Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 15

Emerging Virus Diseases

Emerging disease is a term used to describe the appearance of a previously unrecognized infection in a particular host species, or a previously known infection that has expanded into a new ecological niche or geographical zone, often accompanied by a significant change in pathogenicity. Prominent examples in the last two decades include the emergence of SARS in 2003, the sudden crossing of H5N1 avian influenza virus into humans in 1995, and the unexpected West African outbreak of Ebola virus in 2014. In the last few years Zika virus, thought for decades as causing only a mild febrile illness in East Africa, has emerged to cause significant morbidity in regions as far apart as Polynesia and South America. Difficult to predict, emerging threats to public health are the direct manifestation of a number of factors, singly or collectively, that cause significant changes in the constantly evolving relationship between pathogen and host. There is general agreement that factors include population growth, migration into large conurbations, climatic changes, ease of transportation and changes in human behavior.

Among 1400 pathogens of humans over 50% have originated from animal species, with over 300 being recognized as having emerged in the years 1940 to 2004, coinciding with the rapid changes in agricultural practice plus the rapid growth in urbanization over this period. Thus emerging or re-emerging pathogens are more likely to be zoonotic, that is, naturally transmitted from animals to humans. Furthermore, viruses are over-represented in this group, with RNA viruses accounting for a third of all emerging and re-emerging infections.

Recent interest in emerging virus disease has focused on understanding three key areas. First, how the interplay of climate, environment, and human societal pressures can trigger emergence. Second, how viruses can transmit between an established reservoir species and a new host species and what determines pathogenicity in each species. And third, which aspects of these processes offer opportunities for therapy and prevention. To these must be added a broader understanding of how viruses evolve over time; further clues to this are now being uncovered by studying host genetic elements responsible for resisting virus invasion.

INCREASED RECOGNITION AND CHANGES IN DISEASE PATTERNS

The perception that a new disease has recently emerged does not always reflect the situation that a new virus is actually circulating among humans. For example, the identification of a virus for the first time and the development of new diagnostic tests can create the impression of a new or increasingly prevalent disease even if the virus is already endemic, through allowing a better definition of the true distribution of infection within the community. In the years following the introduction of new tests for hepatitis B, hepatitis C, rotavirus, and human papillomaviruses, more accurate recognition of the true extent of infection contributed to a sense of new risks of disease. Of course, some true increase in prevalence had also occurred with some of these examples.

Furthermore, changes in human behavior can alter the epidemiology of a virus infection that is already endemic, leading to the appearance of new diseases. The slowing in circulation of polioviruses that followed improved sanitary conditions in the early 20th century led to infection being acquired at older ages with a greatly increased rate of paralytic disease. The introduction of more widespread parenteral medical procedures (e.g., parenteral therapy for syphilis, blood transfusion, renal dialysis) led to dramatic outbreaks of hepatitis B caused by a virus that was already endemic in the community. This transmission route has now been largely eliminated by rigorous screening of donated blood and infection control measures, while widespread dissemination of blood-borne infections among intravenous drug users has led to new patterns of disease. Changes in sexual practices and in numbers of sexual partners can affect an individual's exposure to sexually transmitted infections including HIV, and if this applies to groups of individuals or a population, changes in the disease prevalence will be seen.

The appearance of the new disease dengue hemorrhagic fever/dengue shock syndrome in Manila in the 1950s is thought to be due to the increase in sequential superinfection with a second related strain of dengue virus, the result of increased virus circulation that occurred following the migration of

Fenner and White's Medical Virology. DOI: http://dx.doi.org/10.1016/B978-0-12-375156-0.00015-1

people from rural areas into towns and cities. A regular driver of the reappearance of infectious diseases is the social and economic dislocation caused by war. For example, Syria had been free of poliomyelitis from 1999 until the outbreak of war in 2011; in 2013, the appearance of 35 cases was reported, leading to an intensified polio vaccination campaign.

Finally, for completeness, mention should be made of the spectrum of previously unknown diseases and syndromes, caused by common or endemic human viruses when they infect immunosuppressed individuals.

Theoretically, a new human virus disease might emerge purely by mutation of a currently endemic virus to a more lethal or transmissible phenotype. In practice, although viruses in circulation are constantly evolving by mutation and recombination and are under constant selection pressure, these changes do not seem to be a common basis for new diseases or increased virulence. The new genetic material responsible for most of the newly emerging diseases is in most cases derived from infections of non-human species.

FACTORS AFFECTING EMERGENCE

Some of the factors affecting the emergence and distribution of virus diseases are shown in Box 15.1. These include properties of the particular virus, factors affecting transmission, and aspects of host resistance, and many of these operate concurrently or cooperatively to affect the occurrence of disease.

Given that many emerging diseases are zoonotic, it is perhaps not surprising (and indeed fortunate) that many do not appear capable of sustaining human-to-human transmission, and thus R_0 approaches zero (see Chapter 13: Epidemiology of Viral Infections). This means that for an outbreak of such infections to occur, there needs to be repeated exposure to the animal reservoir. This may be the case with Lassa fever, for example, where there is good evidence showing that local communities in West Africa are continually exposed to the virus. Where human-to-human transmission occurs more readily, R_0 approaches 1 and therefore multiple outbreaks may occur. These pathogens generate the most concern, as comparatively small change to R_0 as a result of adjustments to the host–pathogen relationship may have led to a significant escalation as to the risk of outbreaks.

Once passage between humans becomes the sole route of transmission, an infection can no longer be regarded as zoonotic. At this juncture a balance will have been established between the evolving viral genome and the ability of the human immune response to limit the infective process. Thus at any one moment in time, many emerging diseases can be viewed as being in this process of adaptation prior to reaching the ultimate host–parasite balance between virus maintenance and survival of the host.

The emergence of viruses from animals to humans can be considered as progressing through five key stages, although the boundaries are often indistinct (Table 15.1). The rate by which viruses move through these stages inevitably

BOX 15.1 Factors Affecting the Emergence or Distribution of Virus Diseases[a]

A. Involving the virus
- Mutation and selection
- New genetic material—zoonosis or recombination/reassortment

B. Involving transmission
- Climate and weather
- Overcrowding
- Rapid air travel
- Changes in sexual activities or numbers of partners
- Intravenous drug use
- Introduction of new medical interventions
- War and famine
- Humans venturing into new environments
- Vector density and exposure
- Occupational exposure

C. Involving host resistance
- Immunosuppression
- Nutritional state
- Herd immunity

[a]More than one of these factors will often be interacting together simultaneously; for example, genetic changes in a virus frequently coincide with changes in transmission patterns or host species affected, and it may be of less importance which change was a true cause and which was a result.

TABLE 15.1 The Key Stages in the Emergence of a Zoonotic Infection

Stage	Description	Transmission to Humans	Examples
I	Agent only in animals	None	
II	Primary transmission	Only from animals	Rabies, West Nile virus, Hendra, Avian influenza H5N1
III	Limited human outbreak	From animals or a few cycles in humans	Ebola, Marburg, monkeypox
IV	Long human outbreak	From animals or many cycles in humans	Yellow fever, dengue, influenza A, HIV-1[a]
V	Exclusively human agent	Only between humans	Hepatitis C, measles, smallpox, mumps, rubella

[a]*HIV-1 is now maintained as an exclusively human-to-human infection, although its initial emergence in humans is thought to have resulted from a limited number of recent animal–human transmissions.*

slows as environmental barriers become progressively less favorable and host responses adapt to meet virus challenge. Simultaneously, new strains carrying mutations that favor survival in the new host are continually selected.

CLIMATE CHANGE

Our environment is changing on an unprecedented scale. Climate change needs to be distinguished from climate variation: change is where there is statistically significant variation from the mean state over a prolonged period of time.

The most notable manifestation has been the climatic conditions initiated by changes in sea surface temperatures in the Pacific Ocean, known as the El Niño Southern Oscillation (ENSO). For example, in the summer of 1990 an El Niño event occurred, which in turn led to a period of prolonged drought in many regions of the Americas: this led eventually to the emergence of hantavirus pulmonary syndrome caused by Sin Nombre virus (see Chapter 29: Bunyaviruses). Conversely a sudden reversal in sea temperature in the summer of 1995 resulted in heavy rainfalls, especially in Columbia, resulting in resurgence of mosquito-borne diseases such as dengue and Venezuelan equine encephalitis.

The geographical distribution of vector-borne diseases is particularly sensitive to climatic conditions, especially temperature. Even a small extension of a transmission season may have a disproportionate effect, as transmission rates rise exponentially rather than linearly with increasing temperature. Climatic change can also alter vector distributions if suitable areas for breeding become newly available. Again, the effect may be disproportionate, particularly if the vector transmits disease to human or animal populations that lack pre-existing levels of acquired immunity. The result is that clinical cases are more numerous and potentially more severe. Increased temperatures and seasonal fluctuations in either rainfall or temperature favor the spread of vector-borne diseases to higher elevations and to more temperate latitudes. *Aedes aegypti*, a major vector of dengue, is limited in distribution by the 10°C winter isotherm, but this isotherm is shifting, thereby threatening an expansion of disease ever further from the equator.

The relentless change inflicted by humans on the environment in the name of progress has also had a marked effect on rodent habitats. Outbreaks of Bolivian hemorrhagic fever (BHF) in Bolivia and hantavirus pulmonary syndrome (HPS) in the United States have been linked to abnormal periods of drought or rainfall, leading to unusually rapid increases in rodent numbers. Of all species of mammals, rodents are among the most adaptable to comparatively sudden changes in climate and environmental conditions. Small climatic changes can bring about considerable fluctuations in population size, particularly with those rodents inhabiting desert and semi-desert areas. Such variations are directly related to oscillations in food quantity and quality. A prolonged drought in the early 1990s in the Four Corners region of the United States led to a sharp decline in the numbers of rodent predators, such as coyotes, snakes, and birds of prey. But at the end of the drought heavy rainfall resulted in an explosion in piñon nuts and grasshopper populations, which in turn resulted in a rapid escalation of rodent numbers, among them deer mice carrying hantaviruses; the result was the emergence of hantavirus pulmonary syndrome.

Arthropod-borne infections such as Congo-Crimean hemorrhagic fever (CCHF) and Rift Valley fever (RFV) virus (see Chapter 29: Bunyaviruses) could pose a substantial risk to both humans and livestock in Europe should climatic conditions raise further the ambient spring temperature. Immature ticks infected with CCHF virus carried on migratory birds would molt in much greater numbers, although such an enhancement in molting might be offset by a significant reduction in the number of migratory birds. Many experts consider that there are already competent mosquito species in the northern hemisphere to enable the spread of RFV virus should this be introduced into Europe.

Deforestation has accelerated enormously since the beginning of the 20th century, and in the Amazonian basin and parts of Southeast Asia this has had a profound effect on local ecosystems, particularly by constraining the range of natural predators that normally keep rodents, insects, and other potential carriers of infectious disease under control. The reduction in biological diversity can trigger the invasion and spread of opportunistic species, facilitating the emergence of disease through increased contact with local human populations.

EASE OF TRAVEL

Air travel represents a major risk factor for the global spread of a new infectious agent. It is estimated that over 100 million passenger journeys are made by air every year. This is in marked contrast to just 50 years ago when many people rarely if ever traveled any distance from their place of residence. Frequent air travel is now regarded as a major contributing factor to the spread of emerging diseases as evidenced by the rapid spread of the SARS virus in 2003, when the infection was disseminated from China to at least 17 countries in less than a week. Mathematical modeling can be used to predict those regions most at risk in the event of any future SARS epidemic. Were a vaccine available, the initial spread of virus might be contained if only a third of the population were immunized in the regions where the outbreak is focused. This assumes an index case made a single air journey. However, the risk increases substantially in the event of an index case making two journeys, with the whole population requiring vaccination if the same passenger made three trips. Analysis of air traffic from

Mexico at the start of the 2009 influenza H1N1 pandemic suggests the risk of spread is particularly great when the volume of air traffic is high and the resources to report and trace diseased individuals are very restricted.

Ground transport offers another major route for transmission. Approximately 17% of all travel in Europe, for example, is by public ground transport, while air travel represents less than 0.2% of all passenger kilometers traveled. In contrast to airliners, public trains, buses, etc. are rarely fitted with high-efficiency particulate air (HEPA) filters.

It is not only humans who travel: the International Air Transport Association (IATA) estimates that around 80,000 wild-caught animals are air freighted each year, many being placed in holding facilities close to populated areas whilst in transit. Even mosquitoes may be carried: one theory is that West Nile virus (WNV) entered the United States as a result of an infected mosquito surviving the air journey from the Middle East to New York City in 1999 (see Chapter 36: Flaviviruses).

The incursion of WNV into North America is an excellent example of a virus expanding into an ecological niche where transmission-competent vectors were already present. Once established in and around the New York area, the availability of vertebrate hosts, most notably birds of the crow family, together with optimal climatic conditions for vector populations, enabled the rapid spread of WNV across the United States. Epizootic outbreaks of WNV have occurred frequently, with an escalating number of human neurological cases among the immunocompromised and the elderly (see Chapter 36: Flaviviruses) (Fig. 15.1).

ANIMALS AS A SOURCE OF HUMAN DISEASES

The advent of agriculture around 10,000 years ago was pivotal in giving rise to many of the human infections we know today. Agricultural-based societies led to humans living in close proximity both to each other and to livestock. In turn, human settlements provided fertile ground for inter-species transmission between farm animals, rodents, dogs, cats, and insects. Once established in humans, the diseases could be maintained indefinitely if the numbers of susceptible individuals remained above a certain threshold and in frequent contact with diseased persons. It is widely thought that measles emerged at this time, probably from rinderpest in cattle, and diverged into an exclusively human pathogen as human centers of population grew to a level where an animal reservoir was no longer necessary. Similarly, smallpox may have evolved about 4000 years ago from camel pox, its closest phylogenetic relative.

Wild Animal Populations

The emergence of HIV/AIDS provides an interesting example. The different major groupings of HIV-1 strains (M, N, and O) probably arose through separate chains of events involving (1) recombination between different simian immunodeficiency virus (SIV) strains in different monkey species and (2) transmission of these strains to other primates and/or chimpanzees and thence to humans. Many details remain conjectural, including the likely frequency of such events, and the different factors (viral, ecological, human behavioral, etc.) that led to a global, human-to-human pandemic becoming established in the 1980s and not before (Fig. 15.2).

Rodents

Rodents constitute an important part of the Earth's biomass. Among all species of mammals, members of the family *Muridae* have been the most successful and are found in almost all habitats. This family contains species that are the natural hosts of almost all arenaviruses and hantaviruses. As noted above, rodents are highly susceptible to climate

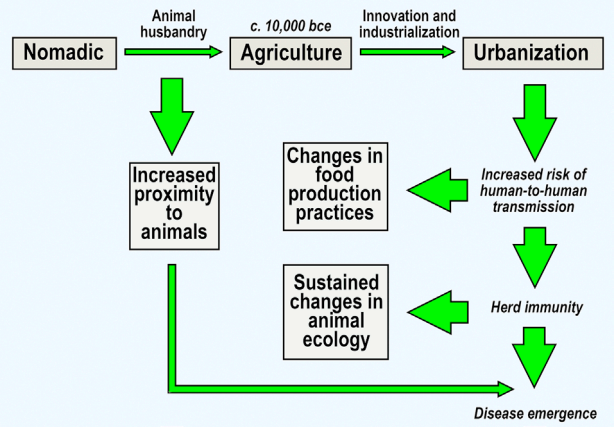

FIGURE 15.1 Historical changes in agriculture and human urbanization. Some of the impacts of these changes on infectious disease transmission (human-to-human, and animal-to-human) are shown. *Adapted from Howard, C.R., Fletcher, N.F., 2012. Emerg. Microbes Infections 1, e46; doi 10.1038/emi 2012.47.*

and ecological change, resulting in variable population numbers. Among the fastest reproducing mammals, field voles can have over 15 broods per year, each with an average of 6 pups. This in turn considerably increases the risk of human exposure to any pathogens they may carry, as well as stimulating such pathogens to undergo mutational adaptations to a changing ecosystem, with rodents thriving on potentially contaminated food and water.

The Four Corners outbreak of HPS in the United States described above instigated intensive research as to how fluctuations of rodent populations precipitate outbreaks of human disease. If the environment can suddenly sustain a rapidly expanding number of animals, population sizes explode, and the chances of rodents encroaching into peri-domestic areas and households also increase, especially when the overabundance of food comes to an end. As a consequence there is a rise in the incidence of human illness, as individuals have a much greater chance of coming into contact with excreta from persistently infected animals. The chance of a virus switching into other rodent species also becomes a greater possibility as rodent territories expand and overlap.

Switching to a new rodent host can have a profound effect on virus evolution. Adaptation of hantaviruses to new hosts can stimulate the development of new virus phenotypes and hence expansion into new ecological niches. Examples of this in Europe include the divergence of Saaremaa virus from Dobrava virus, as a consequence of Dobrava virus switching from the yellow-striped field mouse (*Apodemus flavicollis*) to *A. agrarius*, the striped field mouse (see Chapter 29: Bunyaviruses). The result is a virus with presumed reduced pathogenicity for humans.

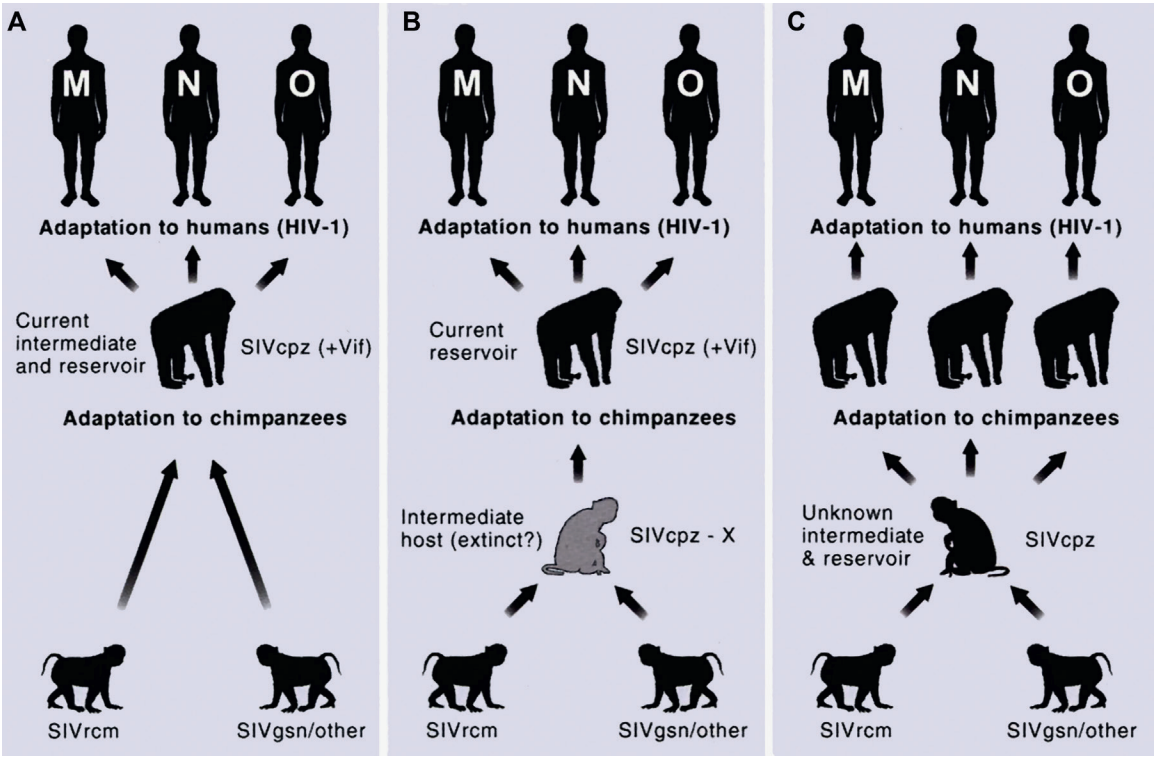

FIGURE 15.2 Simian immunodeficiency virus (SIV) strains and cross-species transmission to great apes and humans. Old World monkeys are naturally infected with over 40 different strains of SIV. These strains are species-specific and hence are denoted with a suffix to indicate their species of origin. The three major types of HIV (N, M, and O) each derived from a separate transfer event. Cartoons showing three possible alternative routes of cross-species transmissions giving rise to chimpanzee SIV (SIVcpz) as a recombinant of different monkey-derived SIVs illustrate the possible complexity of the steps leading to the introduction of viruses into a new host. + Vif indicates the presence of an HIV-like Vif, which is required to overcome the virus inhibitory effects of APOBEC3B. (A) *Pan troglodytes troglodytes* as the intermediate host. Recombination of two or more monkey-derived SIVs (likely SIVs from red-capped mangabeys [SIVrcm] and the greater spot-nosed monkeys [SIVgsn] or related SIVs) and possibly a third lineage requiring co-infection of an individual monkey with one or more SIVs. Chimpanzees have not been found to be infected by these viruses. (B) The SIVcpz recombinant develops and is maintained in a primate host that has yet to be identified, giving rise to the ancestor of the SIVcpz/HIV-1 lineage. *P. t. troglodytes* functions as a reservoir and was responsible for each of the human introductions. (C) Transfer through an intermediate host (yet to be identified) that is the current reservoir of introductions of SIVcpz into current communities of *P. t. troglodytes* and *P. t. schweinfurthii* as a potential source of diverse SIVcpz variants that are each found in limited geographic regions of Africa. *Reproduced from Heeney, J.L., Dalgleish, A.G., Weiss, R.A., 2006. Science 313, 462–466, with permission of AAAS.*

Bats

During an investigation of the 1998 Hendra virus outbreak in Queensland, Australia, it was noticed that grazing horses often sought shelter under trees containing bat roosts. Wild fruit bats in such roosts were found positive for virus and neutralizing antibodies found in otherwise healthy bats. Similarly, the related Nipah virus found in Malaysia and Bangladesh has also been associated with *Pteropus* bats: youngsters had been exposed to the secretions of fruit bats when picking fruit or processing date palm oil from bat-infested trees.

Bats have long since been known as the principal hosts of lyssaviruses, and distinct phylogenetic differences exist between rabies virus strains circulating in bats and terrestrial mammals, such as foxes, raccoons, and dogs. The link between genetic variability and spatial epidemiology among the lyssaviruses gives a particularly good insight as to how viruses of wildlife can adapt and emerge into different animal populations. Rabies virus in Europe has switched host many times over the past century, adapting rapidly to new animal hosts as the virus expands into new species with time. Rabid bats exhibit abnormal behavior, losing their natural fear of people and thus present a greater risk of transmission to humans (see Chapter 27: Rhabdoviruses).

Bats are found in most terrestrial habitats, with species distribution varying widely, some being restricted to a single island, others being found across continents. The fruit bats have evolved along a very different path to the insect-eating species. Fruit-eating bats are not normally cave dwelling, preferring to form roosts in treetops or crevices in decaying trees, and thus present opportunities for spread to humans. Many bats travel distances of several kilometers for food, especially fruit-eating species which respond to ever-varying supplies of food and which must compete with birds and other animals. While both insectivorous and fruit-eating bats have been shown to harbor zoonotic viruses, fruit-eating bats represent the biggest risk for human contact: most of the flesh of fruit is discarded from the mouth of feeding animals, thus providing ample opportunity for virus spread.

Asymptomatic Ebola virus infection has been reported in insectivorous bats trapped in Central Africa and recent exposure to fruit bats has been a feature of at least one outbreak. *Rousettus aegyptiacus* is one species of bat in which antibodies to both Marburg and Ebola viruses have been found. *Rousettus* species are the exception: despite being fruit eaters, these bats form roosts deep within caves. Marburg virus sequences have also been found in wild-caught *Rhinolophus eloquens* and *Miniopterus inflatus*. Intriguingly, filovirus genetic elements have been found in some mammalian species as diverse as shrews and South American marsupials, leading to the suggestion that filoviruses have co-evolved with mammals over many millennia. This latter observation suggests that other filoviruses are yet to be discovered in the New World, or that South American species harbored ancestral filoviruses that gave rise to present-day Ebola and Marburg viruses.

Domestic Livestock and Poultry

Pigs have been implicated in several outbreaks of emerging infections. Starting in September 1998, clusters of human cases of encephalitis were reported from the Malaysian states of Perak and Negri Sembilan. Almost all of the cases had a direct link to the local piggeries, and coincided with accounts of illness among pigs 1 to 2 weeks beforehand. Initially these outbreaks were believed due to Japanese encephalitis virus but a number of cases had been vaccinated previously against Japanese encephalitis virus and there was no evidence of virus antibodies among the remainder. The link with Hendra virus soon followed after the isolation of virus from an infected pig farmer. The new agent, now named Nipah virus after the locality it was first reported, shares 80% sequence homology with Hendra virus, with both viruses now classified as henipaviruses within the *Paramyxoviridae* family. It is clear that Nipah virus is widely distributed across Northeast India, Bangladesh, and Southeast Asia, with phylogenetic analyses revealing the virus to be diverging within specific geographical localities.

Since it was first shown that pigs could be infected with hepatitis E virus (HEV) there has been interest in the zoonotic potential of this agent. In developing countries types HEV-1 and -2 are restricted to humans and are spread by the fecal–oral route, usually via contaminated water. On the other hand, in developed countries HEV-3 and -4 infection is a zoonosis, with pigs and some poultry as the main reservoir, leading to sporadic human cases often acquired by ingestion of poorly cooked meat. Pigs become infected around 3 months of age but suffer only a mild, transient infection. Hepatitis E virus infection may be the commonest form of viral hepatitis worldwide; it is probably underdiagnosed but has recently been increasingly reported due to improvements in diagnostic testing and screening.

Swine in the Philippines have been found to act as reservoirs for Reston virus, a filovirus related to Ebola and Marburg viruses. This was discovered during an unusually severe outbreak of porcine reproductive and respiratory syndrome (PRRS). Previously, Reston virus had been first identified in 1990 among non-human primates that had been imported from the Philippines to several primate-handling facilities in the United States and Europe. In contrast to its African relatives, however, Reston virus does not appear to cause human illness, although there is ample evidence of Reston viral antibodies in humans working in primate-holding facilities or working with swine. Thus, Reston virus appears to be transmitted by the respiratory route but to possess low virulence, while other Ebola species are

highly virulent but do not undergo airborne transmission. Fortunately, no viruses have yet emerged bearing the undesired characteristics of both.

Pigs are susceptible to human, avian, and swine influenza viruses, and thus play an important role in the epidemiology of human orthomyxoviruses. Influenza A virus is one of the comparatively few viral respiratory pathogens of pigs. Currently three subtypes circulate in swine: H1N1, H1N2, and H3N2. Domesticated pigs have often been regarded as a mixing vessel for influenza viruses by allowing the reassortment of the seven viral gene segments presenting an opportunity for new human strains to arise. Until 2009, however, swine influenza was not regarded as a significant cause of serious disease in humans.

However, cases of human infection began to emerge toward the end of April 2009 in what is normally regarded as the influenza season in the northern hemisphere. Beginning first in Mexico, the new virus subtype often referred to as "swine flu" by the popular press, spread rapidly throughout the world in a matter of weeks (see Chapter 25: Orthomyxoviruses). Analyses of human isolates quickly showed the unusual nature of this swine-origin influenza virus (S-OIV) as being a triple reassortment virus containing genes from avian, human and "classical" swine influenza viruses. The ancestors of this virus had probably been circulating in pig populations for over 10 years but had remained undetected. At the time, there was considerable uncertainty as to the pathogenic potential of this virus but data soon showed the severity for humans to be less than that seen with the 1918 pandemic but on a par with the 1957 "Hong Kong" pandemic. Transmissibility appeared higher than is normally the case for seasonal influenza with a higher than normal attack rate. Importantly, younger age groups appeared more susceptible, possibly due to partial immunity among older cohorts as a result of being infected during previous pandemics.

Of more recent concern is the spread of H7N9 influenza: this subtype was previously known to circulate in poultry, but from March 2013 the first human cases were reported, most of these in southern China. By March 2015 there had been over 220 deaths among 640 infected persons. Nearly all cases had been exposed to live poultry or visited live poultry markets, but several very limited family clusters were also reported, suggesting that very limited human-to-human transmission may also be possible. H7N9 influenza virus may become a serious public health threat should it become established among wild birds.

Companion and Captive Animals

Frequent contact with companion animals such as dogs, cats, and horses provides additional opportunities for the transmission of animal diseases to humans. Although companion animals have been kept within households over the centuries, the number of known emerging infections from such sources is remarkably few. There are a number of canine homologs of human flaviviruses. The discovery of a canine flavivirus distantly related to human hepatitis C virus (HCV) raises some intriguing questions as to the origin of hepatitis C virus in human populations. Although evidence was found for virus in the canine liver, there is as yet no evidence of this canine hepatitis C-like virus causing liver disease in dogs. Whether or not hepatitis C virus first emerged from dogs remains speculative, but the finding of virus in the respiratory secretions of infected dogs indicates a potential route of transmission to humans. A related flavivirus has been described among seropositive horses in the State of New York. There was no supporting evidence of clinical disease among all the animals tested but this does not preclude a pathogenic potential for humans.

There is an increasing trend, particularly in more affluent economic countries, to keep more exotic wild animals as pets. It is estimated that approximately 350,000 wild-caught animals are traded around the world each year, adding to the risk of potentially zoonotic infections crossing the species barrier into humans. The finding of a new arenavirus in boa constrictors (*Boa constrictor*) suffering from snake inclusion body disease has raised questions as to how common such viruses might be among captive wild animals. Intriguingly, sequence data from this arenavirus showed diversity compatible with a pre-existing relationship between host and virus over time. Moreover, sequences were found homologous to those of arenaviruses causing severe hemorrhagic fever, e.g., Lassa virus (see Chapter 30: Arenaviruses), but surprisingly the snake arenavirus also shared glycoprotein sequences with filoviruses. This would suggest that there has been recombination along one of the two RNA genome segments at some point in time with an ancestral filovirus that subsequently evolved to become the Ebola and Marburg viruses of today.

The keeping of small rodents and mammals has been linked to zoonotic disease for many decades, a prime example being lymphocytic choriomeningitis virus (LCMV) transmitted as a result of handling persistently infected hamsters. The keeping of prairie dogs is common in the United States, and indirectly led in 2003 to an outbreak of monkey pox in the State of Wisconsin (see Chapter 16: Poxviruses). This totally unexpected occurrence was the result of housing prairie dogs intended for sale in close proximity to small rodents imported from the African continent, most notably rope squirrels (*Funisciurus* spp.) and Gambian giant rats (*Cricetomys* spp.). Although there were no fatalities among the reported cases, it presented an opportunity for the spread of monkey pox into the feral mammal population of North America. It remains to be seen if wild animals become a source of monkey pox outbreaks in years to come.

A worrying complication is the emergence of mild human infections due to vaccinia virus. This virus,

successfully used in the past for the eradication of smallpox, has been transmitted from herds of dairy cattle in Brazil and in buffaloes in India. These instances of "feral" vaccinia may have originated from human vaccines being inadvertently introduced into livestock from whence the virus has been re-introduced among agricultural workers to cause a disease resembling cowpox. There is also evidence for vaccinia virus infection among black howler (*Allouata caraya*) and capuchin monkeys (*Cebes apella*) inhabiting the Amazonian rainforest.

PREVENTION AND CONTROL

Outbreaks of emerging diseases vary widely in duration, frequency, and case numbers. Some can be predicted to occur regularly, for example new strains of influenza, whereas many decades may elapse between episodes, as is the case with Marburg virus. Yet others, as exemplified by Zika virus, have been known for decades but until recently thought to not represent a threat to public health. Thus planning a single, integrated strategy against all eventualities is therefore almost impossible. The task may be compounded by the emergence of escape mutants in populations vaccinated against known diseases, the emergence of strains resistant to antiviral therapy, or even the recycling through livestock of attenuated vaccines designed for use exclusively in humans. It is instructive to compare three major emerging disease outbreaks in recent years—HIV/AIDS, pandemic H1N1 swine influenza 2009, and Ebola in West Africa. For each of these, the transmission routes, transmissibility and R_0 together with the case-fatality rates were very different: the rates of spread also varied, and achieving control presented very different problems requiring specific control measures.

Improved epidemiological surveillance of infectious diseases is the foundation for combating emerging diseases. Integration with the veterinary community is essential: several "One Health" programs have been set up to help developing nations strengthen their overall capacity to react quickly and effectively. Valuable time was lost in 1999 when the first cases of West Nile virus occurred in New York City among both humans and birds.

Technology can play a major role in predicting disease emergence, for example, the use of satellite imagery to detect changing patterns of vegetation in response to rainfall. The use of satellite maps taken over East Africa accurately predicted the outbreak of Rift Valley fever among livestock as a consequence of increased vector activity. The use of the Internet is essential in allowing rapid dissemination of serological, clinical, and molecular sequencing data. Such rapid communications played a vital role in combating the SARS outbreak in 2003 and also in identifying the spread of swine-origin H1N1 influenza virus in 2010.

Crucial aspects for controlling any new outbreak include early recognition of the outbreak, good access to diagnostic facilities, and dissemination and analysis of surveillance data (Table 15.2). As early as possible, an assessment needs to be made of the likely origin of the new agent (in terms of both its virological ancestors, and its likely source or reservoir); its transmission routes; the case-fatality rate; its transmissibility and R_0 (see Chapter 13: Epidemiology of Viral Infections). Based on this information, appropriate control measures need to be quickly activated. These often include instituting appropriate isolation and infection control for cases; quarantining of contacts; travel restrictions; enhanced vaccination programs; provision of antivirals; and mobilization of the local health system to manage the predicted increase in hospitalized patients and community anxiety. Time is of the essence, as delays lead inevitably to an escalation in numbers of cases that can overwhelm locally available manpower and capacity. The immediate closure of hospitals was pivotal in limiting the nosocomial spread of Ebola virus in the original outbreaks in Sudan and Zaire in 1996. The importance of early recognition and the availability of local expertise were highlighted in Uganda, where the discovery of the Bundibugyo strain of Ebola virus in 2000 led to the strengthening of local capacity. Cases of Ebola virus in July and August 2012 have been rapidly diagnosed as a result of this regional investment in infrastructure, thus preventing its spread to Kampala, the Ugandan capital. However, outbreaks may spread even in countries fully equipped to deal with infectious disease outbreaks, unless the clinical and epidemiological data can be reviewed quickly and critically and the appropriate control measures instigated.

Emergence of new infectious diseases has undoubtedly been ongoing for millennia. Although the rate at which new infections are being discovered has accelerated in the past half-century, it is some comfort that newly identified emerging viruses fall invariably within well-characterized

TABLE 15.2 The Major Requirements for Recognition and Response to Emerging Infections

- Alerting clinicians to quickly recognize and react to any unusual clinical presentation
- Access to a high standard of diagnostic capabilities plus availability of reference laboratory expertise
- Formulating practical case definitions for field use
- Instituting isolation and infection control for cases
- Involvement of epidemiologists and communicable disease specialists at the earliest opportunity to assess the crucial characteristics of the outbreak
- Quarantining contacts, travel restrictions where appropriate
- Mobilization of local health system to handle the increased number of sick patients
- Enhanced vaccination programs, access to antivirals where available
- Enhanced education for healthcare staff, families, and general communities

virus families. However this may change as we discover vast numbers of hitherto uncharacterized viruses in what is now commonly referred to as the virosphere.

Viruses can evolve faster than mammals by many orders of magnitude, being near instantaneous compared to the scale of mammalian adaptation over years and decades. This enormous capacity for adaptation is offset by the generally very demanding survival requirements of viruses in their precarious existence between hosts. Emergence of vector-borne diseases can represent a major threat in the short term once conditions for adaptation result in emergence and an extension of host range as a consequence, as was the case for chikungunya virus in 2005 (see Chapter 35: Togaviruses).

How can we ensure we are prepared to combat emerging diseases? A capacity to respond quickly and effectively with appropriate measures is essential (Table 15.2). Many governments now recognize and take into account the likely impact of environmental developments on ecosystems and disease emergence, extending environmental impact studies beyond conservation of natural habitats and species. Responding to the threat of disease emergence, the International Health Regulations sponsored through WHO were substantially revised in 2005, requiring countries to develop national preparedness capabilities, conduct meaningful surveillance, and to promptly report internationally significant events.

Considerable international effort is now being made to collect and record samples of viruses and microorganisms from wild animal populations and potential arthropod vectors in order to expand the current molecular databases. A leading example is the establishment of the WHO-led Global Influenza Surveillance and Response System (GISRS), an international program serving as an alert mechanism for the emergence of influenza viruses with pandemic potential through its continual monitoring of isolates and risk assessments. By making available extensive catalogs of genome sequences across international and political boundaries it is hoped that newly emerging agents would in future be more readily identified and thus control measures put in place much more rapidly.

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