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Viral Outbreaks of SARS-CoV1, SARS-CoV2, MERS-CoV, Influenza H1N1, and Ebola in 21st Century; A Comparative Review of the Pathogenesis and Clinical Characteristics

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ABSTRACT

Throughout the past twenty years, humankind had its fair share of challenges with viral epidemics. In late December 2019, a zoonotic member of the coronaviruses, was responsible for the COVID-19 outbreak of viral pneumonia in Wuhan, China. As a worldwide crisis, meanwhile a conclusive prevention or therapy has yet to be discovered, the death toll of COVID-19 has exceeded 278000 by May 11th 2020. Alike other members of Coronavirus family such as MERS and SARS-CoV-1, SARS-CoV-2 provokes influenza-like syndrome which might further progress to severe state of acute respiratory disease in some patients. Comparably, in 2009 the H1N1 influenza outbreak affected countless people by manifestations of respiratory system involvement. Additionally, Ebolavirus, as a member of Filoviridae family, had also made a global catastrophe by causing hemorrhagic diseases in the past twenty years. The unknown intrinsic nature of SARS-CoV-2, as a great missing piece of this pandemic puzzle, has had physicians to empirically test the possibly efficacious agents of the former viral epidemics on the COVID-19 cases. Here, the current knowledge in SARS-CoV-2clinical features, transmissibility, and pathogenicity are all summed up as against the other emerging viruses in the last two decades, and the data crucially required for a better management of the illness has been spotlighted.

INTRODUCTION

A new fatal infection referred to as severe acute respiratory syndrome (SARS) was identified as a major threat to public health at the start of this century [1]. Ensuingly, near a decade after the original SARS report, occurrences of another abnormal respiratory disorder triggered worldwide alarm in 2012. The illness was known as Middle East Respiratory Syndrome (MERS) and became much more deadly than SARS [2]. Both the causal viruses of the SARS and MERS outbreaks were members of the Coronavirus family [3]. Big groups of influenza-like syndrome cases were identified in Wuhan province, China at the end of December 2019 [4]. History has now recurred with the advent of a new Chinese outbreak at the end of 2019. A novel coronavirus (SARS-CoV-2) has been described as the etiologic factor for this respiratory disorder named COVID-19. In total, SARS, MERS and COVID-19 are triggered by newly identified coronaviruses that induce flu-like disease, albeit with a tendentially more serious clinical result. After near 4 months of COVID-19 pandemic, the number of people afflicted with COVID-19 has exceeded 4 million, and more than 278000 cases have died up until May 11th, 2020. The 2009 H1N1 flu pandemic, much like the clinical manifestation and spreading of COVID-19, affected individuals, involving their respiratory tracts, through droplets and contacts between humans [5]. In addition, Ebola Virus Disease (EVD), another viral epidemic that a family member of Filoviridae first gave birth to in 1976, became the greatest epidemic in 2013 leading to hemorrhagic fever and fatality in countless individuals [6]. In the present review, we seek to evaluate our present knowledge about the 21th century viral outbreaks of SARS-CoV-1, SARS-CoV-2, MERS-CoV, H1N1 influenza, and Ebola in terms of epidemiology, pathogenesis, and clinical futures in order to identify the characteristics of the enigmatic novel coronavirus.

SARS-CoV-1

Coronaviruses, a category of viruses, are the reason for a large

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proportion of all common colds in both children and adults. Four coronaviruses that are specific to humans, comprising 229E and NL63 as alpha coronaviruses and HKU1 and OC43 as beta coronaviruses are widespread and usually provoke common cold presentations in human [7]. The SARS, as a member of coronavirus family, is thought to have moved from animal hosts to human hosts in livestock markets of certain cities in Guangdong province in southern China in mid-November 2002 [7]. SARS-CoV-1 causing SARS has a particular pathogenesis, since it induces infections of the upper and lower respiratory tract. Patients first experience prodromal flu-like manifestations with symptoms such as rigors, headache, malaise, and fever. But there hasn't been any particular symptom or group of symptoms shown to be specific. While the history of being febrile is the most commonly recorded feature, it can be missing from initial speculation. Coughing, shortness of breath, and diarrhea may occur in the first 7 days of the disease, but in fact are noted most frequently in the second week [8]. Up to 70 percent of cases at this point experience diarrhea, which has been identified as watery and abundant without mucus or blood [9]. Extreme cases aggravate by the end of the second week, which quickly develop progressive respiratory problems, while around 20% of them might need intensive care [10]. Laboratory features comprise raised creatine kinase and alanine aminotransferase (AAT) (30%), thrombocytopenia (45%), and lymphopenia (70%) [11]. The accessible pathology

Table.1: Epidemiological comparison of SARS-CoV1, SARS-CoV2, MERS-CoV, Influenza H1N1, and Ebola viral outbreaks.

	Family	Period of outbreak	supposed animal host	Most common transmission	Most afflicted countries	Current status	R0	Incubation period (days)
SARS-CoV-2 [21]	Coronaviruses	2019-Wuhan, China	Bat	Touching infection /human-human close contact	global (China, US, Italy)	Almost all countries are afflicted	2.5-5.7	5-14
SARS-CoV-1 [7]	Coronaviruses	2002-China	Bat to Civet cats to humans	human-human close contact	China, Canada, Hong Kong, Taiwan, Singapore, Vietnam	Some cases are still reported, commonly in China and Hong Kong	2-5	2-7
MERS [41]	Coronaviruses	2012-Saudi Arabia	Camel	Touching infected camels/infected meat or milk consumption	Saudi Arabia, Mostly middle-east	Some cases are still reported, Mainly Saudi Arabia	<1	2-14
Influenza H1N1 [52]	Orthomyxoviridae	2009-North America	Swine	Droplets from coughs and sneezes of infected people, fomites	A current re-emergence of the virus was reported in 2019	A current re-emergence of the virus was reported in 2019	1.2-1.6	1-4
Ebola [6]	Filoviridae	2014-Guinea	Bat to Gorillas to humans	Direct Contact with an infected animal's and person's bodily fluids	Some cases were reported sporadically in 2019 summer in Uganda and Goma	Some cases were reported sporadically in 2019 summer in Uganda and Goma	1.5-2.5	2-21

SARS-CoV: Severe Acute Respiratory Syndrome- related Coronavirus, MERS: Middle East Respiratory Syndrome, R0: Basic Reproduction Number, indicating expected number of cases directly generated by one case in a population where all individuals are susceptible to infection, US: United States

details for SARS-CoV-1 infection have been mainly collected from autopsy procedures. The macroscopic alterations in fatal patients of SARS-CoV-1 were edematous pulmonary tissues with elevated gross weights and numerous congestive zones, lymph node enlargement in abdominal cavity and the hilum of lung, as well as a decrease in spleen's weight and size [1, 12]. Significant amounts of SARS-CoV-1 genomic sequences and particles have been found inside lymphoid tissues, circulating monocytes and lymphocytes, as well as within brain neurons, renal distal tubular epithelial cells, mucosa of intestine, airway epithelium, and tissue-resident macrophages of specific organs [13]. Co-location of cellular cytokeratin and SARS-CoV-1 RNA inside pulmonary tissue was demonstrated by immunofluorescence in situ hybridization, suggesting that pulmonary cells have become infected. In addition, SARS-CoV-1 can sometimes be found in the alveolar macrophages within lungs [14]. Large-scale lung injury in SARS-CoV-1-infected cases tends to be correlated with elevated initial viral load, increased plasma pro-inflammatory chemokines and cytokines, high levels of neutrophil, macrophage, and monocyte infiltration in the lungs [15, 16]. Research on alterations in inflammatory profiles in the course of SARS-CoV-1 infection, have shown elevated levels of circulating cytokines, such as interleukin types of 6 and 8 as well as C-X-C motif chemokine and TNF-alpha which possibly will lead to adverse prognosis in SARS-CoV-1 [17]. Moreover, high serum levels IL-1, IL-12, TGF-β, IFN-γ, and CCL2 were observed in SARS cases with serious disease relative to uncomplicated SARS cases. [14, 18, 19]. The magnitude of the illness is oftentimes a significant indirect element in the capacity of the virus to transmit. Since coronaviruses have RNA-dependent polymerases that are susceptible to errors, recombination events and mutations often take place, which results in quasi-species variability; something that is strongly related to adaptive evolution and disease-causing capacity [20].

SARS CoV-2

The COVID-19 outbreak emerged in the winter on a local seafood market, in circumstances comparable to SARS's. In fact two thirds of the initial 41 reported cases have been listed as having ties to the Huanan Seafood Wholesale Market [21]. On 11th march 2020 WHO declared the outbreak of COVID-19, a pandemic [22]. Almost all nations have been challenged with the disease, because of which overall more than 4 million people have been afflicted and 278892 cases have died worldwide until May 11th, 2020 (See Table.1). Roughly after one month from the start of the SARS-CoV-2 outbreak, many clinical and virological elements of the COVID-19 are still under evaluation. The SARS-CoV-2 genome was sequenced very early in the course of the outbreak [23]. This provided for the accelerated production of real-time RT-PCR diagnostic tests uniquely for SARS-CoV-2at the point of patient treatment [24]. In fact the causative virus of 2019 outbreak was called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), regarding its genomic resemblance to the SARS virus [25]. The genetic sequencing study divulged that the novel corona viruses belong to the group beta-coronavirus, with MERS-CoV nucleotide identification at 51.8 percent and SARS-CoV nucleotide identification at 79.0 percent [26]. In addition, nCoV-2019 has been recorded to be 96 percent similar to a bat coronavirus in terms of the entire genetic content [27]. Reportedly, SARS-CoV-2uses the same cell entry receptor, ACE2, to infect human hosts as SARS-CoV [28], therefore the clinical overlap between the two viruses may be anticipated especially in extreme cases. Of note, there are certain evidence that suggest SARS-CoV-2infection has had a clustering onset which tends to impact elderly people with comorbidity and may contribute to serious respiratory symptoms along with other acute organ injuries [29, 30]. It is now very obvious that an effective human-to-human transmission exists and it's indeed a requisite for the extensive SARS-CoV-2distribution [21]. The main clinical signs of SARS-CoV-2infection at the prodromal level include fatigue, dyspnea, dry cough, and nausea [29, 31, 32]. Numerous cases have developed lymphopenia as well [33]. The majority of documented patients, asymptomatic ones included, were presented with abnormal chest CT findings such as ground glass opacity or consolidation [34]. Early concentrations of, IL-1, IL-7, IL-8, IL-9, IL-10, VEGF, TNF-α, PDGF, IFNγ, GMCSF, GCSF in plasma were greater among SARS-CoV-2cases as against healthy controls. Furthermore, ICU-admitted cases demonstrated greater levels of TNF-α, GSCF, IL-10, IL-7, and IL-2 in plasma, compared to non-ICU-admitted cases [35]. Similar to SARS-CoV-1, respiratory droplets can transfer the novel coronavirus directly from one person to another, while evolving data indicates it might even be spread by touch and fomites. In addition, it was reported that the asymptomatic incubation period for people afflicted with SARS-CoV-2varied from 1 to 14 days, longer than that for SARS-CoV-1. However it stays unclear whether asymptomatic individuals have sufficiently high viral load to spread the viral particles, great focus should be given to minimizing associated risks [36]. The basic reproduction number, which is normally signified by R0, is a very critical threshold quantity correlated with viral transmissibility. The epidemiologic concept of R0 is defined as the total number of people getting the disease from one infectious individual [37]. This refers explicitly to a group of non-vaccinated individuals that have earlier been healthy. There are three possibilities for the possible propagation or regression of a disease, based on its R0 value: 1. If R0 is bigger than 1, number of cases may rise exponentially and trigger an outbreak or even a pandemic. 2. If R0 is equal to 1, the disease will remain alive, but there will be no epidemic. 3. If R0 is less than 1, every current infection can cause less than 1 new infection; in this scenario, the number of cases will decrease and the illness will ultimately vanish(37). Based on what we've learnt by now, the estimated R0 value for SARS-CoV-2is substantially greater than 1[38]. Sanche S. and others, in the early stages of the epidemic, calculated the mean R0 for SARS-CoV-2to be 5.7 [39], greater than those of MERS-CoV and SARS-CoV-1. (See Table.1) In SARS-CoV-2transmission, such as those in MERS-CoV and SARS-CoV-1, super-spreading incidents were involved, but their relative significance has been still uncertain and the super-spreaders have been challenging to map.

MERS-CoV

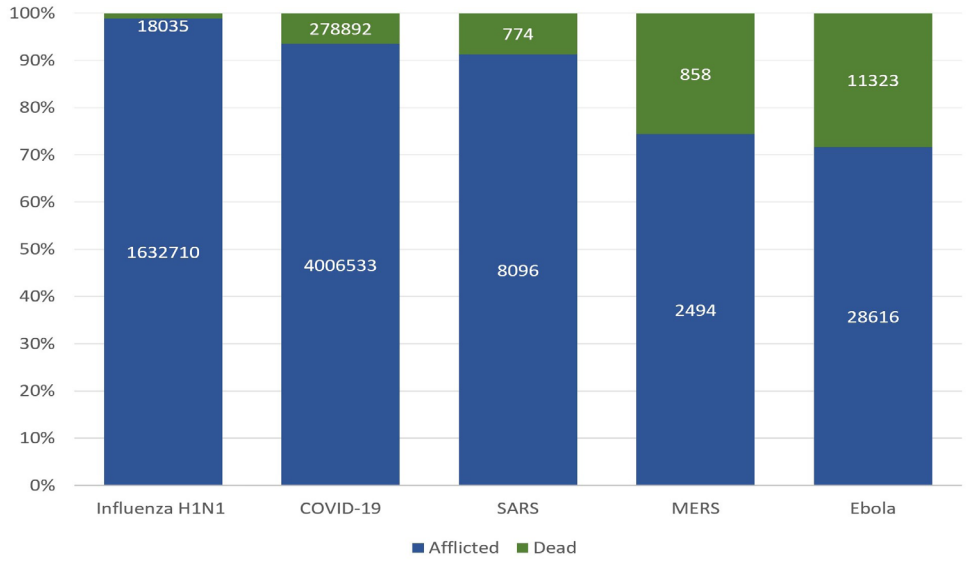
On 13th June 2012 the first MERS-CoV patients in Saudi Arabia, particularly Jeddah, were announced [40]; following this outbreak, coronavirus continued to propagate abroad to multi-

ple American, European, African, and Asian countries. In the course of this outbreak, the majority of patients were in fact reported in Middle Eastern nations; including countries within the Gulf, along with Egypt, Palestine, Lebanon, Syria, and Jordan. [41]. MERS-CoV's mean incubation period is 5 to 7 days but a range of 2 to 14 days has also been recorded [42]. The whole clinical gamut of the disease varies from severe multi-organ failure disease, moderate disease, to completely asymptomatic. Clinical manifestations might include dyspnea, coughing, fatigue, myalgia, rigors, fever, and chills in a symptomatic case. Gastrointestinal presentations such as abdominal pain, nausea, and emesis, can occur either as a separate main complaint or as a part of the upper respiratory syndrome. It should be noted that at the time of presentation pneumonia is normal(2). Extreme infection takes place particularly in older patients with comorbid conditions, presenting with shock, severe renal, and respiratory failure. The average gross fatality rate is 35 percent and 20 percent in primary cases and secondary cases respectively [43]. Pathophysiological modifications induced by MERS-CoV actually depend on the small numbers of biopsy and autopsy procedures. MERS-CoV infection targets specific cells in the lung which are bronchial submucosal cells, multinucleated epithelial cells and pneumocytes [44]. In terms of ultrastructure, viral particles have been discovered in renal epithelial cells and skeletal muscles infiltrated macrophages, as well as pulmonary macrophages and pneumocytes. The entrance receptor of MERS-CoV, Dipeptidyl peptidase-4 (DPP4), has been commonly distributed on the surface of epithelial cells in the prostate, liver, small intestine, alveoli, kidneys, and activated leukocytes [45, 46], Consequently, MERS-CoV has been shown to be capable of infecting multiple human immune cells, considering T-type lymphocytic cells, macrophages, and dendritic cells [47]. Robust and continuous development of pro-inflammatory chemokines and cytokines results in MERS-CoV infections of macrophages and dendritic cells. MERS-CoV T-cell infections contribute to apoptosis induced by a mixture of endogenous and exogenous apoptotic pathways [48]. Besides, it has been stated that MERS-CoV could cause apoptosis of the lung and kidney cells [49]. Of interest, MERS-CoV has not changed substantially since it first emerged, which may be attributed to the fact that the specific cellular receptor (CD26) used by MERS-CoV is rather exclusive, meaning that the virus has a quite restricted ability to mutate without sacrificing fitness. Previous experiments, on the other hand, have shown that SARS-CoV-1 has evolved during the 2002 to 2004 outbreak to a better binding to its cellular receptor, and a more extensive replication in human cells, thereby amplifying virulence [50].

Influenza H1N1

Three big influenza pandemics happened in the last century: 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). The most severe influenza pandemic in modern times remains the 1918 Spanish flu, which infected more than 50 million people around the globe [51]. The influenza pandemic of 2009 that started in both the U.S. and Mexico was caused by a novel swine influenza strain, (H1N1). Many incidents have happened for young adults with nearly 60 percent of recorded cases in the United States having happened for individuals 18 years of age or younger [52]. The explanation for the rise in attack rates in younger individuals is not fully clear, although it has been reported that adults, particularly those born since 1957, have low levels of cross-reaction neutralizing antibodies, possibly due to repetitive exposures to seasonal H1N1 viruses [53]. Reverse transcriptase PCR was considered as the standard procedure for the detection and confirmation of influenza A infections during pandemic 2009. Approved PCR tests for hospital laboratories indicate that the specimen is positive for influenza A but negative for seasonal H3 and H1 viruses [54]. The clinical features in patients diagnosed with the 2009 influenza A pandemic virus were close to the normal influenza manifestations which involve myalgia, chills, rhinorrhea, sore throat, headache, cough, and

Figure.1 Mortality rate comparison of COVID-19, SARS, MERS, Influenza H1N1, and Ebola viral outbreaks.



fever [53]. Around one in 10 patients diagnosed with the 2009 influenza A(H1N1) pandemic virus needed hospitalization. The overwhelming majority of patients who were admitted had chronic disorders such as diabetes, asthma, neurological and respiratory disorders, and pregnancy [55]. Thrombocytopenia, anemia, and Leukopenia, follow the above-mentioned signs and symptoms in approximately 20–30 percent of cases [56]. The trachea and main bronchi have demonstrated necrosis and desquamation of infected mucosal epithelium and edema along with mixed inflammatory penetration in the underlying submucosa, in a pathological view of infected cases [52, 57]. The glands in certain airways display depletion of contaminated goblet cells and underlying submucosal necrosis. In such cases the lung parenchyma has demonstrated alterations associated with the various phases of diffuse alveolar injury [57]. Infected pneumocytes have demonstrated reactive modifications, which can desquamate into alveolar spaces which are observed in tandem with infected inter-alveolar macrophages (58). Erythroid phagocytosis and Intra-alveolar hemorrhage were also reported. When mortality occurs weeks after the start of symptoms, a large distribution of fibroblasts can be seen as well [59].

Ebola

Twenty-four outbreaks of Ebola virus disease (EVD) were confirmed between 1976 and 2014, mainly provoked by Zaire Ebola virus (ZEBOV) in Equatorial Africa [60]. As shown in figure 1 most epidemics were small, but the virus caught the world's attention due to mortality levels as high as 90 percent as well as the horrific way it kills [61]. The EVD epidemic in West Africa in 2014 induced by ZEBOV is the deadliest, longest, most large-scale, and most complicated in history. Ebola is a public health threat as it can be transmitted fairly quickly, particularly in a hospital environment where adequate protective measures are not taken, and it is almost always lethal ((6). EVD may be spread between humans by close interaction with body fluids from the infected individuals or fomites. Despite aerosol infection has been demonstrated in experimental models in monkeys, it has not been clinically documented [62]. One reason behind the fact that Ebola is so deadly is that its signs differ and indeed manifest rapidly, but at the same time the presentations are so close to those of other viruses that hemorrhagic fever is not easily detected [63]. Most research have recorded that the incubation period ranges from six days to ten days for percutaneous and touch exposure respectively [64]. Step I of the disease, which can be described as transmitting EBOV from animals bearing the virus to humans, typically by minor skin lesions. During Ebola outbreaks same specific concepts refer to human-to-human transmission. Phase II is described as an early symptomatic stage (usually 4 to 10 days) where signs of viral illness emerge and slowly develop into more advanced manifestations of the disease. Eventually, phase III is severe Ebola virus fever, with hemorrhagic presentations, deficient immune system, and end-organ failure [64, 65]. Since reaching the body via cracks in the skin, mucous membranes, or parenterally, the Ebola virus infects several specific kinds of cells. Dendrite cells and macrophage have been usually the first ones to be infected; filoviruses quickly multiply within these common sentinel cells, inducing their necrosis and releasing vast amounts of newly created viral particles into extracellular fluid [66]. Inhibition of interferon-type 1 responses which is caused by virus, supports the rapid systemic spread. Affected animal necropsies have demonstrated that certain kinds of cells (except neurons and lymphocytes) can be affected, including adrenal epithelial cells and cortical cells, as well as hepatocytes, fibroblasts, and endothelial cells [67]. Clinical manifestations generally start with abrupt flu-like presentations such as rapidly advancing fever, muscle ache, and headache, which are shortly accompanied with hematemesis, Hematochezia, rashes on the body, conjunctivitis, dysphasia (having difficulty swallowing), erythematous mucus of the oral cavity, back pain, arthralgia (neurologic pain of joints), abdominal pain, malaise, anorexia (loss of appetite), nausea and vomiting [6, 65]. Usually, several days later, between 5 to 7 days after the first presentations patients will start bleeding from the mouth, nose, or eyes. A hemorrhagic rash can appear across the body, which often bleeds [68]. Possible laboratory indicators of Ebola virus disease include a decreased platelet count; a primarily reduced white blood cell count succeeded by an elevated white blood cell count; increased levels of the liver enzymes; and dysfunctions in blood coagulation such as a bleeding time, partial thromboplastin time, and prolonged prothrombin time which usually happen in accordance with disseminated intravascular coagulation (DIC)[69]. EVD detection is verified by virus isolation and finding antibodies for the virus in an individual's blood. The detection of the virus by cell culture, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay (ELISA) are all means which are best put into use in the initial stages of the illness, and also in the detection of virus in human remains [70]. The most effective identification of anti-viral antibodies occurs in the latter phases of the illness and among those that survive. IgG and IgM antibodies can be detected 6-18 days and 2 days after the onset of the symptoms respectively [71]. Like the other viral disease described earlier, data indicates that viral load, confusion, coma, chest pain, and age are correlated with the EVD prognosis, in which viral load can be one of the most prominent factors for the survival from Ebola [72].

Conclusion

The thoroughly detailed lessons learnt from the outbreaks of SARS-CoV-1, MERS-CoV, Influenza H1N1, and Ebola include useful observations and perspectives into how to battle the SARS-CoV-2 pandemic. Drugs that prevent viral transmission may reduce the immediate cytopathic impact of coronavirus, and therapies that suppress inflammatory responses of the host, preferably only in the respiratory tract, minimize immunopathology caused by the viruses. We conclude that the most efficacious clinical approach for more severe human coronavirus infections will be a mixture of these therapies. Although, we must bear in mind that no effective antiviral therapy is currently accessible for SARS, MERS, and SARS-CoV-2, and thus more work into the pathogenesis of human coronavirus infection is indeed necessary in order to establish appropriate therapeutic targets. Furthermore, since anti-coronaviral medicines and vaccinations are still under evaluation, the fear has an undeniable role in the social and economic effects of the outbreak of SARS-CoV. Therefore, it will be necessary to educate the communities and

to reinforce public trust. Providing that the spread of the virus from one human to another can be significantly and reliably disrupted (R < 1), it is highly probable that the disease can be in fact managed and perhaps even eradicated.

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