerosols containing virus from rodent

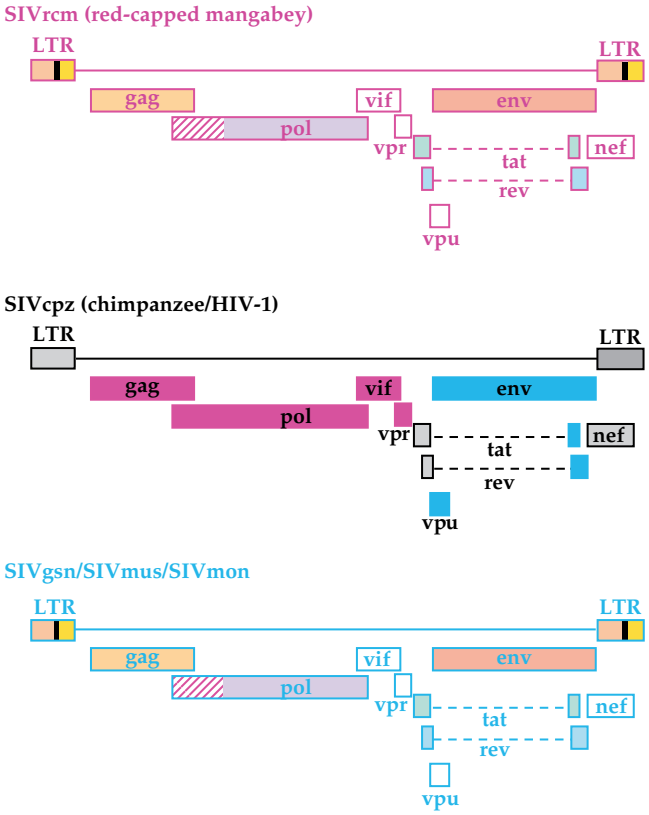


FIGURE 8.13 Diagram of the recombinant origin of SIVcpz. The various genes of SIV in red-capped mangabeys are shown at the top, outlined in magenta. Similarly the genome of SIVgsn (greater spot-nosed)/SIVmus (mustached)/SIV mon (mona) monkeys is shown at the bottom, outlined in blue. In the recombinant genome of chimpanzee/HIV-1 (center), SIVcpz genes derived from **SIVrcm** are magenta, genes from **SIVgsn** are in blue, and genes of unknown origin are in gray. Adapted from Figure 4 in Sharp *et al*. (2005).

excreta. The first hantavirus to come to medical attention was Hantaan virus which caused more than 3000 cases of hemorrhagic fever with renal syndrome in U.S. troops during the Korean War. Since then, many hantaviruses have been identified in both the Old World and in the Americas that cause serious human illness. They are examples of emerging viruses because as the number of humans increases and as they invade more habitat occupied by rodents carrying hantaviruses, the incidence of infection in humans has risen. Very interesting in this regard was the isolation, in May 1993, of a new hantavirus that causes acute respiratory distress in humans that can lead to rapid death, a syndrome now called ***h***antavirus ***p***ulmonary ***s***yndrome (HPS) and originally called ***a***cute ***r***espiratory ***d***isease ***s***yndrome (ARDS). The virus was isolated by the CDC in collaboration with local health authorities following an epidemic in the Four Corners area of the southwestern United States that resulted in approximately 25 deaths. The virus is associated with the deer mouse *Peromyscus maniculatus*. It is thought that the epidemic may have resulted from an abundance of pine nuts in the area during a good growing year, leading the local people to harvest larger amounts of these than usual and store them in their homes when their normal storage areas became full. With abundant food available, the rodent population exploded and invaded homes to get to the pine nuts, and it is thought that this more intimate contact between humans and rodents may have led to the epidemic. The hantavirus responsible for this epidemic is now called Sin Nombre virus, which is Spanish for "without a name." Early suggestions that it be called Four Corners virus or Muerto Canyon virus (after a geographical feature in the area) drew objections from local residents who did not want this major tourist area identified with a fatal disease. Eventually the CDC simply named it Sin Nombre (there is a small creek in the area called the Sin Nombre River that serves as justification for the choice of name).

With the discovery of Sin Nombre virus, searches for viruses in other regions of North America resulted in the isolation of many viruses related to Sin Nombre. These viruses are associated with other rodents in the order *Sigmodontinae* and have been given names of local features in order to distinguish them. These include New York, Monongahela, Bayou, and Black Creek Canal viruses, all of which have caused HPS in the United States (see Fig. 4.26). Related viruses are also found in Latin America. In fact, studies have now shown that hantaviruses are present in virtually all states within the United States and into Latin America, and that fatalities due to infection by the virus have occurred in most states. Retrospective studies of stored sera collected from patients who died of ARDS in the past have identified earlier cases of HPS. Thus these viruses are widespread and have caused many fatal cases of human disease over the years.

As noted in Chapter 4, the epidemiology of arenaviruses is similar to that of the hantaviruses. Several South American arenaviruses have caused increasing numbers of cases of human hemorrhagic fever because of increased contact between humans and the rodent carriers of the viruses. The development of the Pampas of Argentina, in particular, led to increased incidence of human arenavirus disease.

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