

Last Four Decades' Viral Pandemics

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The last four decades have witnessed some of the deadliest viral pandemics with far-reaching consequences. These include the Human Immunodeficiency Virus (HIV) (1981), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (2002), Influenza A virus subtype H1N1 (A/H1N1) (2009), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (2012), Ebola virus (2013) and the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (2019-present). Age- and gender-based characterizations suggest that SARS-CoV-2 resembles SARS-CoV and MERS-CoV with regard to higher fatality rates in males, and in the older population with comorbidities. The invasion-mechanism of SARS-CoV-2 and SARS-CoV, involves binding of its spike protein with angiotensin-converting enzyme 2 (ACE2) receptors; MERS-CoV utilizes dipeptidyl peptidase 4 (DPP4), whereas H1N1 influenza is equipped with hemagglutinin protein.

[COVID-19](#)[Ebola](#)[HIV](#)[influenza](#)[SARS-CoV-2](#)

1. Introduction

Since time immemorial, mankind has been in a constant quest to overcome the threat of infectious diseases. The last 40 years has been no exception, as the world witnessed the emergence and reemergence of viral outbreaks, of which Human Immunodeficiency Virus (HIV) in 1981, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, H1N1 influenza virus in 2009, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, Ebola virus in 2013 and the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in 2019-present, are noteworthy ^{[1][2][3][4]}. Emergence of infectious diseases directly impact human health outcomes paving the way to impaired sustainable development ^[5]. An estimated 34.3 million people worldwide were living with HIV/Acquired Immune Deficiency Syndrome (AIDS) by the end of 20th century ^[6]. The epidemic left millions of children orphaned, disrupted social life and eroded civil order and economic growth, too ^[7]. The consequences of SARS-CoV epidemic were fatal, affecting about 8098 people resulting in 774 deaths by February 2003 ^[8]. However, the outbreak identified a number of shortcomings in hospitals and community control systems in many of the affected regions ^[9]. The 2009 H1N1 influenza pandemic also had far-reaching consequences on global health, which impacted over 214 countries and caused over 18,449 deaths. With a persistent threat from earlier influenza epidemics, the scientific communities were much more prepared in mindset and infrastructure, which allowed for rapid and effective research on basic scientific aspects of the disease, with impacts on its control and lessons for future epidemics ^[10]. MERS-CoV, another coronavirus outbreak, had a very high case fatality rate among the recent pandemics, which is about 43% ^[11]. More recently during 2013–2016, the Ebola viral disease has been one of the largest of its kind in history which resulted in a huge public health menace with large-scale social and

economic impact in the affected countries. This outbreak also presented opportunities for research that might help national and global healthcare systems to better prepare for future outbreaks ^[12].

As a new decade begins, the world engages in fighting to contain another novel virus of pandemic proportions, named SARS-CoV-2, which causes Coronavirus Disease 2019 or COVID-19. It represents one of the greatest public health emergencies in human history. The virus was first detected in December 2019 and isolated from several workers of the Wuhan seafood market in China who were suffering from pneumonia ^[13]. Shortly thereafter, the World Health Organization (WHO) declared it a global pandemic on 11 March 2020 ^[14]. SARS-CoV-2 is highly contagious and has currently spread across 220 countries and territories of the world ^[15]. As of 11 December 2020, SARS-CoV-2 infections have been confirmed in approximately 68.4 million people worldwide, of which about 45 million people have recovered from the virus and more than 1.5 million have succumbed to it. According to these statistics, the recovery and death rates of this disease are about 65.60% and 2.28%, respectively ^[15]. At present, supportive therapeutic strategies and mitigation measures to contain the virus remain the best weapons in the fight to control COVID-19. However, scientists around the world are striving to develop vaccines via accelerated processes in order to confer immunity to the public against the virus .

2. Gender- and Age-Based Differences in the Susceptibility to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Infection in Comparison with other Viruses

Males and females of different age groups often vary in their general response to these viruses. A statistical disparity in the prevalence of disease based on age and gender has been established in many viral outbreaks. During the SARS epidemic of 2002, patients below 25 years of age tended to present with mild to moderate illness, whereas those above 60 years of age had a mortality rate of more than 50% and presented with more severe symptoms ^{[16][17]}. In addition, epidemiological studies showed that males had higher fatality rates compared with that of females (21.9% versus 13.2%, respectively) ^[18]. Similarly, data from the MERS-CoV outbreak of 2012 showed that patients in the age groups of 45–59 years and above 60 years were more likely to be infected, suffer from more severe symptoms and have higher fatality rates compared with younger adults. Furthermore, the disease occurrence in males was higher than that in females, with fatality rates of 52% and 23%, respectively ^[19]. Another study also reported that among the confirmed cases of MERS-CoV, the male–female ratio was approximately 2:1 (67% male and 35% female) with highest prevalence of infected cases (41.2%) seen in the age group of 41–60 years ^[20]. Variations in disease prevalence among men and women may be attributed to the differences in cultural roles and gender norms that influence risk for contracting the disease. Women are more likely to employ themselves in essential services like healthcare and service industries compared to men ^[21]. However, men predominate in other sectors such as construction work and cleaning, security work, taxi services and low-skilled social care ^[22]. Although women are more proactive about their health when compared with men, they frequently receive less intensive diagnostic and treatment interventions, with women's symptoms often being overlooked or assumed to be psychosomatic in many societies ^[23]. Viruses other than those in the family Coronaviridae include the H1N1 virus, which caused a pandemic in 2009 and primarily affected children and young

adults of reproductive age, with the highest attack and hospitalization rates in individuals between the ages of 0 and 40 years [24]. The male-to-female morbidity ratio is more than one for this disease, suggesting that men are more susceptible to the H1N1 virus [25]. This may also be due to the differences in gender-based social stratifiers which influence the patterns of exposure to pathogens, vulnerability to illness and outcome of illness resulting in differences in incidence, duration, severity and fatality rates [26]. The likelihood of exposure to H1N1 virus was more in healthcare workers and people who work with children, professions predominantly employing women. Differences in health-seeking behavior may also have significant impact on acquisition and manifestation of Influenza A. In most of the developing countries the quality of care received by women has mostly been compromised and has not been as good as that received by men [27]. The knowledge and awareness of the pandemic among women has been less than that of men, which is a reflection of the unequal distribution of educational opportunities between men and women in such societies, with women being less privileged including the clinical aspects [28]. Furthermore, there has been disparity in hospitalization rates among minorities in high income countries in North America, too. A study confirmed significantly more hospitalization of H1N1 patients among ethnic minorities as compared to non-ethnic minorities. It was suspected that the non-ethnic minorities may have greater proportion of comorbidities, pregnancy or obesity—the known risk factors of pandemic H1N1 [29]. Another study conducted in the USA confirmed the race/ethnicity-related disparities in accessing healthcare for H1N1 patients. It was found that about 63% of Spanish-speaking Hispanics lacked regularity in healthcare provision, which was significantly different from Blacks, English-speaking Hispanics and Whites. Moreover, 43.6% of the Spanish-speaking Hispanics lacked money or insurance to get a flu shot in comparison to 23% of Whites, 23.3% of Blacks and 24.2% of English-speaking Hispanics [30]. Furthermore, the proportion of poor people with insurance (69.8%) was significantly lower than that of higher-income people (93.5%) [31]. Moreover, the outbreak of the Ebola virus in 2013 was most prevalent in adults of more than 30 years of age [32]. Although there are no prominent biological differences in gender-based susceptibility to Ebola infection, men and women differed in their exposure. Women are believed to be more emotionally attached and thus inclined to nurse their sick household members, too. This is also in accordance with the prevalent societal norms wherein women are considered as the primary caregivers to the diseased children and husbands. However, it is relatively less common for men to take such care of their family members during illness [33]. In this respect, higher death rates were seen in women, as their involvement in caring for the sick was higher [33]. In West Africa, a significant gender inequality has been noted in terms of susceptibility and healthcare access, and as a result women were rendered more vulnerable to Ebola infection. Socio-cultural barriers are believed to have denied women the access to proper health information and healthcare facilities [34][35]. The Ebola outbreak in central and eastern Africa also indicated the role of gender-related factors as key determinants of inequality in exposure and infection [36]. The grave ramifications of this are illustrated by estimated gender asymmetries in Ebola infection and fatalities [37]. There have also been evidences of racial discrimination of healthcare access of Ebola patients in the USA, and the minorities, the poor and the immigrants are not believed to receive the same care in the USA as their majority, affluent and native-born counterparts [38]. For instance, an Ebola patient travelling to the USA from Liberia was prematurely released from hospital as he lacked a health insurance just to be readmitted when his condition worsened [39][40]. During the HIV epidemic, the infection rate was high among younger populations of reproductive age (15–30 years), who accounted for 61.5% of the cases in East Africa [41]. In sub-Saharan Africa, about 60% of the individuals living with

HIV/AIDS were women, particularly those in the age range of 15–24 years, indicating that their susceptibility to the disease was higher than that of men ^[42]. On the other hand, less than 25% of people living with HIV/AIDS in North Africa and the Middle East were women ^{[43][44]}. In the USA, women accounted for only 23% of new HIV infections ^[45]. In Nigeria, HIV-infected women have largely remained devoid of prevention and treatment services because of the prevalent socio-cultural norms, stereotypes and expectations. Young women of age range 15–24 years were affected twice as much as men of the same age. The inequalities remain evident even after death. A HIV-infected deceased man is buried with full ritual and rites but if it is a woman then the ceremony passes off without any elaborate funeral rites ^[46]. In the USA, racial and ethnic disparities were also witnessed during the HIV epidemic, especially in the Western societies where African-Americans are less likely to have an infectious disease specialist as a regular source of care in comparison with White patients. Natives of Alaska, American-Indian, Asian, Pacific Islander or mixed racial background have also been less likely to have an infectious disease specialist than the Whites ^[47]. According to the US Centers for Disease Control and Prevention (CDC), African-American and Hispanics accounted for 42% and 27% of the HIV diagnoses. Certain subpopulations within ethnic and racial minority groups such as Black African-American gay, bisexual and other men who have sex with men were more affected by HIV than any other group in the USA ^[48].

Clinical and epidemiological data suggest that the prognosis of COVID-19 is worse in patients aged above 60 years than those who are younger than 60. Patients under 60 years tend to have less severe symptoms and higher recovery rates than older patients ^[49]. Studies have shown that older patients (more than 60 years of age) suffering from COVID-19 have an increased risk of death compared with younger adult patients (aged less than 60 years) ^[50]. The risk of disease occurrence and death increases substantially in older patients who suffer from comorbidities, such as diabetes, hypertension and pulmonary and respiratory diseases. Epidemiologically, men are at greater risk of infection and severe COVID-19 outcomes than women ^[51]. There are roughly similar numbers of confirmed cases between men and women ^[52], however, the sex bias in COVID-19 fatality has been confirmed. Reports from China, South Korea, the USA and several other European countries have indicated higher fatality rates in male patients in comparison with females ^{[53][54][55]}. Female patients are also in less demand of intensive care and are significantly less likely to develop the severe form of the disease, too ^{[56][57]}. It is worth mentioning that worse outcomes and higher deaths in men as compared with women have so far been independent of age ^[57]. Furthermore, male patients with comorbidities have a higher risk of getting critically ill compared with men without comorbidities; whereas there is no such association in women ^[58]. Symptoms such as cough and fever are experienced more by men, too ^[59]. While men and women have an equal prevalence of disease occurrence, the death rate is about 2.4 times higher in males than in females, and the age data of deceased patients have revealed comparable trends between men and women ^[57].

Thus, a comparison of the age- and gender-based characteristics between SARS-CoV-2 and other viruses suggests that the novel virus most resembles SARS-CoV and MERS-CoV in this regard.

3. Mechanism of Host Cell Invasion of SARS-CoV-2 in Comparison with other Viruses

Viruses possess unique strategies to invade host cells. Although individual viral entities have specific variations in their mechanisms of host cell invasion, the overall process can be somewhat generalized. To gain access to the interior of the cell, enveloped viruses fuse directly with the cell plasma membrane, whereas other viruses need to be endocytosed by the host cells. The introduction of viral genetic material to the host cell soon leads to intracellular disruptions [60].

Enveloped viruses contain fusion proteins on their surfaces that interact with cell–surface receptor proteins [60]. The process of fusion comprises two major steps. First, the monolayers of the virus and the cell merge in a process called hemifusion, which is followed by the collapse of unmerged monolayers into each other to create a single bilayer, called the hemifusion diaphragm. In the second step, the single bilayer is disrupted by a pore created by fusion proteins, through which the viral genome gains entry to the interior of the cell [61]. Once inside the cell, the virus hijacks the cellular machinery to produce virally encoded proteins that replicate the genetic material of the virus [60].

H1N1 influenza A virus, which is equipped with the hemagglutinin protein, initiates the infection process in the respiratory tract. The virus attaches to receptor glycoconjugates of unknown identity with linearly placed terminal α -2,3-linked sialic acid residues [62][63]. Hemagglutinin-mediated binding to the receptor triggers endocytosis of the virion, which can occur in a clathrin-dependent manner or through macropinocytosis [64][65]. This is followed by the opening of the matrix 2 protein ion channel, which acidifies the inside of viral particles and subsequently releases viral RNA [65][66]. The invasion mechanism of the Ebola virus has been partially explored; it infects a variety of cellular targets, such as endothelial cells, fibroblasts, hepatocytes and adrenal cortical cells [67]. The virus has surface glycoproteins that attach to various cell surface receptors in the C-type lectin family of proteins. The family includes asialoglycoprotein receptors, dendritic cell-specific intercellular adhesion molecule (ICAM)-3-grabbing non-integrin, human macrophage galactose, acetylgalactosamine-specific C-type lectin and lymph node sinusoidal endothelial cell C-type lectin, which have all been shown to interact with Ebola virus surface glycoprotein [68]. Following attachment, virus particles are taken up by various endocytic pathways, such as clathrin-dependent and caveolin-dependent pathways and macropinocytosis [68][69]. Recent studies have shown that the endocytic pathway of Ebola virus entry is dependent on the enzyme cathepsin, which cleaves the viral glycoprotein in acidic conditions, thus facilitating the internalization of the viral genome [70][71]. HIV invades the male and female genital tracts through the mucosal epithelial surface. Glycoprotein 120 (gp120) on the surface of HIV interacts with two surface glycosphingolipids—sulfated lactosylceramide and galactosyl ceramide on the vaginal and ectocervical epithelium, respectively—to initiate transcytosis [72][73][74]. Once within the epithelium, HIV encounters and binds directly to CD4+ T cells and dendritic cells [75]. Gp120 and gp41 on the surface of the virus attach to CD4 and chemokine coreceptors, such as C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) of the leukocyte, which is followed by endocytosis of the virus, although other non-endocytic pathways of entry also exist [76]. Membrane labeling studies have shown that the viral envelope fuses with the endocytic compartment, releasing the viral genome and enzymes into the cytosol [77].

SARS-CoV and MERS-CoV belong to the Coronaviridae family and β -Coronavirus subtype, and thus, they have fairly similar patterns of host cell invasion. As mentioned earlier, the first step of virus entry is the interaction

between viral spike proteins and receptors on the cell. The receptor-binding domain of these coronaviruses resides in the C-terminus of the spike protein sub-segment S1 [78]. Different coronaviruses use different cellular receptors for their entry: for example, as cell surface receptor proteins, SARS-CoV uses angiotensin-converting enzyme 2 (ACE2), which is expressed in vascular endothelial cells, renal tubular epithelium and various other organs, while MERS-CoV utilizes dipeptidyl peptidase 4 (DPP4), which is expressed on the surface of most cell types [79][80][81]. Acid-dependent proteolytic cleavage of viral spike proteins leads to the fusion of viral and host cell membranes in the acidic environment of the endosome. Ultimately, an antiparallel six-helix bundle is formed from the cleaved spike protein, which allows for the mixing of viral and cellular membranes, leading to the release of the viral genome into the cytosol [82][83].

The invasion mechanism of SARS-CoV-2, similar to SARS-CoV, is initiated when its spike protein comes into contact with the ACE2 receptor on the cell surface of the target organ [84]. This is followed by the fusion of the viral membrane and the host cell [85]. After fusion, a conformational change in the viral spike protein is initiated by type II transmembrane serine protease on the cell surface, which allows the virus to enter the cell [86]. The highest ACE2 expression has been detected in nasal epithelial cells and ciliated secretory cells of the respiratory tract, which is the prime reason that these tissues are the primary target of this virus [87]. Recently, high-sensitivity RNA in situ mapping revealed a striking gradient of SARS-CoV-2 infectivity along the nasal pulmonary epithelial tissue, with a relatively high rate of infection in the proximal portion of the lungs in comparison with the distal portion. Such variations are the result of the higher nasal ACE2 expression levels in the bronchial pathway in the proximal portion and their progressive decline towards the distal portion [88]. ACE2 has also been detected in the stomach, small intestine, colon, skin, lymph node, thymus, bone marrow, brain, spleen, liver, kidney and reproductive tract; in fact, it is expressed in the endothelial and smooth muscle cells of virtually all organs, which is suggestive of the fact that SARS-CoV-2 not only invades the respiratory system but also poses potential threats to digestive, urogenital, circulatory, central nervous and reproductive systems [89]. Upregulation of ACE2 following inflammation may increase the susceptibility of several tissues to further damage that may lead to multiple organ failure in severe cases of SARS-CoV-2 infection [90]. Once inside the cell, the virus releases its genetic material and starts the process of viral replication, which is followed by the assembly of numerous viral particles and their release from the cell [91]. The process of replication in coronaviruses is unique among RNA viruses in the sense that the viral RNA synthesizes replicase and other non-structural proteins with the help of host ribosomes and ultimately forms the replicase–transcriptase complex. The process of transcription produces genomic and sub-genomic RNA that further undergoes translation to synthesize viral structural proteins [92].

From this comparative analysis of invasion mechanisms of SARS-CoV-2 and other viruses, SARS-CoV-2 clearly shares similarities with SARS-CoV in the overall pattern of invasion and receptor specificity. Furthermore, evidence of organ-to-organ transmission of SARS-CoV-2 based on the presence or absence of the ACE2 receptor has also been reported. Therefore, in addition to the respiratory system, the virus may infect other organs, including the cardiovascular, gastrointestinal, nervous, renal and reproductive systems.

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