**Emergence of new viruses**

Emerging viruses can be defined as *the causative agents of infectious diseases whose incidence is increasing following its appearance in a new host population or whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology.*

Incidences of emerging and/or re-emerging infections have significantly affected human health since ancient times. The “Spanish flu” responsible for tens of millions of casualties in the early twentieth century, was the most devastating natural calamity in human history. The flu pandemic returned in 1957 as “Asian flu” and then in 1968 as “Hong Kong flu” that killed about three million people.

Re-emergence of influenza was in 2009 as “swine flu” that claimed 18,500 lives.

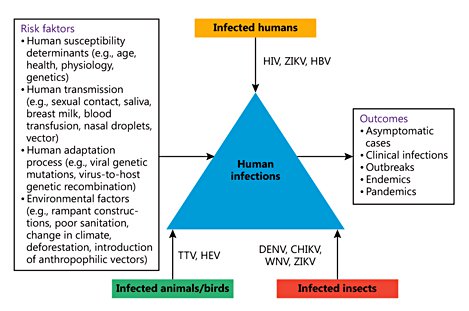
On its pandemic course in 2002/2003, a novel severe acute respiratory syndrome coronavirus (SARS-CoV) infected >8,000 people, causing 774 deaths in 27 countries.

Actually, it was the discovery of the human immunodeficiency virus (HIV) in the early 1980s that initiated a worldwide awareness of and research interest in emerging novel viral pathogens. Over the past several decades, new outbreaks of infections have led to the discovery of a diverse array of highly pathogenic viruses mainly those belonging to the Filoviridae, Arenaviridae, Bunyaviridae, Paramyxoviridae, Coronaviridae, Flaviviridae, Togaviridae and Hepeviridae families. Some examples include BK virus (BKV), JC virus (JCV), Merkel cell polyomavirus (MCV or MCPyV), severe fever with thrombocytopenia syndrome virus (SFTSV), hantavirus (HTNV), and Sin Nombre virus (SNV). Lassa virus (LASV), first reported in Nigeria in 1969, re-emerged in Guinea, Liberia, and Mali in 2009, in Ghana in 2011, and in Benin in 2014.

Human metapneumovirus (hMPV) was first identified in the Netherlands in 2001, and was subsequently linked to an acute lower respiratory tract infection in children, similar to respiratory syncytial virus (RSV). In 2013, a novel avian influenza A strain (H7N9) of “bird flu” in China and the Middle-East respiratory syndrome (MERS)-CoV have been identified. Of note, while 2015 was threatened by the re-emergence of the Ebola virus, 2015/2016 has been challenged with the resurgence of the Zika virus (ZIKV). Despite substantial advancements in the understanding of the biology of pathogens, the breakthroughs in prevention, and their effects on public health and the global economy, the emergence of novel pandemic viruses remains an enduring puzzle. An example of important emerging/re-emerging viral infections worldwide, their possible origin, evolution, natural reservoirs, human adaptations, and risk factors is shown in Figure below.

**Fig. 1**

A cartoon depiction of important emerging/re-emerging viral infections and their possible origins, evolutionary drivers, natural reservoirs, and risk factors. HBV, hepatitis B virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; CHIKV, chikungunya virus; DENV, dengue virus; TTV, Torque Teno virus; WNV, West Nile virus; ZIKV, Zika virus.



**Origin**

Of the known viruses that infect humans, about 80% perpetuate naturally in non-human “reservoirs,” largely farm mammals and poultry and, to a lesser extent, in wild animals and arthropods. It is estimated that zoonotic infectious agents constitute about 60% of the known human pathogens and up to 75% of “emerging” human pathogens. There is, however, limited knowledge of such zoonosis and the diversity of these viruses in their known reservoirs. The data on some of the domestic mammals harboring dozens of virus species is limited and insufficient knowledge about the wild animals that are estimated to host thousands of virus species. Examples include emerging human viruses like novel influenza strains, human (h)CoV, Hendra virus, Nipah virus, and several others, all linked to zoonosis. The deadly outbreak of MERS-CoV was linked to its zoonotic origin because of its close genetic homology to bat CoV, but not to any other known hCoV. Current data shows that bats harbour the greatest diversity of CoVs, which vary from species-to-species and region-to-region. Rabies virus (RABV), the archetypal lyssavirus, is historically one of the most dreaded viruses, with zoonotic potential in dogs, cats, and ferrets, and includes other domestic and wild mammals.

Globally, several mammalian species, including the deer mouse, rice rat, and cotton rat are recognized as potential reservoir of HTNV. In China, Hantaan virus (HTNV) and Seoul virus (SEOV) are zoonotically linked to the striped field mouse and the Norway rat, respectively. Also in China, the Fugong virus (FUGV), a novel HTNV has been identified in small oriental voles  (small rodents that are relatives of lemmings and hamsters). HTNVs have also been detected in shrews and bats, but their link to human illness remains to be established.

Moreover, in addition to humans and pigs, there is a growing chain of mammalian hosts for the hepatitis E virus (HEV) that includes deer, boar, mongoose, rabbit, rat, goat, camel, bat, ferret, moose, etc.

Arboviruses like dengue virus (DENV), chikungunya virus (CHIKV), ZIKV, and West Nile virus (WNV) are the arthropod-borne viruses that have re-emerged in many tropical and subtropical regions in the last 2 decades. Notably, ZIKV was known as a neglected tropical disease confined to Africa and Asia until an outbreak was reported in 2007 on Yap Island and in 2013/2014 on islands in the Pacific, thus expanding its geographical territory. WNV remains the most important mosquito-borne encephalitis pathogen in North America, involving *Culex* sp. and the American Robin in its transmission cycle. Since its emergence in the West in 1999, it has undergone adaptive genetic changes as it spreads throughout North America. Furthermore, Crimean-Congo hemorrhagic fever virus (CCHFV) is considered to be one of the major emerging diseases spreading to and within the European nations, following the expanding distribution of anthropophilic ticks. Every year, >1,000 cases of CCHFV, due to human-to-human transmission, are reported in southeastern Europe, including Turkey.

SFTSV ([Severe fever with thrombocytopenia syndrome virus), a previously](https://www.ncbi.nlm.nih.gov/pubmed/26923953)

unidentified tick-borne bunyavirus, has emerged later in China with fatality rates as high as 30%.

**Evolution and Adaptation to the Human Host**

While DNA viruses are believed to have been evolving and diversifying for millions of years, most RNA viruses are likely to have a much more recent evolution and “human-adaptation” for only thousands of years. Owing to their error-prone polymerase/reverse-transcriptase (approx. 10-4/site/replication cycle) that seems to operate at optimal fidelity, RNA viruses exist as more genetically diversified populations than DNA viruses. Nevertheless, of the hitherto recognized 158 species of human RNA viruses consisting of 47 genera and 17 families, only a minority has adapted to humans. In contrast, of the known 91 DNA virus species with 22 genera and 8 families, nearly 87% are adapted to human hosts. In the human-adaptation process, the viral genetic mutations, re-assortment or virus-host genetic recombination might lead to the establishment of stable virus lineages in human populations. It is, therefore, quite possible that such human-adapted viruses could circulate asymptomatically and remain undetected until their novel clinical manifestations are noticed. To understand this further, HEV genotype 3 from a chronic hepatitis E patient containing a recombinant virus-host RNA genome was shown to infect cultured human, pig, and deer hepatocytes.

It is assumed that there is a pool of human virus species still to be discovered. The composition of such a viral pool is dynamic, changing over time, i.e., while some virus species tend to become extinct, others continue to evolve in their natural hosts. More commonly, new species arise as a result of jumps from one host to another, thus crossing the species barrier. Humans are, therefore, no more than “incidental” or “spillover” hosts for pathogens. However, only a minority of such viruses are capable of persisting in certain human populations (endemics) or spreading across populations (epidemics) in the absence of a reservoir.

*Differential host factors like age, health, physiology, nutritional status, exposure history, simultaneous infection with >1 pathogen, immunocompetence, and genetics are determinants to human susceptibility to an infection*. The field of phylodynamics, combining a modeling framework for host, epidemiological, and molecular data, especially for RNA viruses, shows particular promise for understanding the patterns of viral evolution during epidemics. Moreover, our underappreciated aspect of growing human populations, global changes in land usage, and the introduction of anthropophilic vectors create selective pressure on hosts and reservoirs. For example, both WNV and CHIKV evolved rapidly after being introduced to new locations and encountering new vectors. When *Aedes albopictus* rather than *A. aegypti* became the main vector of CHIKV in the Indian subcontinent after the 2004-2009 epidemic, the same viral strain spread rapidly, and the subsequent mutants seemed to circulate and persist more efficiently.

ZIKV, initially known to be transmitted by mosquitoes, was recently reported as being transmitted, albeit more rarely, via sexual contact, saliva, breast milk, blood transfusions, and from mother to child.

**Evolutionary Drivers**

The key to understanding the emergence/re-emergence of novel viruses is to know the intricate “host-pathogen-environment” relationship in the evolution of pathogens. While the emergence of infectious diseases in naive regions is caused primarily by the movement of pathogens via trade and travel, local emergence is driven by a combination of environmental and social change. Notably, virus transmission rates are often higher in dense than in sparse populations, and the spread is often greatly enhanced by air travel or migration. Pathogens introduced into novel regions often cause explosive epidemics followed by a declining incidence whereas those that emerge locally due to land usage or social changes usually show consistent increases. An example is the emergence of ZIKV in Brazil in 2015. Phylogenetic studies suggested that ZIKV from the Pacific islands outbreak in 2013/2014 was probably introduced into Brazil during the FIFA World Cup or the 2014 FIA World Endurance Championship auto racing series. The dispersal of the virus in Brazil resulted in an explosive epidemic of Zika fever, and the infection spread to other countries due to frequent travel.

While most human infections are known to have zoonotic origins, it is certain that alterations in the environment, due to industrialization and urbanization, are an important but completely neglected factor. Though the origins of most of the human viruses are not known so far, the great majority can be categorized as “crowd diseases” that require a relatively high host-density to persist. Notably, the outbreaks of H1N1, hCoV, Hendra virus, Nipah virus, and MERS-CoV suggest that the Asia-Pacific region is the global hot-spot for the emergence of novel RNA viruses. In this case, an order-of-magnitude estimation of 1 such event per 100 years is broadly consistent with human demographic history.

The mathematics of spreading events is well known today, and a sophisticated array of computational and mathematical models can be used to accurately back-predict such events. An example of this is the first case-clusters of the SARS outbreak and the subsequent global spread, including the country-by-country distribution of human cases.

wild animals constitute an important but poorly understood reservoir for known and undiscovered human pathogens, including viruses. Furthermore, the relative importance of an animal species as a source of human infection is a function of the prevalence of zoonotic agents in that species and the probability of close contact (direct or indirect) with susceptible humans. Clearly, these factors vary geographically, and changes in patterns of human and animal disease will continue to result from socio-economic and ecological changes at the human-to-animal interface.

**Potential Risks and Control Measures**

If risk is a function of frequency of contact and a probability of successfully adapting to human hosts, viruses acquired from non-human primates might already be better adapted to successful transmission than those from other mammals, like bovine, porcine, feline, and rodent mammals. For example, SARS-CoV has been detected in masked-palm or gem-faced civet cats which are sold at Chinese wildlife markets.

Recurring epidemics caused by emerging viruses have necessitated the formulation of effective control measures, but the zoonotic transmission of many of these viruses has contributed significantly towards the challenges associated with their prevention and control. For instance, the prevention of arthropod-borne infections (e.g., DENV, CHIKV, and ZIKV) using vector control methods has only been partially successful. Preventing mosquitos breeding can be mediated by avoiding the accumulation of rain water in endemic regions. Other preventive measures like the use of repellent creams and clothes that cover the body should be employed to avoid mosquito bites. Insectidal sprays should be utilized in endemic regions to control the mosquito population.

Additionally, prevention of the transmission of other zoonotic viruses should also be addressed in a systematic manner to combat the infection of humans with these pathogens. It is now well known that many emerging human viruses can be transmitted via contact with infected animals and the consumption of animal products, including freshwater and seafood products. *The new approach to food safety and to protecting humans against food-borne health risks is the most effective measure to control the human illnesses associated with animal diseases.* However, the vast majority of human infections are not reported to clinicians, and so such etiological agents remain unidentified and continue to contaminate the population. As discussed, poultry are high-risk birds for emerging novel influenza A strains. Pork is another potential source of chronic HEV. Precautions and proper care should therefore be taken when selecting, purchasing, and hunting high-risk animals and when cooking meat. The current biosecurity measures appear to have been generally more successful for constraining bacterial diseases, but less effective for viral diseases. Surveillance of the emerging human viruses must include livestock, wild animal, and potential arthropod vectors as well as their environments at an international level of coordination.

Notably, many viruses that affect the respiratory tract, like influenza, RSV, MERS-CoV, SARS-CoV, and hMPV are transmitted by respiratory secretions and aerosol droplets. Effective measures for preventing their transmission in a community and their nosocomial spread are the adoption of good practices like frequent hand-washing and avoiding direct contact with patients. In addition, generating awareness in the general public about various aspects of these diseases will also assist in the better management and control of these emerging viral infections.