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Review Article

Epidemiology of emerging viruses

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ABSTRACT

Newly emerging viruses such as West Nile virus, coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2), H1N1pdm09, Ebola virus, Zika virus and Monkeypox virus are of global concern as they have caused serious public threats. Among the several outbreaks caused by emerging viruses, the worst pandemic was caused by SARS-CoV-2. The Omicron variant is the dominant variant among SARS-CoV-2 variants and the lineages BA.5.2 and BF.7 were responsible for the recent Chinese surge. Genome sequencing studies of MERS-CoV revealed that it is evolving with mutations in spike protein. West Nile virus is still circulating among birds in Europe, Mediterranean and North American countries. Several West Nile virus cases were reported from Europe and neighboring countries in 2022. The 2009 H1N1 pandemic caused by H1N1pdm09 is a variant strain evolved from H1N1 in swine. Though it caused more than 60 million infections, the mortality rate was 0.02%. Staggeringly, severe infections occurred among obese people. Zika virus has jumped borders from Africa and is adapting to become endemic in new geographical habitats such as South East Asia, India and Europe due to uncontrolled breeding of Aedes mosquitoes. Recently, autochthonous vector borne transmission of Zika virus was documented in France. During the Monkeypox pandemic, the virus demonstrated a lower infectious and mortality rate in individuals vaccinated for smallpox. A lower virulence of Monkeypox virus compared to smallpox was due to mutations in the ORF regions. Surveillance efforts and measures must be incessantly undertaken to prevent future outbreaks caused by emerging viruses.

1. Introduction

Since the dawn of the 20th century, the global population has experienced several epidemics and pandemics due to emerging viruses. Although certain viruses are endemic to a particular geographical habitat, some have spread beyond their original habitats. They are the emerging viruses, and a vast majority of them are RNA viruses. Viruses with RNA genomes successfully cause pandemics because of the higher rate of mutations associated with the error prone replication enzyme RNA dependent RNA polymerase.[1] Other factors that contribute to the emergence of viruses include spillover from reservoir animals, vector displacement and human mobility.

Animals inhabit diverse ecosystems and can come into contact with a wide variety of microorganisms present in their environment. Humans share genetic similarities with animals, particularly mammals, making it easier for certain pathogens to cross species barriers and infect both humans and animals. These pathogens can adapt to the new host environment and continue to circulate within animal populations, posing a risk for spillover infections in humans.[2,3] In the 20th and 21st centuries, successful spillover of viruses from animals to humans is due to climate change, especially in tropical regions where the climate is warming rapidly.[2] As human populations expand and

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encroach upon natural habitats, there is increased interaction between humans, domestic animals, and wildlife. This close proximity provides more opportunities for pathogens to jump between species and potentially infect humans. Additionally, human mobility by air travel causes the faster dissemination of emerging viruses resulting in the surge of epidemics and pandemics.[4] Coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are novel viruses that have caused pandemics. The primary reservoir for SARS-CoV and MERS-CoV is bat and dromedary camels served as an intermediate reservoir for MERS-CoV.[5] The most likely SARS-CoV-2 reservoir is horseshoe bat. These viruses caused pandemics due to cross-species transmission and human mobility. The primary reservoir for Ebola virus is fruit bat that frequently causes epidemics in Democratic Republic of the Congo and neighboring countries.[6] The most likely reservoirs of monkeypox virus are squirrels, rodents and monkeys. Monkeypox pandemic that occurred in 2022 immediately after COVID-19 caused an unusual and unprecedented crisis. Therefore, many emerging viruses have reservoirs in animals.

Successful viral pandemics are also caused by viruses that originate from animals and transmitted through respiratory droplet aerosols such as Influenza and coronaviruses. The 2009 Influenza A H1N1 pandemic (H1N1pdm09) virus evolved from swine causing 60 million infections. Air pollution additionally contributes to increase the mortality and hospitalization with respiratory viral infections in urban locations.[7]

The introduction of vectors from their native habitats to foreign geographical habitats and their adaptation in new habitats is added factor for some emerging viruses. The Dengue virus was once limited to the African continent but has since spread to other regions like Asia, Southeast Asia, and Latin America after introducing Aedes species mosquitoes. A similar occurrence of a jump from Africa to other continents was observed with the Zika virus, due to the displacement of *A. aegypti* and *A. albopictus*.[3] The successful establishment of vector-mediated emerging viral diseases depends on adapting of the virus in the biological vectors and their sustained maintenance through transovarial transmission.[8] Once established, the viruses remain endemic in the newly introduced habitat. The Zika virus outbreak that occurred in the Americas and some Asian countries was due to vector displacement and adaptation in new geographical habitats.

Emerging viruses have garnered significant attention due to their potential to cause widespread disease outbreaks and pose substantial public health challenges. With our global population becoming increasingly interconnected, the study of emerging viruses has become even more pertinent. Notable examples include diseases caused by West Nile virus, Ebola virus, Zika virus, H1N1pdm09 and the more recent Monkeypox virus and SARS-CoV-2. Therefore, this review aims to delve into the epidemiology of emerging viruses, shedding light on their characteristics, animal reservoirs, current global infection status and implications for public health.

2. Epidemiology of West Nile virus

West Nile virus (WNV) genome is a single stranded, non-segmented, positive sense RNA virus that belongs to the flavivirus group. It is transmitted primarily by the arthropod vector Culex mosquitoes. WNV was first isolated from a patient in the West Nile district of Uganda in 1937. Several outbreaks of WNV occurred between 1950 and the early 2000s, the first recognized outbreak occurred in 1951 in Israel with non-fatal cases. Between 1951 and 1954, several epidemics occurred in Egypt with a seroprevalence close to 60%. Children were more likely to develop symptomatic illnesses than adults, who had little central nervous system involvement.[9] The neurologic manifestations of WNV were first noticed during the second outbreak in Israel in 1957. In 1996, more frequent outbreaks of WNV started to occur in Europe and Middle East regions. One significant factor was a lack of efforts to control mosquito breeding.

It was in 1999 that WNV started to cause infections in the USA. The real source of WNV that was introduced into the USA was not confirmed but speculated to be originating from the Middle East.[10] Among the 62 cases, 59 were hospitalized, and neurologic manifestations occurred in elderly patients above 60 years. From then, WNV started to spread to other parts of the USA. It was in 2002 that the largest outbreak of WNV occurred in North America with meningoencephalitis. By early 2003, approximately 4156 cases had been reported, with 2942 cases of neurologic manifestations of meningitis, encephalitis or meningoencephalitis and 284 deaths.[11] Birds are the reservoirs for WNV as it was found to be epizootic among birds with a high fatality rate.[12] In recent years, molecular characterization studies have been conducted for WNV circulating in avian species and equines in Israel. WNV RNA was detected in bird species such as the yellow-legged gull (*Larus michahellis*), long-eared owl (*Asio otus*), pheasant (*Phasianus colchicus*), and four hooded crows (*Corvus cornix*), as well as in domesticated geese (*Anser anser*) and other animals such as horses and donkeys. All the birds and animals that were positive for WNV RNA demonstrated moderate to severe neurological signs.[13] WNV was detected in bird populations in Germany, Italy and Canada.[14,15] The results show that WNV is in constant circulation and maintained in bird populations in North America, European Union and European economic area (EU/EEA) countries. As of November 2022, EU/EEA countries had reported 965 human cases of WNV with a mortality rate of 12.5%.[16] Constant surveillance of birds, equines and vector mosquitoes is required to prevent future WNV outbreaks.

3. Epidemiology of Coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2)

Coronaviruses are a group of RNA viruses with single-stranded, non-segmented positive-sense RNA. These viruses cause respiratory tract infections in birds and mammals and are classified into four genera: alpha, beta, delta, and gamma coronaviruses. The most common human coronaviruses include 229E, NL63, OC43, and HKU1, which cause upper respiratory tract infections such as the common cold.[17] Rarely, they can cause lower respiratory tract illnesses such as bronchitis and pneumonia. The human coronaviruses that have serious public health impacts and the ability to jump species, causing pandemics with significant morbidity and mortality, are SARS-CoV, MERS-CoV, and SARS-CoV-2, which belong to the beta coronavirus.

3.1. SARS-CoV

SARS-CoV causes upper respiratory tract infections and pneumonia. It emerged in southern China in November 2002 with a high transmissibility rate. About 55 patients were admitted with complaints of pneumonia, all of whom were positive for SARS-CoV, and 87% were positive for SARS-CoV antibodies. It is likely that SARS-CoV reached Hong Kong through a 64-year-old nephrologist who visited in late February 2003 and died on March 4th. Global spread began through air travel by passengers from Hong Kong, as the virus was transmitted through virus-laden respiratory droplet aerosols. Due to its incubation period of up to 10 days, asymptomatic passengers spread the virus to other countries. Clinical symptoms of SARS start with a high fever, myalgia, and mild upper respiratory tract infections. After a week, the majority of patients develop pneumonia. Between November 2002 and July 2003, SARS spread to 29 countries, with 8,098 cases and 774 deaths, resulting in a fatality rate of 9.6%. Laboratory findings in SARS patients included reduced white blood cell counts such as lymphopenia, thrombocytopenia, and raised enzyme levels of alanine transaminases, lactate dehydrogenase and creatine kinase. Since 2004, no additional cases of SARS-CoV have been reported.

Molecular epidemiological studies conducted in 2003 showed that the SARS-CoV that circulated earlier in the human population was of animal origin. Animal-to-animal transmission occurred before the spillover from animals to humans.[18] Initially, palm civet cats were believed to be the reservoirs since SARS-CoV was isolated from them in the South Chinese markets. By late 2005, it was identified that the natural reservoir for SARS-CoV is a horseshoe bat in the genus Rhinolophus. Experimental infection of palm civet cats with SARS-CoV resulted in the development of symptoms, including fever, lethargy, and loss of aggressiveness.[19] The susceptibility of palm civets to SARS-CoV and their wide distribution in the markets of China might have contributed to the SARS-CoV outbreak.

3.2. MERS-CoV

MERS-CoV first appeared in Saudi Arabia in 2012. The first case was reported from Bisha, Central-West Saudi Arabia, in September 2012. A total of 27 countries reported cases of MERS-CoV infection. Since April 2012 to present, globally, a total of 2591 cases of MERS-CoV were reported, with 894 deaths (global case fatality of 35%). 84% of cases occurred in Saudi Arabia, with a case fatality rate of 37%. The second highest occurrence was in Asia (11%). European countries and the USA recorded cases of 0.8% and 0.1%, respectively. Between 2022 and early January 2023, 6 MERS cases were reported from Saudi Arabia (3), Qatar (2), and Oman (1) with one fatality.[20] MERS clinical manifestations range from asymptomatic to mild or moderate to severe respiratory illnesses such as pneumonia. MERS typically presents with a fever, cough and shortness of breath. However, other clinical manifestations such as abdominal pain, nausea, vomiting, diarrhea and acute renal failure were also observed.

Bat is MERS-CoV's natural and primary reservoir, and the dromedary camels are the intermediate reservoirs. From camels, it spread to humans as a zoonotic transmission. The presence of MERS-CoV antibodies in camels shows that dromedary camels play a significant role in transmitting MERS-CoV to humans. Additionally, genome sequencing showed a higher sequence identity between the MERS-CoV isolated from humans and camels.[21] MERS-CoV was isolated from the nasal swabs in camels. Therefore, droplet transmission or direct contact with dromedary camels is the mode of zoonotic transmission. Cases with animal contact were predominantly male and elderly with underlying complications, and the fatality rate was 35%. A recent study in Saudi Arabia showed that the MERS-CoV continuously evolves with the accumulation of mutations in the spike receptor binding domain.[22] Genome sequencing of the MERS-CoV positive cases must be performed from time to monitor the emergence of any new variants and prevent outbreaks.

3.3. SARS-CoV-2

SARS-CoV-2 belongs to beta coronaviruses and causes the coronavirus disease 2019 (COVID-19). Compared to its beta coronavirus counterparts, SARS-CoV-2 caused a severe pandemic and is still a global threat. The most likely source of SARS-CoV-2 is bats. Nevertheless, the intermediate host or amplifier host is yet unknown. SARS-

CoV-2 started to mutate at a faster rate and emerged with several variants, some designated as variants of interest and the others as variants of concern (VOC). The VOCs are designated as alpha, beta, gamma, delta, epsilon and omicron.[23] The alpha variant appeared in the United Kingdom in late 2020 and became dominant. The beta and gamma variants appeared in South Africa and Japan in 2020 and lacked the ability to become dominant variants.[23] The delta variant first appeared in India in 2020 and became the most dominant variant, raising serious concerns. The delta variant was superseded by the omicron variant in its dominance in causing infections. Due to some key mutations in the spike protein residues, the alpha, beta and gamma variants exhibited enhanced transmissibility and disease severity compared to the wildtype SARS-CoV-2. The transmissibility and disease severity were in the order of omicron > delta > alpha between the variants.[24,25] Omicron quickly replaced delta as the dominant variant. Omicron caused less severe disease than delta because it multiplied efficiently in the upper respiratory tract. The omicron variant lineages BA.5.2 and BF.7 were responsible for the recent Chinese surge, accounting for 97.5% of infections. 763,740,140 confirmed cases of COVID-19 and 6,908,554 deaths have been reported to the WHO as of April 2023.

4. Epidemiology of Ebola virus

Ebola virus is a single stranded, non-segmented negative sense RNA virus that causes Ebola virus disease (EVD), a hemorrhagic fever disease associated with high mortality. It affects humans and animals such as monkeys, chimpanzees, and gorillas. There are four strains of the Ebola virus: the Zaire ebolavirus, the Sudan ebolavirus, the Taï Forest ebolavirus, and the Bundibugyo ebolavirus. Fruit bats are primary reservoirs for the Ebola virus since there is evidence of asymptomatic infection.[6] Additionally, evidence of Ebola virus antibodies was demonstrated in fruit bats.[26]

Zaire is the most common among the four strains, and Sudan is the second most common strain responsible for the outbreaks. The first case of EVD was reported in 1976 in the Republic of Congo, caused by the Zaire strain. The case mortality rate was 88%, with 318 cases and 280 deaths. Another outbreak occurred in the same year in Sudan caused by the Sudan strain, with 284 cases and 151 deaths (mortality rate 53%).[27] After 1976, several outbreaks occurred, until recently. The world's largest outbreak of EVD occurred between 2014-2016 at three different locations in Africa. It occurred in Sierra Leone with 14,124 cases and 3956 deaths (28% case fatality rate), Liberia with 10,675 cases and 4809 deaths (45% case fatality rate) and Guinea with 3811 cases and 2543 deaths (67% case fatality rate). The world's second largest outbreak occurred between 2018-2020 in the Democratic Republic of the Congo, with 3481 cases and 2299 deaths (66% case fatality rate). Both outbreaks were caused by the Zaire strain.[27] The third largest outbreak was caused by the Sudan strain that occurred in Uganda, with 425 cases and 224 deaths (53% case fatality rate). The fourth largest outbreak was caused by the Zaire strain in 2007 in the Republic of Congo, with 264 cases and 187 deaths (71% case fatality rate). The first reported jump in Ebola virus infection outside of Africa occurred in 2014 in the USA (4 cases), UK (1 case), Spain (1 case) and in 2015 in Italy (1 case). All the reported cases were caused by the Zaire strain with no case fatalities in the UK, Spain, Italy and 1 case fatality in the USA.[27] The latest outbreak of EVD was reported on 21 August 2022 in North Kivu province in the Democratic Republic of Congo with 1 case that resulted in mortality. As of 27 September 2022, no cases of EVD have been reported.[28]

5. Epidemiology of H1N1pdm09

H1N1 is an Influenza A virus that belongs to the Orthomyxoviridae. The genome is a single stranded, segmented negative sense RNA. The earliest record of H1N1 pandemic was in 1918, with 500 million cases and approximately 50 million deaths. The origin of H1N1 is presumed to be due to reassortment between human H1 and avian N1, which subsequently jumped directly to swine.[29] Almost a century later, H1N1 yet again caused a global pandemic of concern in 2009. It is the first pandemic caused by the Influenza A virus in the 21st century. The 2009 H1N1 pandemic (H1N1pdm09) was a swine Influenza A virus, but genetically and antigenically distinct from the virus that was in circulation in the human population from 1977-2009.[30] The H1N1pdm09 strain was the product of the evolution of the 1918 H1N1 strain in swine.[31] Compared to other influenza illnesses, people under the age of 65 were vulnerable to infection with H1N1pdm09 associated with hospitalizations and death. An unusual risk factor was a direct correlation between obesity and disease severity.[32] In the USA, the virus affected blacks, American Indians and natives more than whites. There were 60.8 million cases and 12,469 deaths in the USA due to the H1N1pdm09 virus with a significantly lower mortality rate of 0.02%. Though the pandemic with H1N1pdm09 is over, the virus still remains in circulation, causing seasonal outbreaks.

6. Epidemiology of Zika Virus

Zika virus is an arbovirus that belongs to the Flavivirus group. The genome is a non-segmented, single stranded positive sense RNA. Zika virus was first discovered in Uganda in 1947. Two major outbreaks occurred in 2007 and 2013 in the Yap Islands and French Polynesia. It is transmitted by the mosquitoes Aedes aegypti and Aedes albopictus. The reservoirs of the Zika virus are monkeys such as rhesus macaques, wild African green monkeys,

Table 1: A comprehension of different emerging viruses, reservoirs and current global status of infection

Emerging viruses	Reservoirs	Current global status of infection
West Nile virus	Yellow-legged gull (*Larus michahellis*), long-eared owls (*Asio otus*), domesticated geese (*Anser anser*), pheasant (*Phasianus colchicus*), four hooded crows (*Corvus cornix*), horses and donkey.	Maintained in reservoir birds in Europe, Mediterranean and North America. 965 confirmed cases were reported from EU/EEA countries in 2022.
SARS-CoV	Primary reservoir: Horse shoe bat (*Rhinolophus sp*).	No cases were reported since 2004.
MERS-CoV	Primary reservoir: Bats, intermediate reservoirs - dromedary camels.	Still cases are reported from Middle-East. Virus is gradually evolving with mutations.
SARS-CoV-2	Indecisive	Omicron variant is the dominant variant globally. Recent Chinese surge was due to Lineages BA.5.2 and BF.7.
Ebola virus	Primary reservoir: Fruit bats	Last detected – 1 case with mortality on 21st August 2022 in DRC.
H1N1pdm09	Variant strain evolved from H1N1 in swine.	Still in circulation among humans causing seasonal outbreaks.
Zika virus	Primary reservoir: Monkeys (rhesus macaques, wild African green monkeys, baboons and stump-tailed macaques)	Last outbreak was reported in August 2021 in Singapore.
Monkeypox virus	Most likely reservoirs: squirrels - *Funisciurus* and *Heliosciurus*, rodents - *Cricetomys* and *Graphiurus*, monkey - sooty mangabey and chimpanzee - *Pan troglodytes verus*.	Still cases are reported from EU/EEA countries.

baboons and stump-tailed macaques.[33,34] The incubation period ranges from 3-14 days. The disease is asymptomatic to mild or moderate. The primary mode of transmission of the Zika virus is mosquitoes, but it can also be transmitted sexually. The clinical manifestations of Zika virus disease (ZVD) are fever, rash, arthritis, conjunctivitis, headache and myalgia. In pregnant women, the virus can be transmitted transplacentally causing congenital anomalies. Microcephaly is the most common congenital anomaly found in neonates.[35] The virus infection is also associated with neurological complications such as Guillain-Barré syndrome.[36] Zika virus has been found in the Americas, the Pacific Islands, and parts of Africa and Asia.[37] The peak incidence of a Zika virus outbreak in the Americas was in the middle of 2016. In 2020, a total of 22,885 cases of ZVD were reported from the Americas. Approximately, 18,941 cases (83%) were reported from Brazil in 2020. Although the overall cumulative incidence of ZVD was 2.34/1,00,000 in the Americas. However, some countries showed a higher cumulative incidence, such as Brazil with 9.08, Paraguay with 8.60, and Bolivia with 6.49 per 1,00,000 people. Between 2015-2018, several cases of ZVD were reported in Europe that were associated with travel to endemic countries. But vector borne transmission of the Zika virus was documented in France in 2019.[38]

Since the Southeast region has a wide prevalence of the vector Aedes aegypti, the region is at risk for ZVD. The first report of ZVD in India was reported in November 2016 in a pregnant woman in the state of Gujarat. Subsequently, outbreaks were reported in several other states such as Rajasthan, Tamil Nadu, Kerala, Maharashtra and Gujarat between 2017-2018.[39] The prevalence of vectors might favor the virus remaining endemic in India. Cases of Zika virus infection were also reported from Malaysia, Singapore and Laos. In Singapore, an outbreak of ZVD that occurred in 2016 was reported in the Kallang-Aljunied neighborhood. The first case of Zika virus infection in Singapore was imported from Sau Polo, Singapore.[40] In Malaysia, only eight cases were found to be positive for Zika virus infection among 4043 suspected cases between June 2015 to December 2017. Despite a similar ecological background in Malaysia, likened to Brazil and Singapore, an outbreak of ZVD didn't occur in Malaysia for unexplained reasons.45 Recently, Zika virus infections were reported in 2021 from Uttar Pradesh, Kerala and Delhi.[41] In Singapore, new cases of Zika virus infection occurred in August 2021, as reported by news media agencies.[42]

7. Epidemiology of Monkeypox

The first human Monkeypox (Mpox) case was diagnosed in 1970 in the Democratic Republic of Congo (DRC). The disease is caused by the Mpox virus, an orthopoxvirus belonging to the Poxviridae family. The genome is a linear double-stranded DNA. Between 1970 and 2003, all the cases of Mpox occurred in Africa, with a vast majority of them in DRC.[43] The first recorded cases of Mpox outside Africa occurred in 2003 in the USA. Forty-seven cases were reported with all of them in contact with pet prairie dogs that were kept in close proximity with rodents, mice and squirrels, imported from Ghana. No human to human transmission was observed.[44] Between 2003 and 2018, sporadic Mpox cases occurred in several African countries such as DRC, Sierra Leone, Cameroon and Liberia.[45] The animals that could serve as reservoirs of Mpox virus are squirrels of genus- Funisciurus and Heliosciurus, rodents of genus - Cricetomys and Graphiurus, monkey - sooty mangabey and chimpanzee - Pan troglodytes verus.[46–48] Since May 2022, there has been a dramatic increase in Mpox cases worldwide, declared a global health emergency by the WHO. The possible reasons were attributed to the discontinuation of smallpox vaccination. Vaccinated individuals were 21-fold less likely to be infected with the Mpox virus, and otherwise infected individuals had a lower mortality rate.[49,50] The recent outbreaks were due to human to human transmission, but were higher among men who have sex with men. Lineage B.1 of the West African clade was responsible for the 2022 outbreak.[51] The mutations in the surface glycoprotein D209N (aspartic acid to aspargine), P722S (proline to serine) and M1741I (methionine to isoleucine) enhanced the transmissibility.[52] As of April 2022, 86,956 confirmed cases of Mpox have been reported globally in 110 locations. Intriguing to note is, Mpox has occurred in 103 locations with no known previous history of Mpox. As per CDC, a total of 26% of cases have occurred in the USA alone, with a mortality rate of 0.07%.[53] Disruptions in the open reading frame (ORF)s of the Western African clade are responsible for lower virulence compared to the Central African clade.[54] Mpox cases are still reported from EU/EEA countries, with the highest rates of reporting from Spain, Portugal and Luxembourg.[55]

A compilation of the above-mentioned emerging viruses, reservoirs and current global status of infection is presented in Table 1.

8. Conclusion

Emerging viral infections are of public health importance. Surveillance is vital to identify emerging viruses in potential reservoirs, biological vectors, and through genome sequencing, enabling early detection of new variants. These measures are essential for averting future outbreaks and pandemics.

9. Source of Funding

None.

10. Conflict of Interest

None.

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