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REVIEW ARTICLE

Emerging and Re-emerging Viral Infections in the 21st Century: Microbiological and Public Health Perspectives

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Abstract:

Pathogens, especially viruses and bacteria are known to have great potential to emerge and evolve for thousands of years and it seems to be a never-ending process. In the last couple of decades, many viruses have reemerged, and several novel viruses have emerged from animals and birds, posing a serious threat to human health and the global economy. Amongst these pathogens, RNA viruses were found to be more pathogenic and are more frequently associated with emerging viral diseases. This is because they have the capabilities to adapt rapidly to changing local and global environments. The ability to undergo mutation, genetic assortment, and recombination, unavailability of effective vaccines, and lack of herd immunity are the compounding factors for the emergence of new diseases and reemergence of old viral diseases. This article outlines virus characteristics, source and transmission of infection, recent outbreaks, and impact on human health, laboratory diagnosis, and preventive strategies of the prominent epidemic and pandemic viral diseases that occurred globally in the 21st century.

Keywords: Coronaviruses, RNA viruses, Emerging infections, Epidemic, Pandemic

Introduction:

The emergence of novel viral infections and reemergence of several old viral diseases pose a serious threat to human health and life [1-2]. The frequent continued outbreaks of viral infections worldwide have resulted in considerable loss of human life [1]. At the fundamental level, emerging diseases are those whose incidence in humans have increased in the past two decades and re-emergence is the reappearance of a known disease after a significant decline in incidence [1-3]. RNA viruses are more frequently associated with emerging and reemerging viral diseases. The key factors (Fig. 1) associated with the emergence of such diseases are evolution of infective agents, increasing human population growth and globalization, changes in human behavior and their habitat, increased domestic and international travel, unplanned urbanization, deforestation, climate changes, and agricultural evolution [3-4]. Emerging infections are linked to either emergent of a new virus due to genetic variation (mutation or recombination) or because of adaptation of the animal virus in humans. Additionally, it could be due to the introduction of a new infectious agent in a determined geographic area [3-5]. In contrast, re-emergent infections generally originate by reactivation of quiescent reservoirs or because of reappearance of previously circulating viruses that have spread to other regions [3]. From the beginning of 21st century, several major outbreaks of

emerging and re-emerging viral diseases (Fig. 2) with a varying degree of severity ranging from mild to highly fatal have been reported from different regions of the world [2]. Amongst, several coronavirus diseases of animal origin (Severe Acute Respiratory Syndrome (SARS), Middle-East Respiratory Syndrome (MERS), and the present ongoing pandemic Coronavirus disease 2019 (COVID-19), Ebola in West Africa, Zika in South America, H7N9 in China and many Asian countries, H1N1 influenza worldwide, Nipah in India, and several arbovirus diseases (Dengue, Chikungunya, Kyasanoor Forest Disease, Crimean Congo Hemorrhagic Fever (CCHF), Japanese encephalitis) especially in Asia were the prominent emerging and reemerging viral diseases (Table 1: Basic characteristics of common emerging/ reemerging viral diseases) recorded so far in the 21st century [1-2]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), the two major health organizations have put a greater emphasis on control of these infectious diseases [6]. This article focusses on recent global epidemic and pandemic viral diseases that occurred in the 21st century with special attention to virus characteristics, reservoir, and mode of transmission, impact on human health, diagnosis, and prevention strategies.

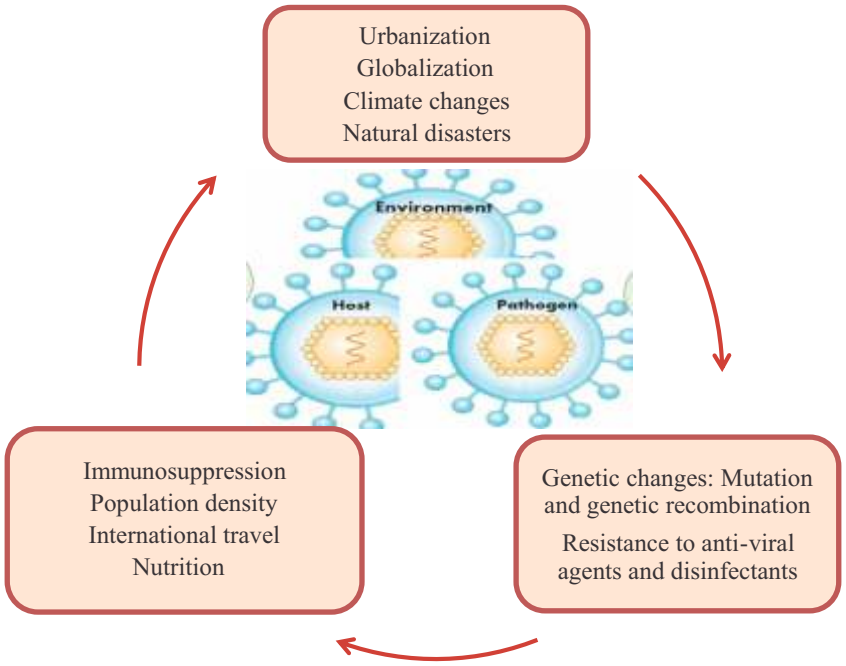

Fig. 1: Contributing Factors for Emergence of Viral Infections

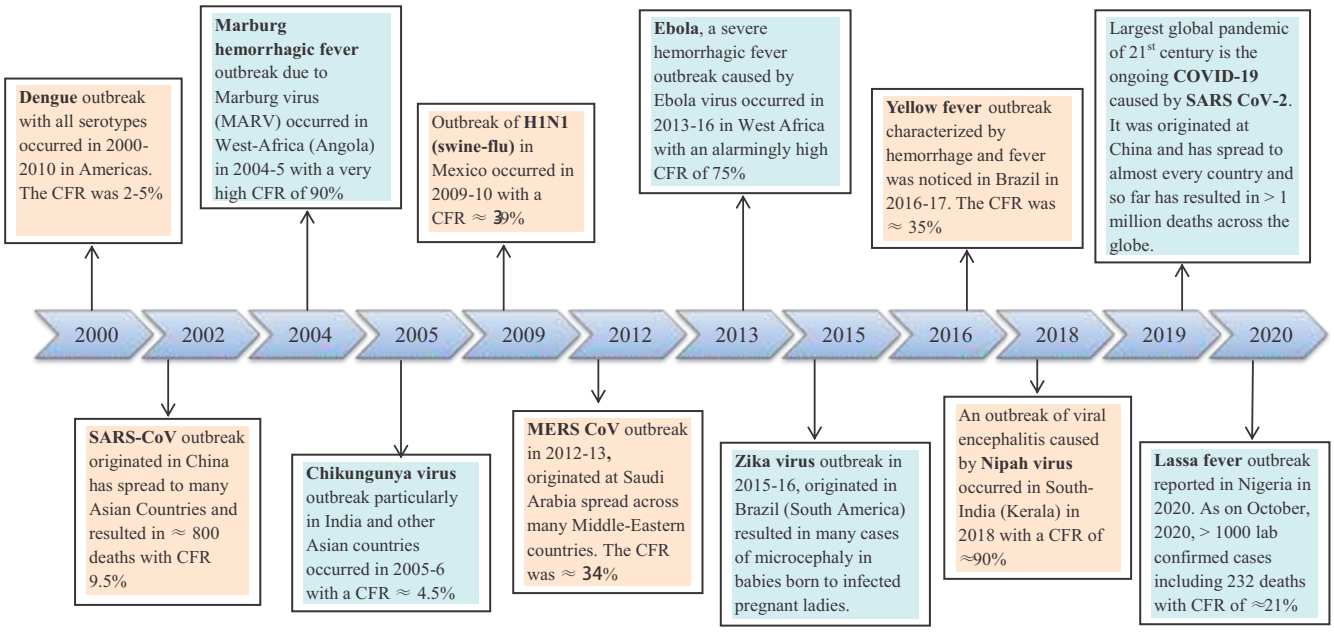

Fig. 2: Timeline of Emerging and Reemerging Viral Diseases of 21st Century

Table 1: Basic Characteristics of Common Emerging/Reemerging Viral Diseases of 21st Century

Causative agent	Disease	Family/Genus	Natural/Reservoir	Transmission	References
SARS-CoV-2	COVID-19	Coronaviridae / Coronavirus	Bats/pangolins	Human-human Animal-human (initial transmission)	7, 8
SARS-CoV	SARS	Coronaviridae / Coronavirus	Bats/palm civets	Human-human Animal-human (initial transmission)	8,9
MERS-CoV	MERS	Coronaviridae / Coronavirus	Bats/camel	Human-human Animal-human	8, 10
Nipha virus	Nipha virus encephalitis	Paramyxoviridae / Henipavirus	Pteropus bats (fruit bats)	Human-human Direct contact with animals, Ingestion of contaminated fruits	11
Zika virus	Zika virus disease	Flaviviridae / Flavivirus	Mosquitoes/ monkeys	Mosquito bite, sexual contact, mother-fetus, blood transfusion	12
Ebola virus	Ebola virus disease	Filoviridae / Ebolavirus	Fruit bats/non-human primates	Human-human	13
CCHF virus	Crimean Congo Hemorrhagic fever	Bunyaviridae/ Nairovirus	Ticks	Tick bite, contact with infected blood/ tissues/ body fluids of infected animals/human	14, 15
Marburg virus	Marburg virus disease	Filoviridae/ Marburgvirus	Fruit Bats (Rousettus aegyptiacus)	Human-human	16
Lassa virus	Lassa fever	Arenaviridae /mamma arenavirus	Multimammate rats	Rodents-human	17
West-Nile virus	West-Nile virus encephalitis	Flaviviridae/ Flavivirus	Mosquitoes/ Birds	Mosquito bite	18

Coronavirus Diseases:

Coronaviruses are a large group of enveloped RNA viruses that belong to *Coronaviridae family.* They carry a surface glycoprotein projection, resembling solar crowns, therefore being termed "coronaviruses". They possess a single stranded positive sense non-segmented RNA genome that has a great potential to undergo high rate of genetic mutation and recombination [7]. Fig. 3 depicts the classification of coronaviruses. There are 4 subtypes (alpha, beta, gamma, and delta), among which alpha and beta coronaviruses gained much attention due to their ability to cause human infection [8]. To date, 7 coronaviruses namely hCoV-OC43, hCoV-HKU1, SARS-CoV, MERS-CoV, SARS-CoV-2 (beta coronaviruses), hCoV-NL-63, and hCoV-229E (alpha coronaviruses) have been documented in human infection. However, hCoV-HKU1, hCoV-NL63, hCoV-229E, and hCoV-OC43 are circulating in humans since they were recognized and are mainly associated with mild upper respiratory and gastrointestinal infections, accounting for approximately 5-30% of common cold [8]. Within a couple of decades in the 21st century, there have emerged three highly pathogenic and dangerous coronaviruses of animal origin namely SARS-CoV, MERS-CoV, and SARS-CoV-2.

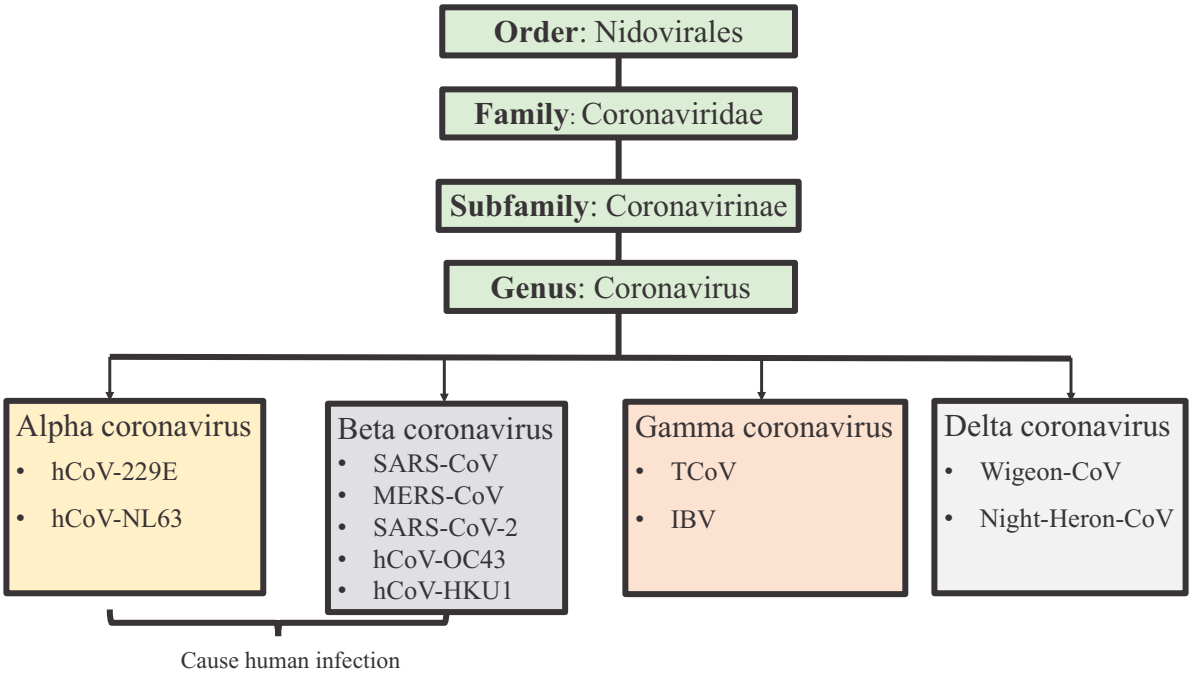

Fig. 3: Classification of Coronaviruses

Coronaviruses were not considered serious until the global emergence of SARS caused by a novel coronavirus SARS-CoV, originated in Guangdong province of southern China in 2002 that had spread across 26 countries globally [5, 7, 19]. It caused dreadful impact on human health affecting lower respiratory tract, resulting in pneumonia, acute lung injury, acute respiratory distress, septic shock, and multi-organ failure with a case fatality rate of 9.8% [9]. A decade later, MERS epidemic due to MERS-CoV emerged in Middle East. It was first identified in Jordan in April 2012, spread across many countries, especially in Middle Eastern region resulting in approximately 876 deaths with a case fatality rate of 34.3% [7, 8, 20]. Since then, it has been causing persistent endemics in Middle Eastern region, sporadically spreading outside the Middle East. The most recent laboratory confirmed cases of MERS were reported from Riyadh, Saudi Arabia in March 2020 [8]. While humans are still threatened by MERS, a novel coronavirus designated as SARS-CoV-2 emerged in 2019, first identified in Wuhan city, Hubei province of China in December 2019 and has swiftly spread across the globe affecting almost every country. Health Regulations Emergency Committee of the WHO declared the outbreak as a public health emergency of international concern on January 30, 2020 [21]. Subsequently, WHO coined the term COVID-19 for the disease in February 2020 and declared this novel disease as a pandemic in March 2020 [22]. The SARS-CoV-2 was recognized to be highly contagious. As of June 24, 2021, SARS-CoV-2 has spread across more than 220 countries and territories, affected >180 million people with > 3.9 million confirmed deaths [23]. The United States, India, and Brazil were the most affected countries in terms of number of cases and COVID-19 related deaths [23]. Uniquely all these dangerous coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 were originated from animals [7-8]. Basic characteristics, crucial events, phylogenicity of SARS-CoV, MERS-CoV, and SARS-CoV-2 is depicted in Table 2. Notably, these coronavirus outbreaks are linked to interaction between animals and humans [19]. SARS-CoV emerge from wet animal markets in China. Subsequently, a strain of coronavirus highly phylogenetically similar to SARS-CoV was identified in bats and palm civets, strongly indicating bats and palm civets as natural and intermediate hosts respectively [8, 24]. Initially infection was transmitted to humans through the contact of infected animals and subsequently person-to-person transmission through respiratory secretions [7]. Bats were also believed to be natural hosts for MERS-CoV while dromedary camels were an intermediate host. The initial human transmission has occurred through contact with the infected camel, subsequently human-to-human transmission through infected respiratory secretions [7, 8]. Conversely, the origin of SARS-CoV-2 is more sophisticated. Like SARS-CoV, SARS-CoV-2 was also emerged from wet animal market in China. Initially, the infection was detected among people who had visited Huanan animal wet market in Wuhan city, suggesting animal-human transmission. Subsequently, infection was noticed increasing in numbers among people outside of Wuhan who did not have exposure to animal markets, pointing to human-to-human transmission [7]. Research studies indicate the phylogenetic

similarity of SARS-CoV-2 with the strain isolated in pangolins and bats, suggesting these animals as most likely sources of infection for the initial animal-to-human transmission [8, 25-26]. Furthermore, it has been confirmed that SARS-CoV-2 shares approximately 80% genomic homology with SARS-CoV and only about 50% similarity with MERS-CoV, suggesting its proximity to SARS-CoV [7-8]. Like SARS-CoV, SARS-CoV-2 also acts through Angiotensin Converting Enzyme-2 (ACE-2) receptors. However, respiratory epithelial cells have shown to provide better growth conditions for SARS-CoV-2 compared to SARS-CoV [7]. In modeling studies, it is observed that basic Reproduction number (R_0) in SARS-CoV-2 to be 2-6.7 compared to 2 in SARS-CoV, indicating high average number of SARS-CoV-2 infected contacts per infected individual [7]. Human-to-human transmission of SARS-CoV-2 primarily occurs either by direct contact with respiratory secretions of infected person or indirectly through contact with the contaminated surfaces, subsequently by touching mouth, eyes, and nose [7]. Generally, incubation period in COVID-19 varies between 2-14 days. Uniquely SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses may result in asymptomatic and mild illness to severe illness characterized by pneumonia, acute respiratory distress, multi-organ failure, and shock and death [8]. With respect to the diagnosis, coronaviruses are identified in clinical specimens primarily by molecular tests such as Reverse-Transcriptase PCR (RT-PCR) which have high sensitivity and specificity [27]. Nasopharyngeal swab was the recommended specimen for SARS-CoV-2. The antigen/antibody detection tests are also available. However, the sensitivity of antigen/antibody tests is generally low compared to molecular tests. Moreover, antibody tests are primarily done for retrospective diagnosis of coronavirus infections [8, 28]. Although the novel coronaviruses are dreadful threat to human health, at present there is no specific antiviral therapy or vaccine to prevent SARS and MERS. Therefore, treatment primarily involves symptomatic and supportive therapy including advanced life support if necessary. These facts highlight the urgent need for deep understanding of novel coronaviruses and thus develop strategies to tackle them effectively. However, numerous research trials worldwide which are in rapid phase to discover and evaluate effectiveness of antivirals, immunotherapies, monoclonal antibodies, and vaccines to COVID-19 have demonstrated promising outcomes. Remdesivir was the first antiviral drug approved for treatment of COVID-19 [29]. The Food and Drug Administration (FDA) also issued an Emergency Use Authorization (EUA) for bamlanivimab (a monoclonal antibody against surface spike protein of SARS-CoV-2), Baricitinib in combination with remdisivir, and casirivimab and imdevimab (a mixture of monoclonal antibodies) [31-32]. Additionally, some pilot studies have shown the benefits of using corticosteroids, tocilizumab (an anti-IL-6 receptor antibody) and etoposide in selected COVID-19 patients with cytokine storm [33]. There are four categories (whole virus, protein subunit, viral vector, and nucleic acid i.e. RNA and DNA) of vaccines, all of which aiming at immunity to the virus, and some might also be able to stop transmission. WHO has listed the Pfizer/BioNTech, Astrazeneca-SK Bio,

Serum Institute of India, Janssen, Moderna, Sinopharma vaccines for emergency use. The vaccines are indicated to be used in people of age years or more and the efficacy of a two-dose administration of the vaccine was expected to be 95% [34-35]. Despite all the latest developments, still the prime strategy to limit the spread of coronavirus diseases rely on strict adherence to control measures such as frequent handwashing with soap and water or alcohol-based hand rub, use of face mask, social distancing, avoiding unnecessary travel and social gatherings [7].

Nipah Virus:

Nipah Virus (NiV) is an emerging bat-borne RNA virus, member of family *Paramyxoviridae*, belonging to Genus *Henipavirus*. It was first recognized in 1999 in Malaysia and since then it has caused several outbreaks in South-East Asia [40]. Investigations confirmed fruit bats of the genus *Pteropus* as the reservoir of infection. The initial spread of infection was found to be by either direct contact with infected bats or their faeces/ urine or consumption of fruits contaminated by saliva of infected bats. Subsequent reports also

Table 2: Basic Characteristics, Crucial Events, Phylogenicity of SARS-CoV, MERS-CoV, and SARS-CoV-2

	SARS-CoV [8, 19, 36]	MERS-CoV [8, 37, 38]	SARS-CoV-2 [8, 39]
First report of emergence	16 November 2002, Foshan, China	4 April 2012, Zarqa, Jordan	7 December 2019, Wuhan, China
First notification of causative agent	March 2003	June 2012	January 2020
Recent status	Completely controlled	Sporadic cases reported	Ongoing pandemic
Primary (natural) host	Bats	Bats	Pangolins, Bats
Intermediate host	Palm civet	Camel	Pangolins
Binding protein	S protein	S protein	S protein
Receptors and cofactors	ACE-2 receptor, TMPRSS2 cofactor L SIGN cofactor	DPP4 receptor, TMPRSS2 cofactor	ACE-2 receptor, Integrin receptor? TMPRSS2 cofactor
No of laboratory confirmed cases	8096	2553	>180 million (As of June 24, 2021
No of confirmed deaths	774	876	>3.9 million (As of June 24, 2021
Case fatality rate (CFR)	9.6%	34.3%	≈2.4% ((As of June 24, 2021)

suggested human-to-human transmission through unprotected close contact with infected patients [41]. Affected individuals show a wide range of clinical manifestations ranging from asymptomatic infection to acute respiratory infection and encephalitis. The case fatality rate was estimated to be high ranging from 40-90%, however, it varies depending on local capabilities of epidemiological surveillance and clinical management [42]. The latest outbreak of Nipah virus infection was reported from Kerala, India in May-2018 [41]. As per the latest report, there were 18 laboratory confirmed cases, out of which 17 had died, accounting for the high mortality rate of 89.4% [41]. The diagnosis of Nipah virus infection is mainly by detection of viral nucleic acid in body fluids by molecular tests such as RT-PCR. Other tests include antibody detection by Enzyme-Linked Immunosorbent Assay (IgM-ELISA) and virus isolation by cell culture [42]. Currently, there are no vaccines or specific antiviral drugs for treating Nipah virus infection. For those who are infected, the treatment is entirely symptomatic and supportive including advanced life support [41]. Preventive measures should be initiated at the earliest, whenever the outbreak is suspected. The establishment of an appropriate surveillance system is also crucial for the rapid detection of the outbreak and initiation of control measures. The public is advised to take necessary precautions such as avoid eating any half-bitten fruits or any fruits that are dropped on the ground, avoid consumption of raw date palm sap or toddy, avoid entering into abandoned wells, and others [43]. Nipah virus is internationally considered as Bio-Security Level-4 (BSL-4) agent and hence clinical samples should be handled in laboratories with BSL-4 facilities. At the same time, healthcare workers treating a confirmed infection or suspected patients or handling clinical specimens are recommended to always adhere to infection control precautions [43].

Ebola Virus Disease:

Ebola Virus Disease (EVD) is another deadly disease with high mortality, can kill up to 90% of infected people, primarily seen in the African continent [44]. EVD is caused by a group of viruses within the *genus Ebolavirus*. The *genus Ebolavirus* is composed of single-stranded enveloped RNA viruses that have a filamentous morphology [45]. Currently, there are five species, out of which four are known to cause infection in humans. Ebola virus was first discovered in 1976 near the Ebola River in the Democratic Republic of Congo (DRC). Since then, it has resulted in several outbreaks from time to time in several African countries [46]. The recent outbreak in DRC which lasted nearly two years (2018-20) was recorded as the second-largest Ebola outbreak [47]. During this outbreak, 3481 laboratory confirmed EBV cases were reported, out of them 2299 died of the disease with an overall case fatality rate of 66% [47]. The origin of the virus is exactly not known. However, studies revealed animal origin either from bats or non-primate humans (monkeys, chimpanzees, apes, etc.). These infected animals can then transmit the virus to other animals and humans. Human transmission occurs either through direct contact with body fluids/tissues of the infected animals or person-to-person transmission through direct contact with body fluids/tissues of a sick or patient died from EVD. It is observed that the virus spreads through broken skin or mucus membranes

in the eyes, nose, and mouth following direct contact with infected body fluids [45, 47]. Other ways to get EBV is through sexual contact with a sick person or touching the contaminated needles and surfaces [45, 47]. However, the infection is unlikely to be transmitted from an asymptomatic patient. Patients with EBV disease, initially develop flu-like illness. As the disease progresses, the virus damages the immune system and organs. Ultimately results in low platelet count, internal hemorrhage, coughing or vomiting of blood, and bleeding in the eyes, ears, and nose. If not treated, the patient will die of hemorrhagic complications. Diagnosis of EVD is primarily by the detection of viral RNA in blood or body fluids by RT-PCR and by antibody tests in patients who have recovered from the disease [48]. The treatment is generally symptomatic and advanced life support in critically ill patients. However, recently, the FDA has approved a vaccine (Ervebo) and drug (Inmazeb), consisting of mixture of three monoclonal antibodies: atoltivimab, maftivimab, and odesivimab-ebgn for treating Zaire ebolavirus infection [49-50]. The vaccine is indicated in people of age 18 years or older, while drug can be used in adults and pediatric patients [49-50]. The preliminary results of efficacy of vaccine or monoclonal antibody therapy was favorable [49-50]. Currently, reducing the risk of human transmission during outbreaks by early detection and advising the public to follow strict preventive measures is of primary concern. World Health Organization advises people to avoid contact with animals such as bats and non-primate humans during outbreaks, avoid consumption of raw meat, wear gloves and other appropriate clothes while handling animals, and adequate cooking of animal products before consumption to prevent animal-to-human transmission [48]. Similarly, the risk of human-to-human transmission can be reduced by avoiding direct or close contact with symptomatic patients of EVD, particularly their body fluids. Other preventive measures include wearing gloves and other appropriate Personal Protective Equipment (PPE) while caring for sick patients, regular handwashing after visiting sick patients, strengthening infection control practices at healthcare facilities, and avoiding sexual contact with infected persons at least for 3 months [47-48].

Zika Virus:

Zika virus is a member of the family *Flaviviridae* and genus *flavivirus* has recently attracted the attention of the medical community due to its ability to have an impact on fetal development resulting in severe neurodevelopmental abnormalities in the newborns [51]. Zika virus was first identified in 1947 in the Zika forest area in Uganda from a rhesus monkey [52]. Due to silent transmission with rare sporadic cases and the absence of severe disease, Zika virus was not in the limelight for almost 60 years. The Yap Island outbreak in 2007 has marked the resurgence in the history of Zika virus. Six years later (2013-14), a large outbreak occurred in the pacific islands. Subsequently, the virus was introduced and spread rapidly into Brazil and the Americas resulting in a larger epidemic that peaked in 2015 [53]. During May 2015–December 2016, Zika virus transmission was reported from 48 countries and territories in the Region of the Americas with more than 175,000 laboratory-confirmed cases. In the majority of the cases, the infection resulted in a subclinical or mild flu-like illness [54]. However,

there were several reports of a few complications such as congenital microcephaly and other neurologic abnormalities among infants born to mothers who were infected with Zika virus during pregnancy [55]. Additionally, Guillain-Barr Syndrome, a rare demyelinating disease was observed in a few adults and older children. On November 18, 2016, WHO declared that Zika virus and associated complications remain a considerable public health challenge requiring long-term coordinated action, but no longer represent a public health emergency of international concern [56]. Regarding the mode of transmission, Zika virus predominantly is transmitted by Aedes mosquito bites. However, recent outbreak investigations confirmed other modes of transmission such as mother-fetus, sexual contact, and blood transfusion [52].

Detection of Zika virus RNA in blood, urine, other body fluids, and amniotic fluid (for congenital infections) by RT-PCR is the investigation of choice for the diagnosis. ELISA for viral IgM in the serum is recommended for up to 12 weeks after exposure. However, all positive and inconclusive IgM-ELISA reports need to be confirmed by Plaque Reduction Neutralization Test (PRNT). Furthermore, these tests may also give rise to false-positive results in individuals who had a previous history of exposure to other flavivirus infections or vaccinated against other flaviviruses [52]. Generally, serological results are difficult to interpret in patients residing in the endemic areas and in returning travelers who had a previous history of flavivirus infection [52]. Currently, no vaccine or specific drug is available for treating Zika virus infection, and hence patients are treated symptomatically if required. The prevention basically involves measures to avoid mosquito bites, avoiding travel to endemic areas during the outbreak, and others [52].

Crimean Congo Hemorrhagic Fever:

Crimean Congo Hemorrhagic Fever (CCHF) is a widespread severe vector-borne disease caused by a tick-borne virus that belongs to the genus *Nairovirus* of the *Bunyaviridae* family [57]. The CCHF virus that causes severe viral hemorrhagic fever with a case fatality of 10-40% was first identified in the Crimea region of the former Soviet Union in 1944 and later the disease was recognized in the DRC in 1956. Hence the disease was designated with the current name as CCHF [57]. To date, CCHF has been reported from many countries of Africa, Europe, and Asia including Middle Eastern countries. Ticks, particularly of the genus *Hyalomma* serve both as reservoir and vector and the virus is maintained in nature in an endemic tick-vertebrate host-tick cycle [57]. CCHF transmits to human being either by tick bite or through contact with blood or tissues of infected animals during and immediately after slaughter. The individuals working in the livestock industry such as slaughterhouse workers, agriculture workers, and veterinarians are at high risk of acquiring the infection. Human-to-human transmission is also possible through close contact with the blood, other body fluids, and tissues of the infected person. Nosocomial infections can also occur through improperly sterilized medical equipment, reuse of contaminated medical supplies and needles [57-58]. The most recent outbreak was reported from Mali, Thailand in February 2020. A total of 20 confirmed CCHF cases, including seven deaths, were reported [59]. Laboratory tests include detection of viral RNA by RT-PCR, antigen detection by ELISA utilizing a recombinant virus N

protein. Immunofluorescence (IF) test is also available for detection of IgM/IgG antibodies, viral antigen, and recombinant protein N [60]. Patients with CCHF may also show other laboratory abnormalities such as leukopenia, elevated liver enzymes (alanine transaminase and aspartate transaminase), increased bleeding, and clotting time [60]. Regarding treatment and management of CCHF, there is no vaccine yet for its prevention, though many are under different phases of clinical trials. Ribavirin is the only antiviral drug that showed favorable results against the CCHF virus. Apart from this supportive care involving regular monitoring of the patient's hematological and coagulation status, and electrolytes and fluid level is crucial. Proper administration of fluids, platelets, RBCs, and fresh frozen plasma are necessary [60].

Influenza viruses:

Influenza is a common contagious respiratory illness caused by influenza viruses that belong to *Orthomyxoviridae* family [61]. First influenza outbreak around the world was documented in 1889. Since then, it continued as a major public health threat due to its intermittent style of pandemic outbreaks resulting in significant morbidity and mortality [62]. Fig. 3 shows the major influenza pandemics that occurred in the past. Influenza viruses are enveloped RNA viruses, possess two surface glycoprotein projections namely Hemagglutinin (HA) and Neuraminidase (NA). So far 18 HA subtypes and 11 NA subtypes have been identified. The RNA genome is segmented with 7-8 segments, each encoding for different structural and nonstructural proteins [62]. There are 3 types of influenza viruses; A, B, and C. Human influenza type A and B viruses are known to cause seasonal flu almost every year during winter months. Influenza A viruses have wide host range such as animals and birds and are associated with major pandemics due to emergence of new strains because of the phenomenon of genetic reassortment [61]. The reassortment event could occur between avian, swine, and human influenza type A viruses. Currently, information is clear that influenza pandemics occur when the new subtypes with different hemagglutinin with or without neuraminidase infect humans. Apart from reassortment, point mutation either in HA or NA is another well recognized phenomenon responsible for continuous epidemics [62]. After Spanish flu pandemic in 1918, the strain circulated continuously, triggered subsequent epidemics due to point mutation until the emergence of novel strain in 1957 (Asian flu H2N2) due to reassortment with an avian strain. Because of this phenomenon of point mutation and reassortment, world is continuously witnessing influenza epidemics and pandemics. The most recent pandemic was in 2009 (H1N1pnd09) and at present it is the common circulating strain observed. Other influenza strains that have caused epidemics in the last two decades are H5N1 and H7N9 while H1N2, H5N6, and H6N1 have been noticed in minor epidemics [63]. Avian influenza (H5N1) seen in poultry continuous to cross species barrier to infect humans and other animals and is a major threat to human health, often with fatal outcomes [62]. It is a highly pathogenic strain with a mortality rate of 60%, first identified in Hong Kong in 1997 and subsequently spread to many continents [64]. A total of 862 cases including 455 deaths (case fatality rate 53%) were reported from 17 countries from January 2003 to December 3, 2020 [65]. Another flu strain which is occurring in

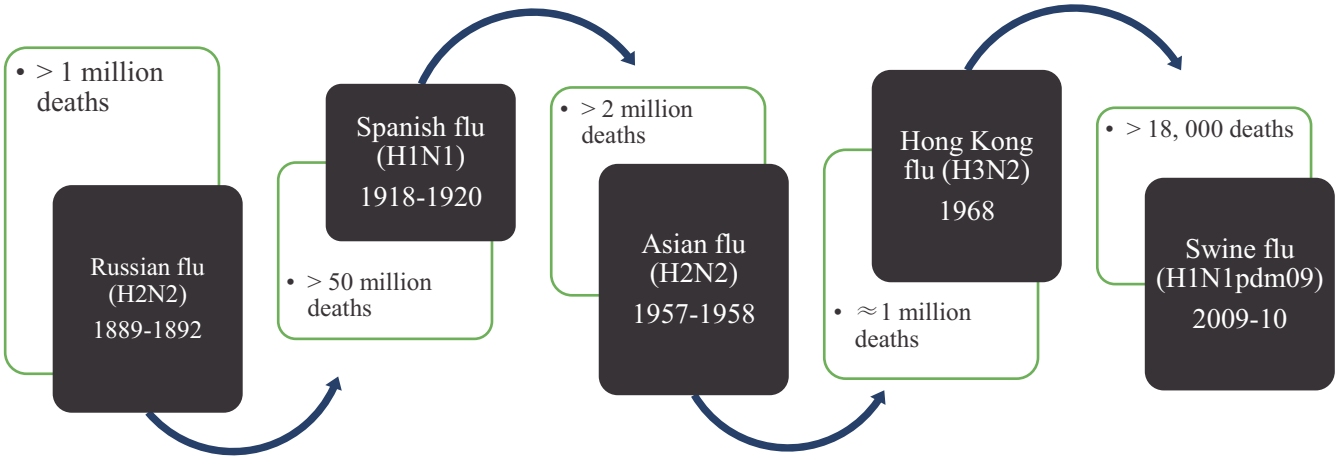

Fig. 4: Timeline of Major Influenza Pandemics in the Past

waves is H7N9. From March till December 4, 2019, H7N9 avian flu has caused six epidemic waves with approximately 1568 laboratory-confirmed cases with approximately 600 deaths [66]. The source of infection is live poultry or potentially contaminated environments, especially animal markets where live birds have been sold. The human-to-human transmission has not yet been reported [67]. Generally, influenza viruses spread mainly through contact or exposure to respiratory secretions of infected animals/birds or respiratory secretions of the infected people when they cough, sneeze, or talk. The clinical features range from asymptomatic/mild illness to severe illness, and at times can lead to death. The proportion of people who get sick from flu and the severity of the illness depend on the influenza strain responsible for it [63]. Furthermore, people of age group more than 65 years and individuals of any age with underlying chronic illness (such as asthma, diabetes, heart disease, etc.), pregnant women, and children less than 5 years are at high-risk. Therefore, season flu vaccine to all these high-risk individuals and children more than 6 months (vaccine contraindicated in infants less than 6 months) is highly recommended. Several diagnostics tests are available for diagnosis of influenza virus infection. Nasopharyngeal swab/ aspirate and bronchial aspirate are the most preferred clinical samples for diagnosis. Nucleic acid detection by molecular techniques such as RT-PCR, Immunofluorescence tests for antigen/ antibody detection, and virus culture are the common available tests for diagnosis. However, sensitivity and specificity vary from one test to another [68]. Antiviral drugs such as oseltamivir/ zanamivir/peramivir are effective in treating influenza cases. Prevention is better than cure and hence strictly adhering to hand hygiene (washing hands with soap and water/ alcohol-based hand rub); cough etiquette, avoiding close contact with sick persons, avoiding touching eyes, nose, and mouth, cleaning and disinfecting the surfaces and objects contaminated with viruses are certain simple measures to prevent the spread of infection [69].

Marburg Virus Disease:

Marburg Virus Disease (MVD)is a severe viral disease often fatal with mortality rate varying from 23-90%, depending on the outbreak [70-71]. The causative agent Marburg Virus (MARV) belongs to *Filoviridae family,* which includes five genera namely *Marburgvirus, Ebolavirus, Cuevavirus, Striavirus, and Thamnovirus* [71]. Amongst, only *Marburgvirus* or *Ebolavirus* genera are known to cause severe hemorrhagic disease in human and non-human primates [71]. *Filoviruses* possess non-segmented negative sense genome packaged within a filamentous virion [71]. Although, less known than Ebolavirus (EBV), it was the first *filovirus* identified in 1967, simultaneously in outbreaks that occurred in Germany and Serbia [72]. Subsequently, the disease was noticed in several countries of Africa. The virus was originated from fruit bats of *Rousettus aegypiacus* species of the *Pteropodidae family.* The most recent outbreak of MVD was reported in 2012 in Uganda with 15 confirmed cases and 4 deaths (CFR 27%). Human infection occurs either via direct exposure to caves inhabited by Rousettus bats or by human-to-human transmission via blood, other body fluids, and tissues of the infected people. Additionally, surfaces and materials (bedding, clothing, needles, etc.) contaminated with infected body fluids are also potential sources of infection and therefore, healthcare workers dealing with infected patients are at high risk of acquiring the infection [73]. MVD begins abruptly, with high fever, severe headache, and severe body ache. Subsequently, patients will develop severe abdominal pain, diarrhea, nausea, vomiting on the 3rd day, followed by hemorrhagic manifestation on the 5th day of illness. In fatal cases, death occurs most often after 8-9 days of onset of illness due to severe internal bleeding and shock. The laboratory diagnosis includes molecular tests, serology and virus isolation. Blood and serum are the most reliable specimens for diagnosis. Saliva (oral swab), urine, and breast milk are less reliable and are considered only if blood sample is not available [74]. Molecular techniques such as RT-PCR which provide rapid results with high sensitivity and specificity are the first line investigations for diagnosis. The main alternative tests for MHF diagnosis is viral antigen detection by ELISA [75]. Virus specific IgM antibodies appear as early as 2 days of post onset of symptoms and may persist for 1-5 months, while IgG antibodies can persist for many years. Hence IgM capture ELISA can also be used for diagnosis of acute MHF, while IgG antibody detection tests are mainly utilized for detection of past infection [74-75]. The samples of the infected patients are extremely biohazardous and hence laboratory personnel need to be extremely cautious while processing these samples. Concerning the management of MVD, there is no proven vaccine or drugs available yet. The supportive care involving rehydration with intravenous fluids and transfusion of blood products improves survival [74]. The prevention or reducing the risk of human-to-human and bat-human transmission is of primary concern and it involves wearing gloves and other PPE, avoiding caves inhabited by bats, thorough cooking of animal products before consumption during outbreaks [74].

West Nile Virus:

West Nile Virus (WNV) encephalitis is an arthropod-borne disease, distributed globally and maintained by a complex transmission cycle involving multiple species of birds and mosquitoes [76]. The causative WNV is an RNA virus that belongs to *Flaviviridae family*. It was first identified in 1937 in Uganda but was first discovered in New York, United States in 1999 [77]. At present, WNV infection is the most important zoonotic diseases of concern in the United States [78]. Since its emergence in 1999, over 50,000 cases with more than 25,000 neuro-invasive cases and 2390 deaths have been reported from the United States [79]. WNV is also significantly pathogenic to animals and birds and has resulted in over 28,000 equine cases and mortality in around 300 bird species [76, 80]. In addition to arthropod-borne transmission, reports suggest the possible transmission of WNV through blood transfusion, organ transplantation, and mother-to-child through breast milk [77]. Generally, infected patients are asymptomatic or show mild self-limiting illness characterized by fever, headache, body ache, skin rash, and enlarged lymph nodes. However, in a small percentage of elderly and immuno suppressed patients, it may lead to fatal encephalitis with a case fatality rate of 1-2% [77]. Laboratory diagnosis mainly involves the detection of specific IgM/IgG antibodies in serum and spinal fluid. Detection of viral RNA by RT-PCR and virus isolation from body fluids and tissues collected during the early course of the infections are the other available investigations [77]. No vaccine or specific antiviral drugs are available. In severe cases, hospitalization and supportive care such as intravenous fluids, nursing care, and pain management is often needed. Prevention mainly involves taking measures to avoid mosquito bite such as using mosquito repellent, wearing long-sleeved clothes, and control of the mosquito population by insecticide sprays indoors and outdoors [77].

Hantaviruses:

Hantaviruses are single stranded negative sense RNA viruses, belong to family *Bunyaviridae*, genus *Orthohantavirus* and are the causative agents of two types of human diseases namely Hantavirus Pulmonary Syndrome (HPS) in Americas and Hemorrhagic Fever with Renal Syndrome (HFRS) in Euroasia [81]. HPS is a Pan-American emerging disease characterized by fever and respiratory syndrome. The disease is often fatal with a mortality rate ranging 35% to 50% [81]. The causative virus was first identified in 1993 in an outbreak illness of unexplained pulmonary syndrome that occurred in the southwestern United States [82]. The Sin Nombre Hantavirus is responsible for the majority of cases of Hantavirus infection in the United States and Canada. Based on national surveillance data collected by the National Notifiable Diseases Surveillance System (NNDSS), as of January 2017, around 728 laboratory-confirmed cases of Hantavirus diseases from 36 states of United States with 36% confirmed deaths have been reported [82]. The latest outbreak of HPS was reported from Los Santos Province, the Republic of Panama in 2018. As per the report of Pan American Health Organization / World Health Organization (PAHO/WHO), there were 48 cases of HPS,

including 4 deaths between January-December 2018 [82]. The reservoirs of Hantavirus causing HPS are certain species of rodents (cotton rats, rice rats, deer mice) and the virus is excreted in the urine, saliva, and droppings of the infected rodents. Human transmission occurs through inhalation of dust contaminated with rodent droppings or by direct contact with urine, droppings, and saliva of infected rodents. Human-to-human transmission is unlikely [83]. Initially patient develops non-specific symptoms such as fever, headache, malaise, and body ache, making it difficult to diagnose early. Subsequently, the patient will develop signs of HPS (usually 4-10 days after the initial phase of illness) characterized by cough, difficulty breathing, respiratory distress, and eventually, death occurs due to respiratory failure if treatment is delayed. Therefore, early diagnosis and treatment are crucial to reducing the death rate. Any patient with a history of exposure to rodents and presenting with fever, headache, myalgia, and shortness of breath should be suspected of HPS. Currently, there is no specific treatment, cure, or vaccine for HPS. However early diagnosis, hospitalization, and treatment with intubation and oxygen therapy would help to recover from respiratory distress and increases the survival chances of the patient [83].

Lassa Fever:

Lassa fever is a zoonotic disease characterized by acute hemorrhagic illness like Ebola and Marburg-virus disease, but comparatively less severe [84]. The disease was first described in 1969 in Nigeria [85]. The causative agent, Lassa virus is a single stranded RNA virus from the family *Arenaviridae* [86]. The reservoirs are rodents, particularly *Mastomys natalensis* (multimammate rats). The disease spreads to humans particularly through exposure to urine or feces of infected rodents [86]. Lassa fever may also spread through contact with body fluids of infected person; hence, healthcare workers are at high risk of acquiring the infection when the standard precautions for infection prevention and control are compromised [84, 86]. Lassa fever is endemic in the rodent populations in several countries (Sierra Leone, Guinea, Liberia, and Nigeria) of West Africa. Some studies have reported, Lassa fever virus infections per year in West Africa is estimated at 100,000 to 300,000 with approximately 5,000 deaths [87]. As per the latest report from Nigerian CDC, there were approximately 1163 laboratory confirmed cases of Lass fever in Nigeria including 241 deaths with a case fatality rate of 20.7% in the year 2020 [84]. In Nigeria, the annual peak of Lassa fever cases is observed in the months of December–April, and the number decreases around May [88]. Fatal outcomes in Lassa fever were more commonly seen in elderly and in those who have not received ribavirin therapy [86]. Approximately 80% of Lassa fever cases are mild and asymptomatic and are usually undiagnosed [87A]. The clinical features of Lassa fever are generally nonspecific and includes fever, fatigue, hemorrhaging, gastrointestinal symptoms such as stomachache, vomiting, and diarrhea, respiratory symptoms such as cough, chest pain, and dyspnea, and neurologic symptoms like disorientation, seizures, and unconsciousness. Case fatality rate was estimated to be 15-20% [86]. With respect to the diagnosis, laboratory specimens are hazardous and must be handled with extreme care, and testing is usually

done in reference laboratories. The definitive diagnosis is by detection of viral RNA in clinical specimens by molecular tests such as RT-PCR. Other available tests for diagnosis of Lassa fever are ELISA, antigen detection, and virus isolation in cell culture. The antiviral drug ribavirin was found to be beneficial if started early in the course of illness. Currently, there is no vaccine to prevent Lassa fever. Therefore, prevention relies on promoting good hygiene in the community such as adequate rodent control measures. In healthcare settings, staff must always adhere strictly to standard infection prevention and control measures such as basic hand and respiratory hygiene, safe injection practices, and use of personal protective equipment when caring for patients irrespective of their presumptive diagnosis. During outbreaks, one should give additional importance to safe burial practices [89].

Conclusion:

In the modern era of globalization, the emergence, and re-emergence of viral diseases is a continuous problem and is a serious concern for human health and economy. The viruses, especially RNA viruses have the ability to undergo rapid genetic change resulting in the emergence of novel or variant strains which have a potential to cause epidemics and pandemics. The common factors contributing to the genetic variations are the presence of error-prone RNA polymerases, mutation, genetic assortment, and recombination. In addition, the lack of herd immunity, unavailability of vaccines to most of the RNA viruses, and the ability of the viruses to adapt to rapidly changing global and local environment such as urbanization, climate changes, rapidly increasing population growth, international travel, deforestation, etc., are the key factors for the emergence and spread of viral diseases across the world. Recent advances in molecular technology have enabled us to understand the evolution of emerging virus due to changes at nucleotide and protein levels. Mutations in structural and non-structural proteins of virus increase its host range and may result in a non-human virus to cause infections in human beings. The majority of emerging and reemerging viral diseases are zoonotic (animals and birds) and vector-borne (mosquitoes, ticks, etc.) and several ecological, sociological, and changing environments have led to their emergence. Therefore, the development and implementation of effective prevention strategies for emerging and re-emerging viral diseases involves the teamwork of expertise from different fields such as doctors, biologists, environmentalists, and ecologists to understand factors contributing to the evolution of emerging viruses and their pathogenic mechanisms. Furthermore, human-to-human transmission in most of the emerging and reemerging viral diseases is because of inadequate hand hygiene and other infection control practices. Therefore, it is advised to strictly adhere to appropriate infection control practices such as hand washing with soap and water or alcohol rub, use of personal protective equipment, social distancing, and others.

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