CTMI (2007) 315:1–31

Introduction: Conceptualizing and Partitioning the Emergence Process of Zoonotic Viruses from Wildlife to Humans

J. E. Childs[1]· J. A. Richt[2]· J. S. Mackenzie[3](✉)

[1]Department of Epidemiology and Public Health, Yale School of Medicine, 60C ollegeS t., P.O. Box2 08034 New Haven, CT 06520-8034, USA

[2]VeterinaryM edicalO fficer,N ational Animal Disease Center, 2300 Dayton Ave, Ames, IA 50010, USA

[3]Premier'sR esearchF ellow, Australian Biosecurity CRC, Curtin University ofT echnology, GPO BoxU 1987 Perth, WA, Australia 6845
J.Mackenzie@curtin.edu.au

Abstract This introduction provides a telegraphic overview of the processes of zoonotic viral emergence, the intricacies of host–virus interactions, and the distinct role of biological transitions and modifying factors. The process of emergence is conceptualized as two transition stages which are common and required for all disease emergence, (1) human contact with the infectious agent and (2) cross-species transmission of the agent, and two transition stages which are not required for emergence and appear unavailable to many zoonotic pathogens, (3) sustained human-to-human transmission and (4) genetic adaptation to the human host. The latter two transitions are presumably prerequisites for the pandemic emergence of a pathogen. The themes introduced herein are amplified and explored in detail by the contributors to this volume. Each author explores the mechanisms and unique circumstances by which evolution, biology, history, and current context have contrived to drive the emergence of different zoonotic agents by a series of related events; although recognizable similarities exist among the events leading to emergence the details and circumstances are never repetitive.

1 Introduction

The process of zoonotic disease emergence can be understood by coupling knowledge of how zoonotic viruses have evolved and are maintained among their wildlife hosts, transmitted across a species barrier to cause productive infection in a taxonomically distinct secondary host, initiate a pathologic process causing disease, and, by repetitive infection within the secondary host species, result in incident morbidity or mortality of sufficient magnitude to be detected and characterized as a novel health concern of local, regional, or global significance (see the chapter by Childs, this volume). Obviously, we possess no such knowledge for any zoonotic virus or zoonotic disease, but casting the emergence process in this context underscores how disciplinary boundaries are blurred; advances require approaches spanning the spectrum of biological inquiry, and solutions to imminent threats require approaches unbounded by the notion of specific scientific discipline.

The emergence process involves ecological interactions at the individual, species, community, and global scale. The dynamic circumstances and relative

importance of the participants reflect the evolutionary context in which zoonotic agents have become accommodated to, and been accommodated by, their reservoir hosts (H_Rs) (see the chapters by Cleaveland et al. and by Holmes and Drummond, this volume), the diversity of reservoir species involved, their geographic ranges and the local dispersion of host and pathogen populations. In turn, historical factors have modified and blurred traditional patterns of species distribution, abundance, and diversity, and are continually transforming the landscape of opportunity on which zoonotic viruses with their H_Rs mingle with novel, potentially susceptible secondary host species (H_S)s (see the chapters by Daszak et al., Field et al., Regnery, and Wang and Eaton, this volume). The current historical circumstances are unprecedented in their efficiency for continually shuffling an expanding repertoire of zoonotic viruses and hosts, introducing them in novel ecologic circumstances to a wealth of previously unavailable and unexplored niches. Within the last decade, the accelerated pace of rapid translocations of infected H_Rs or H_Ss have heralded a sea change in how we view the public health threat posed by zoonotic viruses (Childs 2004), as testified by the emergence of SARs coronavirus (SARS CoV) (Drosten et al. 2003; see the chapter by Wang and Eaton, this volume), influenza A subtype H5N1 (Peiris et al. 2004; see chapter by Webby et al., this volume), West Nile virus (WNV) (Lanciotti et al. 1999), Nipah virus (NiV) (Chua et al. 1999; see the chapter by Field et al., this volume), and Monkeypox virus (Anderson et al. 2003; see the chapter by Regnery, this volume).

1.1 Cross-Species Transmission (Spillover)

Inherent in the term "cross-species transmission" (or spillover) is the ability for a foreign virus, once introduced into an individual of a H_S population, to complete the virus infectious cycle: (1) adsorption, penetration, and uncoating, or separation of the viral nucleic acid from the capsid; (2) transcription, translation, and replication, and; (3) assembly and release (Nayak 2000). Binding and entry into permissive H_S cells is mediated by common or related cellular receptors. Additional bouts of infection following virus release from infected cells lead to the dissemination of virus throughout the host's tissue(s), precipitating, as a byproduct, pathologic alterations in the individual H_S identifiable as symptomatic disease.

1.2 Pathogenesis in the Reservoir Host and Secondary Host

The pathogenic course of infection and disease within the secondary host (H_S) may bear little correspondence to the infectious process and outcome within the

reservoir host (H_R). Oral lesions caused by herpesvirus B (CeHV-1) infection among individual macaques of the H_R are transmogrified into an often fatal (~70%) meningoencephalitis in the human H_S (Huff and Barry 2003). Hantaviruses cause subclinical infections or subtle behavioral changes with limited pathology in individual rodents of species constituting the virus-specific H_Rs (Hinson et al. 2004; Llyubsky et al. 1996; see the chapter by Klein and Calisher, this volume), accompanied by no notable loss of fitness (Childs et al. 1989). However, these subtleties are lost in the severe and often fatal hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), developing in the human H_S after virus spillover (Zaki et al. 1995; Tsai 1987).

No matter how different the disease course among the human H_S, the pathologic component of intra- H_R transmission is highly relevant when considering strategies to prevent human infection rather than treating post-spillover disease (see the chapter by Daniels et al., this volume). Ignoring the intricacies of zoonotic virus transmission among wildlife H_Rs guarantees that solutions springing from a traditional anthropocentric disease-treatment/vaccine-preventative approach will consider a limited universe of defensive prevention targets and generate a restricted arsenal of intervention tools.

2
The Comparative Ecology of Zoonosis Emergence and Species Invasion

2.1
Four Transition Stages to Emergence: The First Two Are Prerequisite

The ecologic process of zoonotic disease emergence can be schematized by four transition stages (Fig. 1), of which only the first two are prerequisites for emergence: (1) contact between infectious propagules originating from the wildlife H_R with individuals of a susceptible H_S and (2) cross-species transmission, a transition subsuming the complex interactions of the virus infectious cycle within the H_S (Nayak 2000; Childs 2004). These first two transitions may require a mediating host such as an arthropod vector (H_V) or an intermediary vertebrate host (H_I); these additional host populations are readily accommodated by the modular emergence schema (Fig. 1).

2.2
Two Transition Stages Are Required for Pandemic Emergence

The latter two transition stages demarcate a change in the interrelationship of host and virus (Fig. 1): (3) sustained transmission of the once zoonotic

virus between members of the new H_S, subsequent to, and independent of, new spillover events, and (4) genetic adaptation and phenotypic changes accompanying sustained intra-H_S transmission. Once sustained transmission occurs within the human host, evolutionary adaptation between virus and host can transform the once zoonotic virus into a distinctive new virus with a new human H_R. The new virus associated with humans must be quantitatively and qualitatively different from ancestral strains in genetic and phenotypic characters, in order to designate the emergence of a new biological entity. With HIV and pandemic influenza subtypes, the qualities of the newly adapted viruses to humans are readily apparent in terms of host preference and host pathogenicity (Hahn et al. 2000; Claas 2000). With SARS CoV infecting humans, the specific genetic changes are less clear-cut (Song et al. 2005), most probably because the transmission of SARS CoV was curtailed early its relationship to the new human host. Support for this conclusion is based on the genetic differences accrued by SARS CoVs sustained through multiple generations of human-to-human transmission as compared with those viruses with shorter interhuman passages (Liu et al. 2005).

Some viruses are capable of sustained human-to-human transmission with minimal or no genetic change [i.e., SARS CoV; see the chapter by Wang and Eaton, this volume, although limits to genetic adaptation within humans may be imposed by the requirement for an intermediate vector or extensive prior adaptation to a specific reservoir host (Gould et al. 2003)]. The arboviruses, yellow fever virus, and the four dengue serotypes circulate in a human-to-human transmission cycle mediated by anthropophilic H_Vs after introduction by bridging H_Vs feeding on infected primate H_Rs (de Silva et al. 1999; Wolfe et al. 2001; Monath 1989; Downs 1982); these viruses appear closely related to the wild type viruses circulating in sylvatic cycles, although regional variation is apparent (Bryant and Barrett 2003).

Viral adaptation to the human H_R appears in most cases to be critical to developing a virus with pandemic potential (Mims 1991, 1995). The introduction of avian-like gene segments into preexisting, aerosol-transmitted, human influenza A viruses, or alternatively, the introduction of key genetic components into preexisting avian viruses (see the chapter by Webby et al., this volume) may be prerequisite to pandemic influenza A emergence (Claas 2000). The emergence of SARS into the human population was accompanied by strong and rapid positive selection of different subtypes of virus as indicated by comparisons of sequence data from humans and from palm civets and rhinolophid bats, putative H_Rs, or intermediate hosts (H_Is) for SARS CoV (Lau et al. 2005; Song et al. 2005; see the chapter by Wang and Eaton, this volume).

2.3
The Basic Reproductive Potential R_0 as a Measure of Viral Relative Fitness

To capture the rate at which outbreaks spread among hosts, epidemiologists have relied upon the reproduction potential, R_0, as a measure of the expected number of secondarily infected and infectious hosts produced during the infectious period of a single infected host when introduced into a freely mixing population of susceptible individuals (Halloran 1998). The relative fitness defined by R_0 is a composite of three terms *c*, the contact rate or number of contacts per unit time, *p* , the transmission probability per contact, and *d*, the duration of infectiousness (see the chapter by Real and Biek, this volume). Examples of zoonotic viruses taking alternative paths to emergence, with highly variable R_0s are discussed below.

3
Modifying Factors in the Emergence Process

The underlying feature distinguishing modifying factors (Fig. 1, right panel) from transition stages in zoonotic virus emergence (Fig. 1, left panel) is that the former requires the substrate provided by the latter on which to act. Modifying

Fig. 1 A schema for partitioning the process of zoonotic disease emergence into four transitions and modifying factors which alter the likelihood of transitions occurring. Disease emergence can occur at the local and regional level or as a pandemic depending on the nature of the pathogen and the influence of modifying factors. Modifying factors are largely responsible for driving the magnitude and geographic scope of an emergent event, but by themselves are insufficient to lead to disease emergence. Although only a single population source for a zoonotic pathogen is indicated, the reservoir host (H_R) population, the schema is modular and readily accommodates inclusion of vector (H_V) populations and intermediate vertebrate host (H_I or H_{SI}) populations antecedent to spillover to humans (see Fig. 1 in the chapter by Childs, this volume). Transition stages, with the exception of contact (*Transition 1*) and cross-species transmission (spillover; *Transition 2*), are not strictly hierarchical in the emergence process. Transition stages are shown to the *left of the population boxes* and the two transitions required for emergence (contact and spillover) are shaded *gray*. *In the center* are two population boxes, the *top shaded box* indicating a H_R population, in which a zoonotic virus or some other zoonotic pathogen circulates, and the *bottom shaded box* indicating the secondary host population (H_S) affected by pathogen spillover (assumed in most instances to be humans). The *graded shaded pyramid within the H_S population* indicates that emergence often proceeds through a gradient of human population sizes and social connectivity. Spillover and human transmission chains in remote villages (apex of pyramid) can lead to spread to urban centers (*base of pyramid*), at which point a pathogen is assumed to have access to the entire H_S population demarcated by the *H_S box*. To the left of the population boxes are

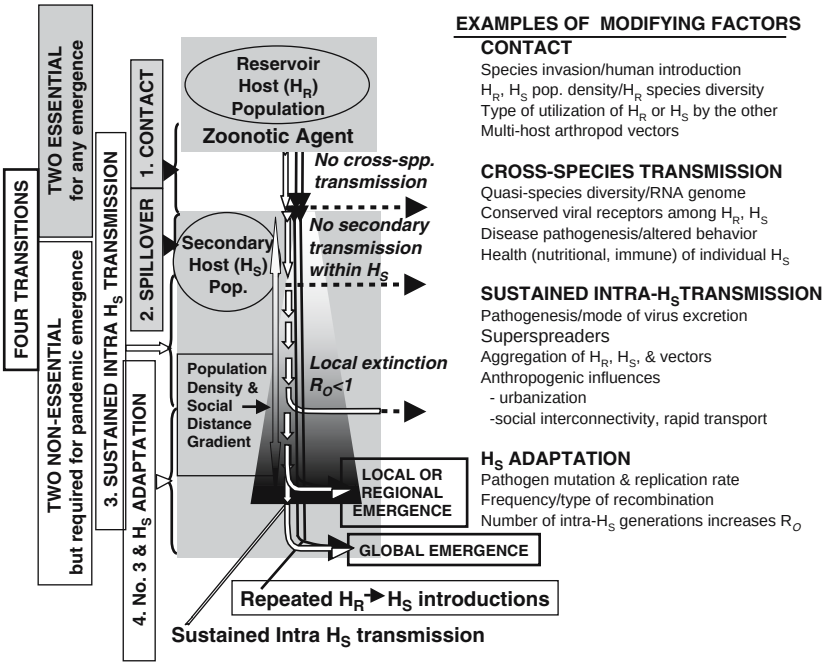

Fig. 1 *Continued* examples of modifying factors. Contact and spillover are sufficient to result in disease emergence at the local, regional, or even continental scale through reiterative introductions, as exemplified by zoonotic diseases such as rabies or West Nile fever. The two *solid black lines with arrowheads leading from the H_R then directly through the H_S to local or regional emergence* (the first emergence box) represent reiterative events as a pathway to emergence. Two other transitions not essential for emergence, but critical to pandemic disease emergence, require sustained intra-H_S transmission of the zoonotic pathogen (*Transition 3*) and, potentially, adaptation to the human host (e.g., SARs coronavirus). Sequential human-to-human transmission of a zoonotic pathogen at the local and regional scales is indicated by the series of *broken white lines in the H_S pyramid*. Evolutionary forces can transform a zoonotic agent into a genetically distinct agent adapted to a new reservoir host, establishing the former H_S as a new H_R (e.g., SIV to HIV; avian influenza to pandemic human influenza). This transition and the modifying factors associated with the geographical location and context of the initial disease outbreak (*white arrows in shaded H_S cone*) can ultimately precipitate a pandemic emergence (e.g., HIV and pandemic influenza). The process of emergence for any zoonotic pathogen can fail at a minimum of three points, indicated by the labeled dashed lines with arrowheads leading out of the H_S population box to the right. Zoonotic pathogens may fail to initiate cross-species infection following exposures (*top dashed line*), fail to generate any additional infections within the H_S (*second dashed line*), or experience epidemic fadeout when sustained human-to-human transmission fails and R_0 decreases below unity (*third dashed line*). The initial transition to sustained intra-H_S transmission is prone to failure when populations are sparse or social connectivity is limited. (Modified from Childs 2004)

factors alter the likelihood of a transition occurring and drive the geographic spread and determine the magnitude of morbidity and mortality resulting from a particular instance of emergence.

3.1
Abiotic Factors in Emergence

Abiotic factors alter the potential for contact between H_R and H_S populations, or infectious intermediaries, and modulate the potential for spillover; zoonotic diseases highly dependent on abiotic factors are often labeled environmentally driven epizootics (Allen and Cormier 1996). On a global scale, climate change has been increasingly linked to instances of zoonotic disease emergence, with El Nino Southern Oscillation (ENSO) providing the largest interannual signal of climate variation (Wang et al. 1999). One hypothesized mechanism by which ENSO triggers increased incidence of zoonotic disease among humans, is through a chain of sequentially induced events referred to as a trophic cascade (Polis et al. 2000), ultimately leading to increased numbers of individuals among H_R or H_V populations and increasing the risk of human exposure to a zoonotic pathogen (Nicholls 1986; Kelly-Hope et al. 2004; Bi and Parton 2003; Glass et al. 2002; Anyamba et al. 2001). ENSO events have been correlated with increased risk of HPS and plague in the southeastern United States (Glass et al. 2002; Parmenter et al. 1999), increased infection by Ross River virus in Australia (Lindsay and Mackenzie 1997; Kelly-Hope et al. 2004), and arthropod-vectored *Bartonella bacilliformis* and visceral leishmaniasis in South America (Chinga-Alayo et al. 2004; Franke et al. 2002).

Local weather conditions, potentially driven by global climate variation, have been repeatedly shown to influence the emergence of zoonotic and vector-borne viruses. Drought can serve to amplify enzootic transmission of St. Louis virus (Shaman et al. 2002) and possibly Japanese encephalitis (Hanna et al. 1999; Mackenzie et al. 2002) and Ebola viruses (Pinzon et al. 2004; see the chapter by Gonzalez et al., this volume), ultimately placing humans at higher risk for spillover. The converse, excessive rainfall, can increase breeding populations of H_Vs, driving enzootic transmission levels of western equine encephalomyelitis virus, Ross River virus, and Rift Valley fever virus to heightened levels, and ultimately increasing zoonotic virus spillover to humans (Lindsay et al. 1993; Wegbreit and Reisen 2000; Linthicum et al. 1999).

3.2
Evolutionary and Intrinsic Biotic Factors in Emergence

Intrinsic biotic and evolutionary factors enhance the ability of certain zoonotic viruses, notably those with RNA genomes (Cleaveland et al. 2001; Dobson and

Foufopoulos 2001; see the chapters by Cleaveland et al. and by Holmes and Drummond, this volume), to cross species barriers. Viruses with high replication rates, high mutation rates, and increased potential for recombination or reassortment may more readily adapt to new fitness landscapes and become transmitted among humans to emerge as pandemic threats (Burke 1998; Nichol et al. 2000); examples include HIV and subtypes of Influenza A (Hahn et al. 2000; Claas, 2000; see the chapter by Webby et al., this volume). The intrinsic genetic variability in susceptibility to infectious diseases within the human H_S (Segal and Hill 2003) is further modulated by an individual's cumulative life experience and history of infection by various pathogens, reflected by acquired immunological memory or, possibly, an individual's ancestry and evolutionary imprint of prior exposure to pathogens (Gillespie 1975; Lipsitch and Sousa 2002). Furthermore, immunologic function and the susceptibility of individual humans to infection and disease are dynamic and vary with factors such as nutritional status and age (Boelle et al. 2004).

Strong evolutionary forces may be in play in circumstances where zoonotically acquired viruses are intermittently maintained among small and sparsely distributed human populations where R_0 may hover close to unity. In theory, virus evolution is affected by socially structured host populations, such as where some human populations are aggregated in remote villages, with limited opportunity for social interchange. Models of virus transmission which assume homogeneous or freely mixing populations are of limited use in such circumstances. In such settings, modest increases in the number of generations of human-to-human transmission sustained by a new virus prior to fadeout (Fig. 1, second terminal dotted line) improves the likelihood of virus evolution to a higher average R_0, and hence emergence (Antia et al. 2003).

Additionally, sparsely distributed populations where contact rates, c, between infectious and susceptible individuals are low can support bistable evolutionary dynamics. One trend leads to the rapid evolution of increasingly virulent viruses. When viruses of relatively low virulence are transmitted among dispersed metapopulations of hosts, the result can be a cluster of infected individuals surrounding an index case, which is rapidly transformed into a semi-impermeable barrier of immune individuals (Boots et al. 2004), effectively terminating additional transmission. Virulent viruses causing lethal infections leave no immune survivors to block transmission and, in the course of removing infected individuals, further enhance the sparseness of the existing social structure. In situations where viruses of relatively low virulence circulate, the introduction of a highly virulent virus strain, either through an infected immigrant or from viral recombination, can alter the evolutionary trajectory of virus–host adaptation favoring selection for increasing virulence and an alternative, evolutionarily stable situation (White et al. 2002; Boots et al. 2004).

3.3
Extrinsic Biotic Interactions in Emergence

Extrinsic biotic interactions, such as natural or human-assisted translocations of infected or latently infected individuals of H_R or H_V species have played an exaggerated role in the rapid emergence of zoonotic diseases within the last few years. Monkeypox transported with African rodents destined for the US pet trade (Centers for Disease Control and Prevention 2003; see the chapter by Regnery, this volume), globe-trotting humans infected with SARS-CoV (Olsen et al. 2003; see the chapter by Wang and Eaton, this volume), domestic dogs incubating rabies accompanying human colonialists (see the chapter by Nel and Rupprecht, this volume), and the stowaway mosquito, bird, or human infected with WNV (Lanciotti et al. 2002) bear witness to the growing problems of a shrinking interconnected world (see the chapter by Daszak et al., this volume). Mosquito-borne viral diseases have resulted from the introduction of exotic viruses into indigenous local populations of mosquitoes previously not involved as vectors (Lanciotti et al. 2002), in addition to the establishment and spread of exotic mosquito species harboring viruses into new geographic locations (Lounibos 2002; Mackenzie et al. 2004).

However, not all biological invasions or disease introductions survive to cause epidemics, as was the case with SARS and monkeypox in North America. In contrast, WNV was an entirely different matter. The rapid establishment and spread of WNV in North America was nearly assured by the presences of indigenous species of competent wild bird H_Rs and mosquito H_Vs. Certain bird species sustained WNV viremias of sufficient titer and duration to infect blood-feeding "bridge vectors" (Turell et al. 2001; Komar et al. 2003), maintaining transmission to humans and spreading WNV as migrating birds followed traditional flyways (Peterson et al. 2003). The same extrinsic phenomena of a community of seemingly preadapted and widely available potential H_Vs and H_Rs in conjunction with the biogeography of avian migration aided the introduction and spread of WNV in Europe and the Middle East (Malkinson and Banet 2002). By an alternate route of introduction, wind-blown infected mosquitoes may have introduced Japanese encephalitis virus (JEV) into northern mainland Australia in 1998 (Ritchie and Rochester 2001).

3.4
Anthropogenic Influences as a Special Class of Extrinsic Factors in Emergence

As indicated above, many of the most important and widely cited factors modifying the scope and scale of zoonotic disease emergence are anthropogenic in origin; a few examples are described to highlight their importance and their distinctiveness from required transition stages.

3.4.1
Habitat Modification, Human Encroachment, and Modern Agricultural Practices

Human population growth and modern agricultural practices have enticed human settlers into clearing patches within ecosystems of maximally high biodiversity, such as tropical rain forests, converting substantial areas into cultivated fields and pastures (Patz et al. 2004; LoGiudice et al. 2003). Commercial farming operations inserted into clearings in forest habitats juxtapose and intermingle humans and livestock with native animal populations (Kock et al. 2002; Daszak et al. 2001; see the chapter by Field et al., this volume), and, coincidentally, with whatever zoonotic pathogens exist within these natural nidi (Pavlovsky1957). In many instances, the cleared land has been used for irrigated agriculture, resulting in an increase in vector-borne diseases such as JEV as mosquitoes and water bird H_Rs are brought in close proximity to domestic pigs in nearby villages (Morse 1995; Keiser et al. 2005). Dams are built to maintain water for human consumption and for use in irrigated agriculture, but they too may lead to increased zoonotic disease emergence as they provide the milieu for intermingling mosquito vectors and reservoir hosts of arboviruses as well as the spread of other diseases such as schistosomiasis.

Modern agricultural practices have also provided the mechanism by which bovine spongiform encephalopathy emerged in the United Kingdom in the early 1980s (Pattison 1998).

3.4.2
Domestic Animals Provide a Bounty of Novel Niches

Species now linked by domestication to *Homo sapiens* provide rich fodder for evolutionary forays by zoonotic viruses into potential new hosts. The emergence of zoonotic viruses among humans or domestic livestock where our species has drifted into preexisting sylvatic foci of zoonotic viruses is driven by local circumstance, history, and serendipity. The role of livestock, such as horses and pigs, can be pivotal in a transmission chain leading to human infection, as illustrated by the henipaviruses (see the chapters by Daniels et al. and Field et al., this volume). NiV and HeV first jumped the species barrier to infect pigs and horses, respectively, and only then were transmitted by these H_Is to humans (Barclay and Paton 2000; Chua et al. 1999). However, these two viruses also demonstrate the importance of transmissibility in the H_Is influencing the ultimate emergence of human disease; NiV was readily transmitted among pigs while HeV was rarely transmitted among horses or from horse to human (see the chapter by Daniels et al., this volume).

Rabies virus associated with domestic dogs incubating infection and transported with humans was the likely source of endemic cycles of rabies involving most terrestrial mammals in North and South America and in many areas of Africa (Childs et al. 2002; Smith et al. 1992; see the chapter by Nel and Rupprecht, this volume). In addition to causing an estimated 50,000 human deaths annually, rabies virus associated with domestic dogs have driven naïve indigenous populations of African wild dogs (*Lycaon pictus*) and Ethiopian wolves (*Canis simensis*) to the threshold of extinction and caused declines among other large carnivore populations (Roelke-Parker et al. 1996; Sillero-Zubiri et al. 1996; Gascoyne et al. 1993; Chapman 1978; see the chapter by Nel and Rupprecht, this volume).

Other domesticated species have become efficiently enlisted as H_Is or H_Rs, in a bridging process leading to human disease. Swine production management practices have improved the efficacy of this economically important livestock species as an amplifying H_I for JEV and NiV transmission to humans (Daniels et al. 2002; Singh and Jamaluddin 2002; Mohd Nor et al. 2000; see the chapter by Field et al., this volume). Swine may also serve as the mammalian mixing vessel for influenza A viruses of domestic and wild birds, offering the opportunity for avian viruses to obtain the complement of genes required for their sustained transmission within mammalian hosts, such as humans (Suarez et al. 2002; Gibbs et al. 2001; see the chapter by Webby et al., this volume).

3.4.3 Human Population Demographics and Urbanization

Significant changes in the demography of global human populations during the past five decades have been driven not only by population growth, but by changes in population distribution and social structuring brought about by migration, the ongoing movement of persons from rural to urban environments and the resettlement of refugees. The concentration of humans in the urban environment has given rise to mega-cities where a large proportion of persons may live in substandard conditions in marginal areas, sometimes referred to as shanty towns, surrounding the urban core. The crowded living conditions within shanty towns are further degraded by poor sanitation and lack of water; these conditions have been associated with the emergence of diseases, notably those involving vector-transmitted pathogens (Gratz 1999; Gubler 2002; Mackenzie et al. 2004).

Urban and periurban changes in land use have altered the availability and quality of habitat available to wildlife, and ecological changes in resource availability have in instances increased the potential for human–animal–vector interactions. Later chapters illustrate how ecological changes have influenced

the abundance and accessibility of wildlife species serving as reservoir hosts for different pathogens, leading to the emergence of zoonotic pathogens associated with pteropid bats (see the chapter by Field et al., this volume) and white-tailed deer (see the chapter by Paddock and Yabsley, this volume).

3.4.4 The Miracle of Modern Transport

Perhaps the most influential and certainly the most infamous anthropogenic modifiers driving the emergence process have been those enhancing social connectivity through road construction (Larkin 2000), railroads, and, the crown jewel of rapid modern transport, jet plane-assisted travel (Fig. 1; Childs 2004; see the chapter by Daszak et al., this volume). Nowhere has the role of rapid transportation been more evident than with SARS CoV (Table 1), where a presumed focus of human infection in the wet markets of Guangzhou, Guangdong Province, China, where live animals or their products are available for purchase, was transformed into a global health problem affecting 27 nations on every populated continent (Heymann 2004; see the chapter by Wang and Eaton, this volume). The human SARS CoV appears to have been inadvertently transported to a wet-market, along with an infected H_I or H_R, on a journey destined to end with human consumption (Bell et al. 2004). Wildlife farming and an immense network of illegal national and international trade in wildlife has been fueled by human demands for wildlife products of unusual culinary or putative medicinal properties (Bell et al. 2004). These cultural propensities enriched the range of opportunities for novel host/zoonotic virus interchange, but alone, as with rapid transport of persons, would not have resulted in a case of SARS without the biological capabilities of the virus to readily establish spillover.

3.4.5 The Miracle of Modern Medicine

Modern medical practices requiring the widespread use of needles, increased application of immunosuppressive therapies, organ transplant, and blood transfusions have contributed substantially to the spread and emergence of zoonotic pathogens (Institute of Medicine 2003; see the chapter by Paddock and Yabsley, this volume). In certain exceptional instances, medical technology has permitted zoonotic viruses, generally limited in their capacity for human-to-human transmission, to flirt briefly with the transmission route prerequisite to pandemic emergence (Fig. 1). Illustrative of this phenomena were instances of WNV and rabies virus transmission from infected donors to susceptible recipients receiving blood transfusion (WNV) and organ and tissue transplants

Table 1 Examples of transitions and modifying factors in zoonotic disease emergence; SARS CoV and HIVs

Transition	Initial context and circumstances	Examples of modifying factors
Contact between H_R or infectious propagules from H_R and H_S	Coronaviruses extant among sylvatic species of mammals and birds Coronaviruses extant among commensal and domestic animals, and humans raising potential for coinfection or superinfection SIVs circulate in at least 40 species of nonhuman primates in West Africa, most of which are used for human consumption. High potential for retrovirus transmission through contact with primate blood as indicated by infection of humans with primate foamy viruses	• Wildlife consumed as culinary delicacies or medicinal purposes; national and international trade in wildlife • Increased connectivity between humans in remote sites to cities via public and commercial roads (logging, mining, etc.); increased availability of ground transportation • Rapid transportation of game animals to national and international markets • Concentration of diverse wildlife species, domestic animals and humans in wet markets • Exposure to animal blood and tissues during butchering by humans and during predation by animals
Cross-species transmission	SARS CoV infected several orders of mammals in wet markets of China SIVs circulating in nonhuman primates are often mosaics of several SIV subtypes, indicating contact and recombination among nonhuman primate H_Rs	• RNA genomes, most notably retroviruses, capable of high-frequency mutation and recombination. High intrahost genetic diversity provides wide range of genotypic/phenotypic viral variants for selection by H_S during spillover • SARS CoV ability to infect multiple orders of mammals suggests evolution has of a viral "generalist" preadapted for species invasion • Close taxonomic relationship between H_R and H_S may facilitate viral adaptation once SIV has been introduced into individuals of H_S • Contact with blood and other tissues containing high titers of virus ensured by use of H_Rs as food by human H_S

Sustained intra-H_S transmission	Once SARS CoV or HIV established within a human H_S, access to urban setting with high density of susceptibles increases potential for average $R_0 > 1$ Respiratory transmission of SAR CoV Long period of infectiousness without overt clinical disease contribute to high R_0 with HIV	• SARS CoV pathology in H_S results in respiratory transmission by droplet or possibly aerosols • Superspreader phenomena • Increased number of intrahuman passages may have increased R_0 of SARS CoV • Medical technology (reused nonsterile needles, blood transfusion, etc.) provides new routes of transmission for HIV
Sustained intra-H_S transmission and adaptation to H_S and global emergence	High degree of within individual diversity of HIV viral subtypes driven by immune pressure Long period of infectiousness prior to clinical disease increase number of intrahuman passages of HIV Infectiousness of SARS CoV coincides with clinical disease and peaks several days after disease onset	• Rapid international transport of infected persons with SARS or HIV • Recombination may have produced novel SARS CoV adapted to humans • Poor surveillance and reporting in China slowed control measures • SARS controlled by traditional public health measures (quarantine, isolation of exposed persons, etc.) because infectiousness and disease coincident (pandemic averted) • Reparatory transmission aided SARS CoV spread • Sexual transmission and high R_0 assured HIV global spread

(WNV and rabies virus) (Iwamoto et al. 2003; Goldrick 2003; Centers for Disease Control and Prevention 2004; Gode and Bhide 1988). These rare instances involved transient, human-to-human transmission of viruses normally requiring a mosquito vector (WNV) or direct contact (rabies virus) for their transmission. Medical interventions limited further transmission, although biologic constraints inherent to the virus and host would have self-limited any sustained human-to-human transmission.

4
Invasion Biology as a Paradigm for Disease Emergence

The schema for emerging diseases (Fig. 1) emphasizes viral interactions within the newly colonized secondary host, of which humans may be but one of several susceptible species ($H_{S...n}$). The process outlined is similar to the schema developed to characterize biological invasions by nonindigenous species (Kolar and Lodge 2001). The transition states proposed for emerging diseases and those for invasive species are largely parallel: (1) contact with infectious propagules aligns with the nonindigenous species in a transport pathway to a foreign shore; (2) cross-species transmission aligns with the nonindigenous species surviving transport and being introduced into a foreign environment; (3) sustained intra-H_S transmission of a zoonotic virus aligns with the establishment (self-perpetuation) of the invasive species within the new environment; and (4) sustained intra-H_S transmission accompanied by evolutionary adaptation of the once zoonotic virus to a new H_R, prior to emergence, aligns with adaptive radiation and spread of the invasive species beyond the local site of introduction (Grant et al. 2001).

4.1
Termination Points and Pitfalls on the Route to Emergence or Invasion

The potential terminating points in the process of virus emergence or biological invasion (broken arrows leading outside of the H_S population block in Fig. 1) are consequences of similar circumstances. Failure to cross the species barrier (spillover) aligns with "fails in transport"; failure to sustain transmission, with a transmission potential, $R_0<1$, aligns with "fails to establish"; and interruption of sustained intra-H_S transmission, an average $R_0<1$, aligns with "noninvasion" by the nonindigenous species. Differences between disease emergence and biological invasion exist, as transitions leading to disease emergence are not strictly hierarchical. Reiteration of contact and spillover (Fig. 1, transitions 1 and 2) at

sufficiently high levels can suffice for a disease to emerge, but if an invading species never moves and perishes at the site of its introduction, even if repeatedly introduced to the site, further establishment and spread, prerequisites of invasion, is precluded.

In addition to biological factors which establish the setting in which zoonotic pathogens may emerge (see the chapters by Cleaveland et al. and Daszak et al., this volume), the emergence of a zoonotic agent within human or animal populations must be detected by humans. Too often the presence of a zoonotic agent is first identified by the presence of disease in humans, and surveillance for disease emergence is largely restricted to identifying incident cases of disease in humans rather than monitoring infection or disease among wildlife H_Rs or H_Is (see the chapters by Childs, by Merianos, and by Stallknecht, this volume). The challenges present to designing programs aiming to disrupt transmission of a zoonotic pathogen within a wildlife reservoir host population prior to spillover and disease emergence are discussed in the chapters by Childs and by Stallknecht in this volume.

4.2 Human Invaded or Human Invader?

Altering the environmental unit being invaded produces a radically different schema. The invasion process in Fig. 1 has an organismal or medical orientation, which can be transformed to a population or community orientation by regarding humans, rather than a zoonotic pathogen, as the invasive species. Human invasion of new habitats and new environments is a frequently cited factor in the emergence process of viral zoonoses (Morse 1995; Institute of Medicine 2003). Where native H_Rs and H_Vs and their co-evolved viral pathogens exist in natural foci (Pavlovsky 1957), enhanced opportunities for novel ecologic interactions await. Initial instances of emergence have proven unpredictable as exemplified by HPS resulting from transmission of hantaviruses maintained by sigmodontine rodent H_Rs in North America (Monroe et al. 1999), HIV resulting from transmission of SIVs circulating among nonhuman primate H_Rs in West Africa (Apetrei et al. 2004), and NiV and HeV viruses from pteropid bat H_Rs in Asia and Australia (Field et al. 2001). Herein, we stress the organismal– medical orientation, humans colonized or invaded by zoonotic viruses. Human intrusion into novel environments is regarded as an anthropogenic factor which modifies the likelihood of contact and spillover transitions occurring. However, without the preexisting sylvatic zoonotic cycle, human invasion alone would not engender the first case of illness along the path to emergence.

5
Qualities of Zoonotic Viruses Emerging by Different Transition Routes

Insights as to why and how certain zoonotic viruses appear predisposed to spillover and the various paths they take in the emergence process, are to be gleaned by examining the evolutionary history and current context of where and how zoonotic viruses exist and just how they become identified as etiologic agents of human disease (see the chapter by Childs, this volume). Predisposing biological characteristics include evidence of multiple H_Rs (Dobson and Foufopoulos 2001; Cleaveland et al. 2001; see the chapters by Cleaveland and by Holmes and Drummond, this volume), high replication rates, high mutation rates, and the potential for homologous or heterologous recombination, which reach maxima in zoonotic viruses with RNA genomes (Holland et al. 1982; Arias et al. 2001).

5.1
Emergence Via Reiterative Processes of Contact and Spillover

Two zoonotic viruses with histories of reemergence are rabies virus and WNV, both of which depend solely, with the exception of rare instances mentioned above, on repetitive contact and spillover between infected H_Rs or infected H_Vs (WNV) for their transmission to the human H_S. Although the RNA genomes of these two zoonotic viruses are markedly different in terms of organization, polarity, and replication strategy, both viruses show evidence of reduced positive selection (Woelk and Holmes 2002), even where established within novel H_Rs or H_Vs (Holmes et al. 2002). The term "evolutionary generalists" has been applied to both viruses as they share, to some extent, the requirement of being able to infect and multiply within cells belonging to different species and, in the case of vector-borne WNV, the need to infect and multiply within avian, mammalian, and insect H_Rs, H_Vs, and H_Ss. The rare instances of human-to-human transmission of these viruses are epidemiologically insignificant (Dietzschold and Koprowski 2004; Iwamoto et al. 2003).

5.2
Spillover Subsequently Sustained by Human-to-Human Transmission

Although humans are, with few exceptions, incidental hosts for zoonotic viruses emerging from sylvatic transmission cycles, a few zoonotic arboviruses can be maintained by human-to-human transmission mediated by anthropophilic vectors in urban settings where large populations of humans and competent

H_Vs coexist, particularly in environments with poor sanitation and overcrowding. Yellow fever virus (Wolfe et al. 2001; de Silva et al. 1999) and dengue virus serotypes (Kuiken et al. 2003; Ksiazek et al. 2003) are arboviruses where major epidemics are associated with urban transmission cycles rather than sporadic spillover from sylvatic H_Rs and H_Vs, and dengue serotypes have become endemic among some suitably large human populations in Asia (Gubler 2002).

Rabies virus crosses mammalian orders and species and can establish sustained transmission within new H_Rs (Badrane and Tordo 2001), as has been observed on several occasions where bat-associated variants of rabies virus have achieved temporary sustained transmission among terrestrial carnivores, such as red foxes (*Vulpes vulpes*) and striped skunks (*Mephitis mephitis*) (Daoust et al. 1996; Engeman et al. 2003). The maintenance of rabies virus, considered a single species of *Lyssavirus*, serotype 1/genotype 1, is achieved as a myriad of distinct viral variants maintained within different specific mammalian H_Rs, rather than a homogeneous virus infecting multiple H_Rs; control or elimination of rabies in a specific H_R may be achieved but the diversity of host–virus dyads is a formidable buffer against any overall elimination scheme.

Epidemics of rabies virus are sustained when there are sufficient individuals of the primary H_R(s) to sustain intra-H_R transmission, with coincidental spillover to H_Ss by reiterative introductions by inoculation of infectious virus in saliva. As rabies is fatal among most mammalian species, population declines among the principal H_R generally coincide with declines in incidental rabies epizootics among H_Ss (Gordon et al. 2004; Wandeler et al. 1974). Epizootics can reemerge at periodic intervals as H_R populations recover above the critical threshold density (K_T) required to sustain virus transmission at $R_0 > 1$ (Anderson et al. 1981; Childs et al. 2000; Coyne et al. 1989).

In an analogous manner, epidemics caused by WNV involve reiterative introductions of infectious virus by any of a number of competent mosquito H_V (s). WNV readily infects at least three classes of vertebrates (Avia, Mammalia, Reptilia) and mosquito species, and some species of ticks (Gould et al. 2003; Komar et al. 2003; Lvov et al. 2004; Sardelis et al. 2002; Turell et al. 2001). Although WNV appears to be reasonably homogeneous in regions of North America over time, geographic clustering of genetically similar strains is detectable and certain epizootiologically dominant genetic clades have emerged, some with shorter extrinsic incubation periods within North American vectors (Davis et al. 2003; Ebel et al. 2004). Subtleties associated with host–vector–virus relationships are being uncovered, such as the greater frequency of *Flavivirus* recombination among mosquito H_Vs compared to tick H_Vs (Twiddy and Holmes 2003).

The temperature and humidity requirements for survival and breeding of mosquito vectors, and the demand for temperature-sensitive extrinsic viral incubation within H_Vs, drive the strong seasonal transmission dynamics of

WNV and other arboviral diseases. With the onset of cold temperatures in temperate zones, WNV transmission ceases and epidemics of human disease desist (Woodring et al. 1996).

5.3
The Road to Human Adaptation: A Still-Life with SARS CoV?

That SARS-CoV is new to science is not in question. However, the origin of SARS-CoV as a human pathogen arising from direct cross-species transmission of a preexisting, but previously unknown virus (Gibbs et al. 2004; Holmes and Rambaut 2004; see the chapters by Holmes and Drummond and by Wang and Eaton, this volume) or as a virus formed from the recombination of existing mammalian and avian coronaviruses (Rest and Mindell 2003; Zhang et al. 2004) has been the subject of debate. SARS- CoV is sufficiently distinct in genetic sequence from previously known coronaviruses (Rota et al. 2003) that a long history of preexistence with its natural H_R population is surmised (Parashar and Anderson 2004). Recently, coronaviruses related to SARS-Cov have been amplified by PCR from three communal cave-dwelling species of the genus *Rhinolophus* in the family Rhinolophidae. Genome sequence analysis indicated that SARS-like coronaviruses among these bats have an almost identical genome organization to those of SARS-CoVs isolated from humans or civets (Li et al. 2005; see the chapter by Wang and Eaton, this volume). These data suggest that bats serve as the H_R of SARS-CoV and that palm civets served as a H_{S1} in a chain of events leading to infection of humans as secondarily infected H_{S2}. SARS-CoV's global emergence may be an extraordinary example of a relatively unmodified zoonotic virus, successfully sustained by intrahuman transmission. However, increasing data suggest SARS-CoV was a virus rapidly adapting to its new human host and the rapid and effective public health response terminating its transmission halted an evolutionary dramas in the making (see the chapter by Wang and Eaton, this volume).

Genetic sequence data indicate that strong positive selection accompanied SARS-CoV's emergence and that distinctive human-associated changes in the genome distinguish virulent SARS-CoV from isolates of virus from palm civets (Song et al. 2005). Additional data indicate genetic changes were accompanying longer chains of human-to-human transmission. Heterogeneous viral sequences recovered from a single patient's samples (Liu et al. 2005) indicate the degree of viral variation available for selection within the individual human. These findings are compelling evidence of evolutionary events underway, presaging the emergence of a virus with a unique genetic signature associated with its human host.

Whatever the exact origin of SARS-CoV, the genetic endowments of this virus facilitated cross-species infection. An evolutionary history that includes

viral preadaptation permitting infection to occur among a broad range of H_Rs and H_Ss is suggested by SARS CoV's ability to infect a range of mammalian orders (Ng 2003; Song et al. 2005; Bell et al. 2004). Such preadaptation can be assumed to have endowed SARS-CoV with a suite of traits readily adaptable for establishing sustained intrahuman transmission (Riley et al. 2003; Isakbaeva et al. 2004). Pathogenesis within the novel human host's respiratory tissues offered an efficient means for sustained transmission by expressed droplets, or possibly aerosol (Yu et al. 2004).

The biological properties of SARS-CoV, the human behaviors and societal practices which increased the likelihood of contact and spillover and the rapid transport of already infected individuals drove the trajectory of the emergence of this global health problem. The distinctions and critical interactions between required biological transitions and modifying factors are clearly illuminated by this emergence process (Fig. 1, Table 1). Fortunately, SARS-CoV was effectively controlled by tried and true public health measures serving to increase social distance and diminish infectious contacts, c , perhaps curtailing a rapid evolutionary path toward a R_0 sufficiently high to bypass these methods (Song et al. 2005; Antia et al. 2003; Fraser et al. 2004).

5.4 Adaptation of Zoonotic Viruses to the Human H_R and Pandemic Emergence

The zoonotic viruses leading to potentially uncontrolled, pandemic health problems have adopted unique qualities associated with their sustained transmission within the human host. Adaptation to the human host may be mediated by viral preadaptation to a genetically similar intermediate host, as is hypothesized to occur among swine for avian-adapted influenza A subtypes (see the chapter by Webby et al., this volume). Permissive cells for subtype A influenza virus replication in the pig's respiratory track have cell-surface glycoprotein receptors recognized by some avian-adapted viruses, in addition to some human-adapted influenza viruses (Basler et al. 2001). In the case of HIV, the H_R for SIVs giving rise to HIV-1 was our closest living genetic relative, the chimpanzee (*Pan troglodytes troglodytes*) (Gao et al. 1999), and the H_R for HIV-2 was a sooty mangabey (*Cerocebus atys*) (Hirsch et al. 1989), a respectfully close relative of the order Primates. Spillover was enhanced by the enormous population of candidate viruses within the genetically heterogeneous "quasi-species" of viruses present in the infected H_R at spillover. Sustained intrahuman transmission was accompanied by viral adaptations to the human host, readily detectable and quantifiable by sequence changes in the RNA genome and marked by qualitative phenotypic changes identifiable by host species preference and pathogenic interactions (Hirsch et al. 1989; Gao et al. 1999).

Evaluations of the genetic relatedness of HIV-1 and HIV-2 to SIVs circulating among nonhuman primates has led to wide acceptance that these distinctive human lentiviruses, now globally distributed in humans, originated from cross-species transmission in the not so distant past, perhaps within the first half of the twentieth century (May et al. 2001). The human lentiviruses, HIV-1 and HIV-2, have evolved and escaped from remote African settings on at least eight independent occasions to emerge as distinctive genetic subtypes responsible for regional or pandemic human disease (Apetrei et al. 2004; B. Hahn, personal communication). These recognized cases of emergence are certainly not the first instances where SIVs have successfully crossed species and evolved as distinctive HIVs of humans. Early emergences were likely restricted to local occurrences in remote locations where human contact rates, c , and population size were insufficient to support a $R_0 > 1$, even if infections were of a long duration, d; such occurrences would be highly prone to transmission fadeout (Fig. 1). Road construction, automotive transport, and, perhaps, reuse of nonsterile needles (Gisselquist 2003) were presumably key anthropogenic factors increasing the level of social connectivity by providing HIV-infected individuals access to larger aggregates of susceptible hosts in cities (Apetrei et al. 2004).

The number of SIVs described among nonhuman primates in Africa as of 2004 was approximately 40 (Zhuang et al. 2002). The biological capacity of lentiviruses includes rapid replication, high mutability, and the highest recorded rates of recombination known in virology. Knowledge of the frequency of potential opportunities for SIV spillover, based on transmission of a zoo of diverse simian foamy viruses during encounters between monkeys, apes, and human hunters in West Africa (Wolfe et al. 2004) indicate transmission of blood-borne retroviruses is not rare. These facts highlight two important features of emergence; first, emergence is a process, not an event; second, the probability of new genetic lineages of human HIVs arising approximates unity. The same lessons apply to numerous other conditions which make up the body oft hisv olume.

References

Allen LJ, and Cormier PJ (1996) Environmentally driven epizootics. Math Biosci 131:51–80

Anderson MG, Frenkel LD, Homann S, Guffey J (2003) A case of severe monkeypox virus disease in an American child: emerging infections and changing professional values. Pediatr Infect Dis J 22:1093–1096

Anderson RM, Jackson HC, May RM, Smith AM (1981) Population dynamics of fox rabies in Europe. Nature 289:765–771

Antia R, Regoes RR, Koella JC, Bergstrom CT (2003) The role of evolution in the emergence of infectious diseases. Nature 426:658–661

Anyamba A, Linthicum KJ, Tucker CJ (2001) Climate-disease connections: Rift Valley Fever in Kenya. Cad Saude Pub 17 Suppl:133–140

Apetrei C, Robertson DL, Marx PA (2004) The history of SIVS, AIDS: epidemiology, phylogeny and biology of isolates from naturally SIV infected non-human primates (NHP) in Africa. Front Biosci 9:225–254

Arias A, Lazaro E, Escarmis C, Domingo E (2001) Molecular intermediates of fitness gain of an RNA virus: characterization of a mutant spectrum by biological and molecular cloning. J Gen Virol 82:1049–1060

Badrane H, Tordo N (2001) Host switching in Lyssavirus history from the Chiroptera to the Carnivora orders. J Virol 75:8096–8104

Barclay AJ, Paton DJ (2000) Hendra (equine morbillivirus). Vet J 160:169–176

Basler CF, Reid AH, Dybing JK, Janczewski TA, Fanning TG, Zheng H, Salvatore M, Perdue ML, Swayne DE, Garcia-Sastre A, Palese P, Taubenberger JK (2001) Sequence of the 1918 pandemic influenza virus nonstructural gene (NS) segment and characterization of recombinant viruses bearing the 1918 NS genes. Proc Natl Acad Sci U S A 98:2746–2751

Bell D, Roberton S, Hunter PR (2004) Animal origins of SARS coronavirus: possible links with the international trade in small carnivoRes Philos Trans R Soc Lond B Biol Sci 359:1107–1114

Bi P, Parton KA (2003) El Nino and incidence of hemorrhagic fever with renal syndrome in China. JAMA 289:176–177

Boelle PY, Cesbron JY, Valleron AJ (2004) Epidemiological evidence of higher susceptibility to vCJD in the young. BMC Infect Dis 4:26

Boots M, Hudson PJ, Sasaki A (2004) Large shifts in pathogen virulence relate to host population structure. Science 303:842–844

Bryant JE, Barrett AD (2003) Comparative phylogenies of yellow fever isolates from Peru and Brazil. FEMS Immunol Med Microbiol 39:103–118

Burke DS (1998) Evolvability of emerging viruses. In: Nelson AM, Horsburgh CR Jr (eds) Pathology of emerging infections 2. American Society for Microbiology, Washington, DC, pp 1–12

Centers for Disease Control and Prevention (2003) Multistate outbreak of monkeypox–Illinois, Indiana, and Wisconsin 2003. MMWR Morb Mortal Wkly Rep 52:537–540

Centers for Disease Control and Prevention (2004) Investigation of rabies infections in organ donor and transplant recipients--Alabama, Arkansas, Oklahoma, and Texas 2004. MMWR Morb Mortal Wkly Rep 53:586–589

Chapman RC (1978) Rabies: decimation of a wolf pack in artic Alaska. Science 201:365–367

Childs JE (2004) Zoonotic viruses of wildlife: hither from yon. Arch Virol Suppl1–11

Childs JE, Glass GE, Korch GW, LeDuc JW (1989) Effects of hantaviral infection on survival, growth and fertility in wild rat (*Rattus norvegicus*) populations of Baltimore Maryland. J Wildl Dis 25:469–476

Childs JE, Curns AT, Dey ME, Real LA, Feinstein L, Bjornstad ON, Krebs JW (2000) Predicting the local dynamics of epizootic rabies among raccoons in the United States. Proc Natl Acad Sci U S A 97:13666–13671

Childs JE, Krebs JW, Smith JS (2002) Public health surveillance and the molecular epidemiology of rabies. In: Leitner T (ed) The molecular epidemiology of human viruses. Kluwer Academic, Dordrecht, pp 273–312

Chinga-Alayo E, Huarcaya E, Nasarre C, del Aquilla R, Llanos-Cuentas A (2004) The influence of climate on the epidemiology of bartonellosis in Ancash Peru. Trans R Soc Trop Med Hyg 98:116–124

Chua KB, Goh KJ, Wong KT, Kamarulzaman A, Tan PS, Ksiazek TG, Zaki SR, Paul G, Lam SK, Tan CT (1999) Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. Lancet 354:1257–1259

Claas EC (2000) Pandemic influenza is a zoonosis, as it requires introduction of avian-like gene segments in the human population. Vet Microbiol 74:133–139

Cleaveland S, Laurenson MK, Taylor LH (2001) Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. Philos Trans R Soc Lond B Biol Sci 356:991–999

Coyne MJ, Smith G, McAllister FE (1989) Mathematic model for the population biology of rabies in raccoons in the mid-Atlantic states. Am J Vet Res 50:2148–2154

Daniels TJ, Williams DT, Mackenzie JS (2002) Japanese encephalitis virus. In: Morrilla A, Yoon KJ, Zimmerman JJ (eds) Trends in emerging viral infections of swine. Iowa State Press, Ames IA, pp 249–263

Daoust PY, Wandeler AI, Casey GA (1996) Cluster of rabies cases of probable bat origin among red foxes in Prince Edward Island Canada. J Wildl Dis 32:403–406

Daszak P, Cunningham AA, Hyatt AD (2001) Anthropogenic environmental change and the emergence of infectious diseases in wildlife. Acta Trop 78:103–116

Davis CT, Beasley DW, Guzman H, Raj R, D'Anton M, Novak RJ, Unnasch TR, Tesh RB, Barrett AD (2003) Genetic variation among temporally and geographically distinct West Nile virus isolates United States, 2001, 2002. Emerg Infect Dis 9:1423–1429

De Silva AM, Dittus WP, Amerasinghe PH, Amerasinghe FP (1999) Serologic evidence for an epizootic dengue virus infecting toque macaques (*Macaca sinica*) at Polonnaruwa Sri Lanka. Am J Trop Med Hyg 60:300–306

Dietzschold B, Koprowski H (2004) Rabies transmission from organ transplants in the USA. Lancet 364:648–649

Dobson A, Foufopoulos J (2001) Emerging infectious pathogens of wildlife. Philos Trans R Soc Lond B Biol Sci 356:1001–1012

Downs WG (1982) History of epidemiological aspects of yellow fever. Yale J Biol Med 55:179–185

Drosten C, Gunther S, Preiser W, van der WS, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguiere AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Muller S, Rickerts V, Sturmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H, Doerr HW (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 348:1967–1976

Ebel GD, Carricaburu J, Young D, Bernard KA, Kramer LD (2004) Genetic and phenotypic variation of West Nile virus in New York, 2000–2003. Am J Trop Med Hyg 71:493–500

Engeman RM, Christensen KL, Pipas MJ, Bergman DL (2003) Population monitoring in support of a rabies vaccination program for skunks in Arizona. J Wildl Dis 39:746–750
Field H, Young P, Yob JM, Mills J, Hall L, Mackenzie J (2001) The natural history of Hendra and Nipah viruses. Microbes Infect 3:307–314
Franke CR, Ziller M, Staubach C, Latif M (2002) Impact of the El Nino/Southern Oscillation on visceral leishmaniasis Brazil. Emerg Infect Dis 8:914–917
Fraser C, Riley S, Anderson RM, Ferguson NM (2004) Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A 101:6146–6151
Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH (1999) Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. Nature 397:436–441
Gascoyne SC, Laurenson MK, Lelo S, Borner M (1993) Rabies in African wild dogs (*Lycaon pictus*) in the Serengeti region Tanzania. J Wildl Dis 29:396–402
Gibbs AJ, Gibbs MJ, Armstrong JS (2004) The phylogeny of SARS coronavirus. Arch Virol 149:621–624
Gibbs MJ, Armstrong JS, Gibbs AJ (2001) The haemagglutinin gene, but not the neuraminidase gene, of 'Spanish flu' was a recombinant. Philos Trans R Soc Lond B Biol Sci 356:1845–1855
Gillespie JH (1975) Natural selection for resistance to epidemics. Ecology 56:493–495
Gisselquist D (2003) Emergence of the HIV type 1 epidemic in the twentieth century: comparing hypotheses to evidence. AIDS Res Hum Retroviruses 19:1071–1078
Glass GE, Yates TL, Fine JB, Shields TM, Kendall JB, Hope AG, Parmenter CA, Peters CJ, Ksiazek TG, Li CS, Patz JA, Mills JN (2002) Satellite imagery characterizes local animal reservoir populations of Sin Nombre virus in the southwestern United States. Proc Natl Acad Sci U S A 99:16817–16822
Gode GR, Bhide NK (1988) Two rabies deaths after corneal grafts from one donor. Lancet 2:791
Goldrick BA (2003) West Nile virus update: a new route of transmission is found. Am J Nurs 103:27
Gordon ER, Curns AT, Krebs JW, Rupprecht CE, Real LA, Childs JE (2004) Temporal dynamics of rabies in a wildlife host and the risk of cross-species transmission. Epidemiol Infect 132:515–524
Gould EA, de Lamballerie X, Zanotto PM, Holmes EC (2003) Origins, evolution, and vector/host coadaptations within the genus *Flavivirus*. Adv. Virus Res 59:277–314
Grant PR, Grant BR, Petren K (2001) A population founded by a single pair of individuals: establishment, expansion, and evolution. Genetica 112–113:359–382
Gratz NG (1999) Emerging and resurging vector-borne diseases. Ann Rev Entomol 4451–4475
Gubler DJ (2002) The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res 33:330–342
Hahn BH, Shaw GM, De Cock KM, Sharp PM (2000) AIDS as a zoonosis: scientific and public health implications. Science 287:607–614
Halloran ME (1998) Concepts of infectious disease epidemiology. In: Rothman KJ, Greenland S (eds) Modern epidemiology. Lippencott Williams Wilkins, Philadelphia, pp 529–554

Hanna JN, Ritchie SA, Phillips DA, Lee JM, Hills SL, van den Hurk AF, Pyke AT, Johansen CA, and Mackenzie JS (1999) Japanese encephalitis in North Queensland, 1998. Med J Aust 170:533–536

Heymann DL (2004) The international response to the outbreak of SARS in (2003) Philos Trans R Soc Lond B 359:1127–1129

Hinson ER, Shone SM, Zink MC, Glass GE, Klein SL (2004) Wounding: the primary mode of Seoul virus transmission among male Norway rats. Am J Trop Med Hyg 70:310–317

Hirsch VM, Olmsted RA, Murphey-Corb M, Purcell RH, Johnson PR (1989) An African primate lentivirus (SIVsm) closely related to HIV-2. Nature 339:389–392

Holland J, Spindler K, Horodyski F, Grabau E, Nichol S, VandePol S (1982) Rapid evolution of RNA genomes. Science 215:1577–1585

Holmes EC, Rambaut A (2004) Viral evolution and the emergence of SARS coronavirus. Philos Trans R Soc Lond B Biol Sci 359:1059–1065

Holmes EC, Woelk CH, Kassis R, Bourhy H (2002) Genetic constraints and the adaptive evolution of rabies virus in nature. Virology 292:247–257

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

Institute of Medicine (2003) Microbial threats to health; emergence, detection, and response. National Academies Press, Washington, DC

Isakbaeva ET, Khetsuriani N, Beard RS, Peck A, Erdman D, Monroe SS, Tong S, Ksiazek TG, Lowther S, Pandya-Smith I, Anderson LJ, Lingappa J, Widdowson MA (2004) SARS-associated coronavirus transmission United States. Emerg Infect Dis 10:225–231

Iwamoto M, Jernigan DB, Guasch A, Trepka MJ, Blackmore CG, Hellinger WC, Pham SM, Zaki S, Lanciotti RS, Lance-Parker SE, DiazGranados CA, Winquist AG, Perlino CA, Wiersma S, Hillyer KL, Goodman JL, Marfin AA, Chamberland ME, Petersen LR (2003) Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med 348:2196–2203

Keiser J, Maltese MF, Erlanger TE, Bos R, Tanner M, Singer BH, and Utzinger J (2005) Effect of irrigated rice agriculture on Japanese encephalitis, including challenges and opportunities for integrated vector management. Acta Trop 95:40–57

Kelly-Hope LA, Purdie DM, Kay BH (2004) El Nino Southern Oscillation and Ross River virus outbreaks in Australia. Vect Borne Zoonot Dis 4:210–213

Kock R, Kebkiba B, Heinonen R, Bedane B (2002) Wildlife and pastoral society--shifting paradigms in disease control. Ann N Y Acad Sci 969:24–33

Kolar CS, Lodge DM (2001) Progress in invasion biology: predicting invaders. Trends Ecol Evol 16:199–204

Komar N, Langevin S, Hinten S, Nemeth N, Edwards E, Hettler D, Davis B, Bowen R, Bunning M (2003) Experimental infection of North American birds with the New York 1999 strain of West Nile virus. Emerg Infect Dis 9:311–322

Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, Tong S, Urbani C, Comer JA, Lim W, Rollin PE, Dowell SF, Ling AE, Humphrey CD, Shieh WJ, Guarner J, Paddock CD, Rota P, Fields B, DeRisi J, Yang JY, Cox N, Hughes JM, LeDuc JW,

Bellini WJ, Anderson LJ (2003) A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 348:1953–1966

Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, Laman JD, de Jong T, van Doornum G, Lim W, Ling AE, Chan PK, Tam JS, Zambon MC, Gopal R, Drosten C, van der WS, Escriou N, Manuguerra JC, Stohr K, Peiris JS, Osterhaus AD (2003) Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 362:263–270

Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, Crise B, Volpe KE, Crabtree MB, Scherret JH, Hall RA, Mackenzie JS, Cropp CB, Panigrahy B, Ostlund E, Schmitt B, Malkinson M, Banet C, Weissman J, Komar N, Savage HM, Stone W, McNamara T, Gubler DJ (1999) Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. Science 286:2333–2337

Lanciotti RS, Ebel GD, Deubel V, Kerst AJ, Murri S, Meyer R, Bowen M, McKinney N, Morrill WE, Crabtree MB, Kramer LD, Roehrig JT (2002) Complete genome sequences and phylogenetic analysis of West Nile virus strains isolated from the United States, Europe, and the Middle East. Virology 298:96–105

Larkin M (2000) Hunting and logging linked to emerging infectious diseases. Lancet 356:1173

Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, Wong SS, Leung SY, Chan KH, and Yuen KY (2005) Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A 102:14040–14045

Linthicum KJ, Anyamba A, Tucker CJ, Kelley PW, Myers MF, Peters CJ (1999) Climate and satellite indicators to forecast Rift Valley fever epidemics in Kenya. Science 285:397–400

Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, Wang H, Crameri G, Hu Z, Zhang H, Zhang J, McEachern J, Field H, Daszak P, Eaton BT, Zhang S, Wang LF (2005) Bats are natural reservoirs of SARS-like coronaviruses. Science 310:676–679

Lindsay M, Mackenzie J (1997) Vector-borne viral diseases and climate change in the Australian region: major concerns and the public health response. In: Climate Change and Human Health in the Asia Pacific Region (eds) Curson P, Guest C and Jackson E. Australian Medical Association and Greenpeace International, Canberra, pp 47–62

Lindsay MD, Broom AK, Wright AE, Johansen CA, Mackenzie JS (1993) Ross River virus isolations from mosquitoes in arid regions of Western Australia: implication of vertical transmission as a means of persistence of the virus. Am J Trop Med Hyg 49:686–696

Lipsitch M, Sousa AO (2002) Historical intensity of natural selection for resistance to tuberculosis. Genetics 161:1599–1607

Liu J, Lim SL, Ruan Y, Ling AE, Ng LPF, Drosten C, Liu ET, Stanton LW, Hibberd ML (2005) SARS transmission pattern in Singapore reassessed by viral sequence variation analysis. PLoSMed 2:162–168

Llyubsky S, Gavrilovskaya I, Luft B, Mackow E (1996) Histopathology of *Peromyscus leucopus* naturally infected with pathogenic NY-1 hantaviruses: pathologic markers of HPS infection in mice. Lab Invest 74:627–633

LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F (2003) The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. Proc Natl Acad Sci U S A 100:567–571

Lounibos LP (2002)Invasions by insect vectors of human disease. Annu Rev Entomol 47:233–266

Lvov DK, Butenko AM, Gromashevsky VL, Kovtunov AI, Prilipov AG, Kinney R, Aristova VA, Dzharkenov AF, Samokhvalov EI, Savage HM, Shchelkanov MY, Galkina IV, Deryabin PG, Gubler DJ, Kulikova LN, Alkhovsky SK, Moskvina TM, Zlobina LV, Sadykova GK, Shatalov AG, Lvov DN, Usachev VE, Voronina AG (2004) West Nile virus and other zoonotic viruses in Russia: examples of ermerging-reemerging situations. Arch Virol [Suppl] 18:85–96

Mackenzie JS, Johansen CA, Ritchie SA, van den Hurk AF, Hall RA (2002) Japanese encephalitis as an emerging virus: the emergence and spread of Japanese encephalitis virus in Australasia. Curr Topics Microbiol Immunol 267:49–73

Mackenzie JS, Gubler DJ, and Petersen LR (2004) Emerging flaviviruses: the spread and resurgence of dengue Japanese encephalitis and West Nile viruses. Nature Med 10: S98–S109

Malkinson M, Banet C (2002) The role of birds in the ecology of West Nile virus in Europe and Africa. Curr Top Microbiol Immunol 267:309–322

May RM, Gupta S, Mclean AR (2001) Infectious disease dynamics: What characterizes a successful invader? Philos Trans R Soc Lond B Biol Sci 356:901–910

Mims CA (1991) The origin of major human infections and the crucial role of person-to-person spread. Epidemiol Infect 106:423–433

Mims CA (1995) Virology research and virulent human pandemics. Epidemiol Infect 115:377–386

Mohd Nor MN, Gan CH, Ong BL (2000) Nipah virus infection of pigs in peninsular Malaysia. Rev Sci Tech 19:160–165

MonathTP (1989) Yellow fever. In: Monath TP (ed) The arboviruses: epidemiology and ecolog. CRC Press, Boca Raton FL, pp 139–231

Monroe MC, Morzunov SP, Johnson AM, Bowen MD, Artsob H, Yates T, Peters CJ, Rollin PE, Ksiazek TG, Nichol ST (1999) Genetic diversity and distribution of *Peromyscus* -borne hantaviruses in North America. Emerg Infect Dis 5:75–86

Morse SS (1995) Factors in the emergence of infectious diseases. Emerg Infect Dis 1:7–15

Nayak DP (2000) Virus morphology, replication, and assembly. In: Hurst CJ (ed) Viral ecology. Academic, New York, pp 63–124

Ng SK (2003) Possible role of an animal vector in the SARS outbreak at Amoy Gardens. Lancet 362:570–572

Nichol ST, Arikawa J, Kawaoka Y (2000) Emerging viral diseases. Proc Natl Acad Sci U S A 97:12411–12412

Nicholls N (1986) A method for predicting Murray Valley encephalitis in southeast Australia using the southern oscillation. Aust J Exp Biol Med Sci 64:578–594

Olsen SJ, Chang HL, Cheung TY, Tang AF, Fisk TL, Ooi SP, Kuo HW, Jiang DD, Chen KT, Lando J, Hsu KH, Chen TJ, Dowell SF (2003) Transmission of the severe acute respiratory syndrome on aircraft. N Engl J Med 349:2416–2422

Parashar UD, Anderson LJ (2004) Severe acute respiratory syndrome: review and lessons of the 2003 outbreak. Int J Epidemiol 33:628–634

Parmenter RR, Yadav EP, Parmenter CA, Ettestad P, Gage KL (1999) Incidence of plague associated with increased winter-spring precipitation in New Mexico. Am J Trop Med Hyg 61:814–821

Pattison J (1998) The emergence of bovine spongiform encephalopathy and related diseases. Emerg Infect Dis 4:390–394

Patz JA, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J, Wolfe ND, Kilpatrick AM, Foufopoulos J, Molyneux D, Bradley DJ (2004) Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. Environ Health Perspect 112:1092–1098

Pavlovsky YN (1957) Human Diseases with Natural Foci (Translated from Russian by D Rottenberg). Foreign Languages Publishing House, Moscow

Peiris JS, Yu WC, Leung CW, Cheung CY, Ng WF, Nicholls JM, Ng TK, Chan KH, Lai ST, Lim WL, Yuen KY, Guan Y (2004) Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 363:617–619

Peterson AT, Vieglais DA, Andreasen JK (2003) Migratory birds modeled as critical transport agents for West Nile virus in North America. Vect Borne Zoonot Dis 3:27–37

Pinzon JE, Wilson JM, Tucker CJ, Arthur R, Jahrling PB, Formenty P (2004) Trigger events: enviroclimatic coupling of Ebola hemorrhagic fever outbreaks. Am J Trop Med Hyg 71:664–674

Polis GA, Sears AL, Huxel GR, Strong DR, Maron J (2000) When is a trophic cascade a trophic cascade? Trends Ecol Evol 15:473–475

Rest JS, Mindell DP (2003) SARS associated coronavirus has a recombinant polymerase and coronaviruses have a history of host-shifting. Infect Genet Evol 3:219–225

Riley S, Fraser C, Donnelly CA, Ghani AC, Abu-Raddad LJ, Hedley AJ, Leung GM, Ho LM, Lam TH, Thach TQ, Chau P, Chan KP, Lo SV, Leung PY, Tsang T, Ho W, Lee KH, Lau EM, Ferguson NM, Anderson RM (2003) Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science 300:1961–1966

Ritchie SA, Rochester W (2001) Wind-blown mosquitoes and introduction of Japanese encephalitis into Australia. Emerg Infect Dis 7:900–903

Roelke-Parker ME, Munson L, Packer C, Kock R, Cleaveland S, Carpenter M, O'Brien SJ, Pospischil A, Hofmann-Lehmann R, Lutz H (1996) A canine distemper virus epidemic in Serengeti lions (*Panthera leo*). Nature 379:441–445

Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, Icenogle JP, Penaranda S, Bankamp B, Maher K, Chen MH, Tong S, Tamin A, Lowe L, Frace M, DeRisi JL, Chen Q, Wang D, Erdman DD, Peret TC, Burns C, Ksiazek TG, Rollin PE, Sanchez A, Liffick S, Holloway B, Limor J, McCaustland K, Olsen-Rasmussen M, Fouchier R, Gunther S, Osterhaus AD, Drosten C, Pallansch MA, Anderson LJ, Bellini WJ (2003) Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 300:1394–1399

Sardelis MR, Turell MJ, O'Guinn ML, Andre RG, Roberts DR (2002) Vector competence of three North American strains of *Aedes albopictus* for West Nile virus. J Am Mosq Control Assoc 18:284–289

Segal S, Hill AV (2003) Genetic susceptibility to infectious disease. Trends Microbiol 11:445–448

Shaman J, Day JF, Stieglitz M (2002) Drought-induced amplification of Saint Louis encephalitis virus Florida. Emerg Infect Dis 8:575–580

Sillero-Zubiri C, King AA, Macdonald DW (1996) Rabies and mortality in Ethiopian wolves (*Canis simensis*). J Wildl Dis 32:80–86

Singh J, Jamaluddin A (2002) Nipah virus infection in swine. In: Morilla A, Yoon KJ, Zimmerman JJ (eds) Trends in emerging viral infections of swine. Iowa State Press, Ames IA, pp 105–116

Smith JS, Orciari LA, Yager PA, Seidel HD, Warner CK (1992) Epidemiologic and historical relationships among 87 rabies virus isolates as determined by limited sequence analysis. J Infect Dis 166:296–307

Song HD, Tu CC, Zhang GW, Wang SY, Zheng K, Lei LC, Chen QX, Gao YW, Zhou HQ, Xiang H, Zheng HJ, Chern SW, Cheng F, Pan CM, Xuan H, Chen SJ, Luo HM, Zhou DH, Liu YF, He JF, Qin PZ, Li LH, Ren YQ, Liang WJ, Yu YD, Anderson L, Wang M, Xu RH, Wu XW, Zheng HY, Chen JD, Liang G, Gao Y, Liao M, Fang L, Jiang LY, Li H, Chen F, Di B, He LJ, Lin JY, Tong S, Kong X, Du L, Hao P, Tang H, Bernini A, Yu XJ, Spiga O, Guo ZM, Pan HY, He WZ, Manuguerra JC, Fontanet A, Danchin A, Niccolai N, Li YX, Wu CI, Zhao GP (2005) Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A 102:2430–2435

Suarez DL, Woolcock PR, Bermudez AJ, Senne DA (2002) Isolation from turkey breeder hens of a reassortant H1N2 influenza virus with swine, human, and avian lineage genes. Avian Dis 46:111–121

Tsai TF (1987) Hemorrhagic fever with renal syndrome: clinical aspects. Lab Ani Sci 37:419–427

Turell MJ, O'Guinn ML, Dohm DJ, Jones JW (2001) Vector competence of North American mosquitoes (Diptera: Culicidae) for West Nile virus. J Med Entomol 38:130–134

Twiddy SS, Holmes EC (2003) The extent of homologous recombination in members of the genus Flavivirus. J Gen Virol 84:429–440

Wandeler A, Wachendorfer G, Forster U, Krekel H, Schale W, Muller J, Steck F (1974) Rabies in wild carnivores in central Europe. I. Epidemiological studies. Zentralbl Veterinar Med B 21:735–756

Wang HJ, Zhang RH, Cole J, Chavez F (1999) El Nino and the related phenomenon Southern Oscillation (ENSO): The largest signal in interannual climate variation. Proc Natl Acad Sci U S A 96:11071–11072

Wegbreit J, Reisen WK (2000) Relationships among weather, mosquito abundance, and encephalitis virus activity in California: Kern County 1990–1998. J Am Mosq Control Assoc 16:22–27

White PJ, Norman RA, Hudson PJ (2002) Epidemiological consequences of a pathogen having both virulent and avirulent modes of transmission: the case of rabbit haemorrhagic disease virus. Epidemiol Infect 129:665–677

Woelk CH, Holmes EC (2002) Reduced positive selection in vector-borne RNA viruses. Mol Biol Evol 19:2333–2336

Wolfe ND, Kilbourn AM, Karesh WB, Rahman HA, Bosi EJ, Cropp BC, Andau M, Spielman A, Gubler DJ (2001) Sylvatic transmission of arboviruses among Bornean orangutans. Am J Trop Med Hyg 64:310–316

Wolfe ND, Switzer WM, Carr JK, Bhullar VB, Shanmugam V, Tamoufe U, Prosser AT, Torimiro JN, Wright A, Mpoudi-Ngole E, McCutchan FE, Birx DL, Folks TM, Burke DS, Heneine W (2004) Naturally acquired simian retrovirus infections in central African hunters. Lancet 363:932–937

Woodring,JL, Higgs,S, Beaty,BJ (1996) Natural cycles of vector-borne pathogens. In: Beaty BJ, Marquardt WC (eds) 'The biology of disease vectors. University Press of Colorado, Niwot CO, pp 51–72

Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, Leung DY, Ho T (2004) Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 350:1731–1739

Zaki SR, Greer PW, Coffield LM, Goldsmith CS, Nolte KB, Foucar K, Feddersen RM, Zumwalt RE, Miller GL, Khan AS, Rollin PE, Ksiazek,TG, Nichol ST, Mahy BWJ, Peters CJ (1995) Hantavirus pulmonary syndrome. Pathogenesis of an emerging infectious disease. Am J Pathol 146:552–579

Zhang XW, Yap YL, Danchin A (2004) Testing the hypothesis of a recombinant origin of the SARS-associated coronavirus. Arch Virol 150:1–20

Zhuang J, Jetzt AE, Sun G, Yu H, Klarmann G, Ron Y, Preston BD, Dougherty JP (2002) Human immunodeficiency virus type 1 recombination: rate, fidelity, and putative hot spots. J Virol 76:11273–11282