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Public Health Threat of New, Reemerging, and Neglected Zoonoses in the Industrialized World

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Learning Objectives

Upon completion of this activity, participants will be able to:

- List animal hosts for different zoonoses
- Identify the type of zoonosis most likely to undergo genetic mutation
- Specify factors that increase the risk for zoonoses now and in the future
- Describe the epidemiology and clinical presentation of rickettsial diseases

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Microbiologic infections acquired from animals, known as zoonoses, pose a risk to public health. An estimated 60% of emerging human pathogens are zoonotic. Of these pathogens, >71% have wildlife origins. These pathogens can switch hosts by acquiring new genetic combinations that have altered pathogenic potential or by changes in behavior or socioeconomic, environmental, or ecologic

characteristics of the hosts. We discuss causal factors that influence the dynamics associated with emergence or re-emergence of zoonoses, particularly in the industrialized world, and highlight selected examples to provide a comprehensive view of their range and diversity.

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The World Health Organization/Food and Agriculture Organization/World Organisation for Animal Health joint consultation on emerging zoonotic diseases, held in Geneva in 2004, defined an emerging zoonosis as “a pathogen that is newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range” (www.who.int/zoonoses/emerging_zoonoses/en). Through continued alterations in human and animal demographics and

environmental changes, new and recurring diseases are likely to continue to emerge.

The effects of zoonoses on human health and economics have recently been underscored by notable outbreaks such as those involving Nipah virus and severe acute respiratory syndrome (SARS) coronavirus (CoV). A recent retrospective study of 335 emerging infectious episodes over a 64-year period (1940–2004) emphasized the role of wildlife as a source of emerging infections. However, research efforts have typically been focused toward either humans or economically related species (1).

The frequency of these events increased substantially over the period of investigation (2). Such infections are now often perceived as agents of biologic warfare rather than infections with a long but insidious history in their appropriate ecologic niche. Why then are these infections becoming a serious public health concern? The answer is a complex multifactorial set of changing circumstances. To support the growing human population, we have an increasing demand for nutritional support, resulting in intensive agricultural practices, sometimes involving enormous numbers of animals, or multiple species farmed within the same region. These practices can facilitate infection to cross species barriers.

Additionally, we are witnessing increasing globalization, with persons (3), animals, and their products (4) moving around the world. This movement enables unprecedented spread of infections at speeds that challenge the most stringent control mechanisms. Furthermore, continual encroachment of humans into natural habitats by population expansion or tourism brings humans into new ecologic environments and provides opportunity for novel zoonotic exposure. Climatic changes have facilitated the expansion of compatible conditions for some disease vectors, remodeling dynamics for potentially new, emerging, and reemerging zoonoses (5). In the next 2 decades, climate change will be the most serious issue that dominates reemergence of pathogens into new regions.

Climate change also effects evolution of pathogens, and where relevant, their vectors. Continual mutation and recombination events give rise to variants with altered levels of fitness to persist and spread. Changing ecologic circumstances and pathogen diversity can give rise to variants with altered pathogenic potential. However, the host must not be ignored. Increased longevity and therapies for persons with diseases can modulate host susceptibility and concomitant infections and upset the evolving and dynamic infection balance.

Emerging, Reemerging, and Neglected Zoonoses

Data for this review were identified in PubMed searches and relevant journal articles and excluded those studies not published in English. Emerging or reemerging pathogens

must be considered on multiple levels. First, pathogens not previously known have been identified. For example, alteration in the processing of cattle feed in the United Kingdom resulted in the extended host range and emergence of bovine spongiform encephalopathy in cattle (6). Similarly, mixing of multiple species under stressful conditions can promote a species jump such as that witnessed with SARS-CoV (7). New opportunities can be created by climatic changes such as global warming and ecologic alterations facilitated through changed land use and movements of infected hosts, susceptible animals, or disease vectors.

In 1987, 1997–1998, and 2006–2007, outbreaks of infection with Rift Valley fever virus in Africa were associated with changes in river flow and flooding resulting from damming of rivers or heavy rainfall. Many zoonotic pathogens fall into the category of generalist agents exhibiting extensive host diversity, e.g., *Coxiella burnetii*, the etiologic agent of Q fever. This bacterium can successfully infect hosts ranging from domestic animals to wildlife, reptiles, fish, birds, and ticks.

Others agents have restricted specific transmission dynamics because of limited host ranges. These agents include simian immunodeficiency viruses 1 and 2, which are found in chimpanzees and sooty mangabees, and Rift Valley virus, which is transmitted by *Aedes* spp. and *Culex* spp. mosquitoes and found in sheep and goats. For many zoonotic agents, the potential to cause infection in accidental hosts, such as humans, exists, but often this represents a dead-end host. Pathogens such as *Anaplasma* spp., *Ehrlichia* spp., *Rickettsia* spp., *Bartonella* spp., West Nile virus, and rabies virus can be included in this group.

From an epidemiologic point of view, “A reservoir should be defined as one or more epidemiologically connected populations or environments in which a pathogen can be permanently maintained and from which infection is transmitted to the defined target species” (8). Conversely, some zoonoses in specific conditions show remarkable ability for human-to-human transmission beyond the confines of natural sylvatic cycles. This ability was seen during a recent outbreak of plague among diamond miners in the Congo. This outbreak was initiated by an infection of a miner, which became pneumonic and resulted in 136 secondary cases of pneumonic plague and 57 deaths (9). Transmission of plague is complex and dynamic, with combinations of stochastic and adaptive mechanisms. As seen in this example, rapid transmission often occurs, but this is accompanied by slower, localized transmission among enzootic reservoir species, which often use vector-borne expansion among low-density hosts (10). Other zoonoses, given correct circumstances, can result in human-to-human transmission. These zoonoses include those that cause Ebola fever, influenza A, plague, tularemia, and SARS (11).

New or emerging virulence traits can evolve and result in large-scale transmission and concomitant alteration of pathogenicity. This new pathogenicity may include increased invasiveness, enhanced spread, toxin production, or antimicrobial drug resistance. *Y. pestis* has shown a resurgence in regions such as Madagascar, with isolates showing a marked increase in resistance to antimicrobial agents (12). Similarly, a recently evolved outer surface protein A serotype of a Lyme borreliosis spirochete (*Borrelia garinii* serotype 4), has shown particularly aggressive tendencies and is often associated with hyperinvasive infection (13). Concern has also been noted about increasingly frequent isolation of *Corynebacterium ulcerans* carrying the diphtheria toxigenic phage.

Mutation is the ultimate source of genetic variation, on which natural selection, genetic drift, gene flow, and recombination act to shape the genetic structure of populations. This factor is especially notable in viruses, which have relatively small genomes and short generation times, particularly among viruses with more error-prone RNA genomic replication (14). However, most mutations are deleterious and under pressure of innate and adaptive host immunity, viruses probably always experience selection for mutation rates >0 . The upper limit on mutation rates will be determined by factors such as natural selection, genomic architecture, and the ability to avoid loss of viability or genetic information, albeit, that a loss of genetic information and increased specialization is observed in co-evolution with a host (15).

According to evolutionary theory, higher mutation rates should be favored in a changing environment, such as altered host immune defenses. However, in experimental settings, artificially increased mutation rates are often associated with lower virus titers. In addition, a complex relationship exists between underlying mutational dynamics and the ability to generate antigenic variation, which in turn has serious implications for the epidemiologic potential of the virus.

Evolutionary changes are not always a prerequisite for viral emergence in a new host. Some viruses (e.g., poxviruses), have a wide host range and show a relatively low mutation rate. However, in other viruses such as Venezuelan equine encephalitis virus, evolutionary change is essential for efficient infection and transmission to new hosts (16). Because most viruses replicate poorly when transferred to new hosts, greater variation is more likely to assist viral adaptation to its new host.

All too frequently, the diagnosis of zoonotic disease is delayed through lack of clinical suspicion or failure to obtain adequate clinical histories. Some zoonotic infections are unusual (e.g., scabies infection after handling of pet guinea pigs). Other infections may have a less obvious animal link. Mowing lawns is believed to be a risk factor

for acquiring tularemia (caused by *Francisella tularensis*) in disease-endemic areas where lagomorph reservoirs may be killed by mowers or hedge trimmers (17).

For some infections, zoonotic transmission occurs indirectly through food. Human brucellosis is not usually acquired through animal contact but is transmitted more often by consumption of infected animal products such as unpasteurized dairy products (18). *Salmonella* spp. have repeatedly caused outbreaks of salmonellosis after persons have eaten uncooked eggs (19). Hepatitis E virus has been transmitted through consumption of uncooked deer meat (20).

Exposure routes may be airborne, as demonstrated for several outbreaks of Q fever (21). An ongoing airborne Q fever outbreak in the Netherlands related to goat farming has raised awareness of this previously neglected zoonosis (22). How humans were exposed to these animals would not have been apparent; the exposures were identified by epidemiologic mapping of the distribution of cases. These examples underscore the necessity of gathering comprehensive patient data to effectively diagnose zoonoses.

Recreational Zoonoses

Sporting activities can expose humans to zoonotic infections. Hunting wildlife has been associated with infections such as brucellosis and tularemia (23). Less obvious routes arise from activities such as water sports. *Leptospira* spp.-infected animals excrete viable organisms in their urine, which can persist in aquatic environments for prolonged periods. After a triathlon event in 1998, a total of 52 of 474 athletes tested were diagnosed with leptospirosis (24). Suspicion of water sport-related infections with hepatitis A and *Leptospira* spp. led to closure of an area of Bristol, United Kingdom, where docks were used for recreational water activities (25).

Horses are now moved from countries in Europe to warmer regions (e.g., United Arab Emirates) to prolong the racing season during the winter. Hunting activities have promoted large-scale export of animals such as hares (possible reservoirs of tularemia and brucellosis) from Poland and the movement of potentially rabies-infected raccoons in the United States. In other countries such as the United Kingdom, pheasants are bred and released for shooting in the fall and provide plentiful hosts for questing ticks and increasing their abundance. Importation of pheasants into the United Kingdom from France was associated with introduction of a mild zoonotic infection (Newcastle virus disease) in 2007 (26).

Role of Companion Animals

Companion animals have many forms of contact and opportunities to transmit multiple zoonoses. The sexual stage of the life cycle of *Toxoplasma* spp. occurs in cats,

thus exposing humans to infection in situations in which hygienic measures have not been observed. Cats also serve as reservoir for *Bartonella henselae*, the etiologic agent of cat-scratch fever (27). Cowpox virus can also be transmitted to humans by contact with cats (28). Animal bites can result in zoonotic infections, typified by infection with *Pasteurella multocida*. Even in the absence of a bite, contact with animals (e.g., licking of wounds) can result in infection. More recently, attention has focused on transmission of *Rickettsia felis* into the human environment by cat fleas (29).

Dogs are the most likely source when humans become infected with rabies virus and are potential sources of *Toxocara* spp. This emerging threat is becoming apparent with importation of rescued dogs and global movement of dogs with their owners, which has resulted in several cases of leishmaniasis in the absence of sand fly vectors. Dogs can be a source of methicillin-resistant *Staphylococcus aureus* and could play a role in zoonotic spread of genetic elements responsible for antimicrobial drug resistance (30). Contact with dogs in Mediterranean regions has been implicated as a likely source of infection in recent cases of Mediterranean spotted fever reported in traveling humans (31).

Cats and dogs can introduce plague or rabies into human environments and have been associated with Q fever in humans and dermatophytosis (ringworm). Scavenger habits of these animals bring them into contact with many zoonotic agents, and close living relationships with humans such as sharing meal plates or beds offer many opportunities for disease transmission.

Pet rats have recently been incriminated as the source of *Leptospira icterohemorrhagiae* infection in their owners. Psittacine birds are an established risk factor for acquisition of *Chlamydophila psittaci*. During recent years, the market for exotic pets has greatly increased. This increase has resulted in transmission of several unusual organisms, such as exotic *Salmonella* spp., which are often associated with pet reptiles. Media attention was captured after an outbreak of monkeypox in America that affected ≥ 70 persons in 2003. After infected African rodents had been imported for the pet trade, the infection spread into native North American black-tailed prairie dogs and was subsequently disseminated among humans (32).

Bush Meat

Zoonotic diseases associated with hunting and eating wildlife is of increasing global concern. Bush meat is considered a delicacy by many and has resulted in its growth as a commercial enterprise. Tracking, capturing, handling, butchering in the field, and transporting of carcasses involve risks of cross-species transmission. Particularly high risks are associated with hunting nonhuman primates. The act of butchering is a greater risk factor for acquiring bloodborne

pathogens than transporting, selling, and eating the butchered meat (33).

Zoonotic pathogens from wildlife may infect humans with little or no human-to-human transmission (e.g., avian influenza virus and Hendra virus). Alternatively, increased travel or migration and increased between-person contacts have facilitated emergence of simian immunodeficiency virus/HIV/AIDS in Africa. Increased exposure to wild-caught animals and high mutation rates of many RNA viruses have increased their predominance among emerging zoonoses transmitted from human to human; RNA viruses from bush meat may therefore play a possible role in future disease emergence.

Globalization and Livestock Movement

Large-scale movement of persons, livestock, food, or goods is now commonplace and provides increasing opportunities for rapid spread of pathogens. Trichinellae in horsemeat have been transported across the Pacific Ocean and infected consumers in other parts of the world. Discarded tires provide new habitats for mosquitoes in addition to their usual ecologic niches. The World Organisation for Animal Health and the Food and Agriculture Organisation implement strict control of animal movement. Transport of animals can result in mingling of different species in crowded and stressful conditions. This mingling can suppress immune responses to persistent infections and increase pathogen shedding. Under such circumstances, susceptible species can readily become infected (34).

Tourism

Tourism has exponentially increased in recent years. This finding has resulted in increasing numbers of imported zoonoses, such as a variety of rickettsial spotted fevers, brucellosis, melioidosis, genotype I hepatitis E (35), tick-borne encephalitis (36), and schistosomiasis (37). A rapid increase in cases of African tick bite fever has been associated with travelers to sub-Saharan Africa and the eastern Caribbean. This disease, which is caused by *R. africae*, is transmitted by a particularly aggressive *Amblyomma* sp. tick; >350 imported cases have been observed in recent years (31). Infection sequelae, such as subacute neuropathy, may be found long after travel when tick bite fever eschars have disappeared (37). An estimated ≥ 1 million international journeys are made each day, and a staggering 700 million tourists travel on an annual basis. Detailed travel histories of patients who show clinical signs and symptoms of disease are needed.

Changed Land Use and Urbanization

Deforestation and development of natural habitats have been seen on a global scale to accommodate intensification of agriculture and living areas for humans. As a result, eco-

logic habitats have been disrupted, reservoir abundance has changed, and transmission dynamics have been altered. Reduced host abundance may force vectors to seek alternative hosts, increasing opportunities for disease transmission, as demonstrated by increases in human cases of Lyme borreliosis, ehrlichiosis, spotted fevers, and anaplasmosis. Development of forests to provide rubber plantations in Malaysia has been correlated with increases in schistosomiasis (37). Wildlife may modify feeding practices as a consequence of changing land use, bringing them closer to humans and livestock. This modification was suggested to have been instrumental in the Nipah virus outbreak that affected pigs and humans in Malaysia in 1999. Nipah virus persists as a serious problem in many rural areas of Bangladesh and India, where infected bats living near human dwellings, urinate in date palm sap, which is later consumed raw by humans (38).

Human population growth has been associated with reshaping of population demographics. Increasing from 1 billion at the beginning of the 20th century to 6 billion by the end of the century, current predictions forecast a human population of ≈ 10 billion by 2050. This prediction is accompanied by a staggering increase in urbanization of the population from 39% in urban environments in 1980 to 46% in 1997 and a predicted 60% by 2030. This high-density clustering of the human population paves the way for potential outbreaks on an immense scale (5).

Public Health Risks of Reemerging and Neglected Zoonoses

Many areas are now experiencing a reemergence of zoonotic pathogens, partly resulting from collapse of public health programs during political upheavals. Often, these areas increasingly appeal to those seeking adventurous or unusual holiday destinations.

Delay in development of clinical signs and often insidious onset can challenge appropriate diagnosis and patient management. Furthermore, movements of animals used for agricultural trade, sport, and as companions also offer opportunities for further dissemination of infections. Brucellosis-free countries have seen reintroductions associated with movement of infected livestock. Movement of pets throughout Europe has been associated with an alarming increase in diseases such as leishmaniasis. Moreover, pets can harbor ectoparasites such as ticks, fleas, and lice. All of these parasites, especially ticks, are notorious vectors of multiple zoonotic agents.

We are at risk for airborne transmission of zoonoses by many factors (e.g., from travel to farms, consumption of food, and mowing the lawn, which has been associated with tularemia). Visiting petting farms or having family pets increases the likelihood of potential zoonotic infections, especially if pets are exotic. Water sports may increase the

risk for acquiring leptospirosis. Wilderness camping activities have been associated with hantavirus infection after inhalation of aerosolized urine excretions of rodents. Other sporting activities such as hunting have been associated with brucellosis and tularemia. Travel to other countries opens a range of new potential zoonotic exposures through direct contact or indirectly through fomites, food, or arthropod vectors. Increasingly exotic locations are being sought with associated exotic zoonoses. Some tourists consume local delicacies, such as aborted animal fetuses in Ecuador, which are a source of brucellosis (39).

Conclusions and Future Prospects

Many zoonoses can be considered opportunistic infections. Increasing demands for protein necessitate increased levels of farming. Food can provide a vehicle for spread of pathogens from animals to humans. Contact with animals during farming, hunting, or by animal bites can increase transmission of diseases (e.g., rabies and tularemia). Arthropod vectors can transmit diseases on an immense scale to other hosts as in cases of West Nile fever and plague.

Changing patterns of farming, life style, and transportation influence the dynamics of pathogen ecology. Pathogens are subjected to changes by many intrinsic and extrinsic factors. Mutation, recombination, selection, and deliberate manipulation can result in new traits acquired by pathogens and result in potential epidemic consequences.

Reemergence of diseases through opportunistic host switching is likely to continue as a major source of human infectious disease. Strategies to improve public health have focused on improved surveillance in regions of perceived high likelihood of disease (reemergence). These strategies include improved detection of pathogens in reservoirs, early outbreak detection, broad-based research to identify factors that favor reemergence, and effective control (i.e., quarantine and improved hygiene) (40).

To recognize and combat zoonotic diseases, the epidemiology of these infections must be understood. We need to identify pathogens, their vertebrate hosts, and their methods of transmission. Identification should include knowledge of spatiotemporal disease patterns and their changes over time. These features can be used to identify dynamic processes involved in pathogen transmission (Figure), which can be used to account for observed disease patterns and ultimately forecast spread and establishment into new areas.

Armed with information on expected disease patterns, we can address whether change has occurred beyond that which would normally be expected. However, this analysis may not be suitably responsive to control new and emerging zoonoses. Improved detection may be achieved through use of syndromic approaches rather than searching for specific pathogens.

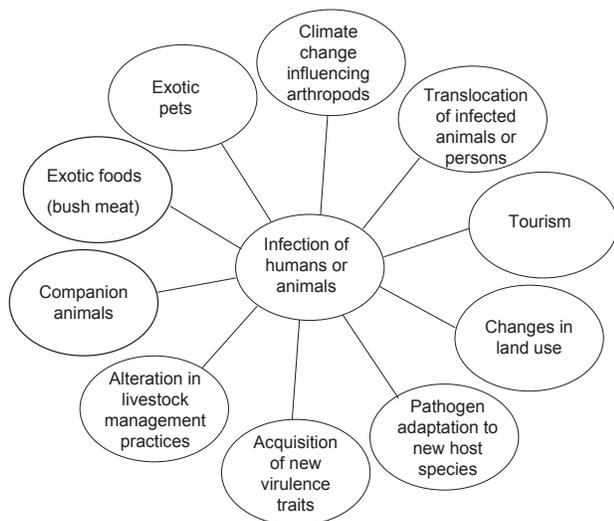


Figure. Factors influencing new and reemerging zoonoses.

Human disease surveillance must be associated with enhanced longitudinal veterinary surveillance in food-producing animals and wildlife. Prompt detection and instigation of control measures such as vaccination are pivotal to prevent disease spread. Novel molecular methods (e.g., DNA microarrays) offer unprecedented opportunities for rapid detection. However, these methods require optimization and validation before they can be used in routine microbiology laboratories. Cloned antigens or attenuated vaccines can be rapidly modified into appropriate antigenic forms. However, for identification of specific pathogens, more research will be needed to provide timely management of a new or emerging disease threat.

Approaches for identification of pathogen replication in vectors are more likely to offer substantial benefits for control of zoonoses. These methods are inappropriate for human vaccines, which must adhere to stricter legislative criteria. However, control of zoonotic infections in reservoir hosts has a pronounced protective effect in human populations. Use and development of antiviral drugs are other useful possibilities, but these drugs are likely to be too expensive for use in large disease outbreaks and emergence of drug resistance may result in concomitant loss of therapeutic options for these agents.

We do not know which zoonosis will be the next serious public health threat. However, as we increase efforts to improve the capacity to respond to this pathogen, we will also increase the likelihood that we can efficiently and effectively respond to new, reemerging, or neglected zoonoses in the future.

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