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VIRAL PANDEMICS OF TWENTY-FIRST CENTURY

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ABSTRACT

Pandemics are regarded as large-scale outbreaks of infectious disease that has the potential to significantly increase morbidity and mortality over a wide geographical area, which is accompanied by economic, social and political disruption. The likelihood of pandemic, especially caused by viral infectious diseases has increased over the past few years. The 21st century is just two decades old but it has already witnessed some of the deadliest viral pandemics having far-reaching consequences. These include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (2002), Influenza A virus subtype H1N1 (H1N1) (2009), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (2012) and Ebola virus (2013) and the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (2019-present). The viruses may adopt various mechanisms to invade and hijack the cellular machinery of the host cell, followed by infection-mediated immunomodulation and progressive inflammation, which in turn, may affect the functioning of different organ systems of the body. Although effective commercial vaccines are unavailable for most of these viruses, those against SARS-CoV-2 are being developed at an unprecedented speed with few of the vaccines already being approved for commercial distribution. Significant policy attention is required to limit the outbreak of such pandemics and to expand and sustain investment to build preparedness and health capacity.

Keywords: SARS-CoV, SARS-CoV-2, MERS-CoV, H1N1, Ebola, outbreak

INTRODUCTION

Since the dawn of mankind, there has been a constant quest to overcome the threat of infectious diseases. The 21st century has been no exception as humanity experienced the emergence of several viral outbreaks, of which Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, Influenza A virus subtype H1N1 (H1N1) 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 (**Zappa et al., 2009; Bloom and Cadarette, 2019; Grubaugh et al., 2019; Cascella et al., 2020; Roychoudhury et al., 2020**).. Such epidemics helped in identifying the shortcomings of public healthcare system and provided opportunities to rapid and effective research on basic scientific aspects of these diseases in order to better prepare for future outbreaks.

GENDER AND AGE-BASED DIFFERENCES IN SUSCEPTIBILITY

Male and female of different age groups differ in general response to the viruses (**Klein and Flanagan, 2016**). The symptoms of SARS-CoV infection were found to be more severe in case of patients above 60 years of age (**Chen and Subbarao, 2007**). Additionally, men infected with this virus had higher fatality rates (21.9%) compared to women (13.2%) (**Karlberg et al., 2004**). Similarly, MERS-CoV infected men had a fatality rate of 52% which was much higher than that of women having a fatality rate of 23%. Furthermore, the fatality rates of patients above 60 years were much higher than that of younger individuals (**Alghamdi et al., 2014**). H1N1 virus, on the other hand, primarily infected children and young adults of reproductive age below 40 years (**Klein et al., 2010**). The male-to-female morbidity ratio has been higher than one, suggesting that males are more susceptible to H1N1 (**Eshima et al., 2011**). In case of Ebola outbreak, adults above 30 years of age were found to be the most effected, with no significant biological differences in gender-based susceptibility (**Bower et al., 2016; Nkangu et al., 2017**). During the recent SARS-CoV-2 outbreak, patients above 60 years of age were found to be suffering from more severe symptoms, along with increased risk of death in such patients (**Roychoudhury et al., 2020; Liu et al., 2020**). While men and women have equal prevalence of disease occurrence, the death rate of SARS-CoV-2 infected males is about 2.4 times more than that of infected females (**Jin et al., 2020**).

MECHANISM OF HOST CELL INVASION

Viruses adopt various unique strategies to gain entry into the host cell. Once inside the cell, the virus hijacks the cellular machinery to produce viral proteins which help in replication of the viral genome (**Cohen, 2016**). SARS-CoV and MERS-CoV uses angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) respectively as the cell surface proteins to gain access into the host cell (**Li et al., 2003; Kuba et al., 2010; Raj et al., 2013; Roychoudhury et al., 2020**). This is followed by proteolytic cleavage of viral spike proteins which leads to the fusion of viral and host cell membranes in the acidic environment of the endosome, which eventually leads to the release of viral genome into the cytosol (**Bosch et al., 2003; Fehr and Perlman, 2015**). SARS-CoV-2 also follows similar mechanism to invade host cell. When the spike protein of this virus comes in contact with ACE2 receptor on the cell surface of the target organ, the fusion process is initiated (**Walls et al., 2020**). This is followed by a conformational change in the viral spike protein initiated by type 2 transmembrane serine protease (TMPRSS2) on the cell surface, which allows the virus to enter the cell (**Simmons et al., 2013**). (Figure 1).

H1N1 Influenza A virus undergoes hemagglutinin-mediated binding to the receptor which results in endocytosis through clathrin-dependent manner or through macropinocytosis (**Roy et al., 2000; Rust et al., 2004; Roychoudhury et al., 2020**). This is followed by opening of matrix 2 protein ion channel, which acidifies the inside of the viral particle and subsequently releases viral RNA (**Martin and Helenius, 1991; Rust et al., 2004**). Ebola virus has surface glycoproteins which binds to C-type lectin family of host cell receptors (**Alvarez et al., 2002**). The virus particles are then uptaken by various endocytic pathways, such as caveolin-dependent manner or macropinocytosis (**Alvarez et al., 2002; Nanbo et al., 2010**). This process is dependent on enzyme cathepsin, which cleaves the viral glycoproteins in acidic conditions, thus facilitating internalization of viral genome (**Moller-Tank and Maury, 2014; Lee et al., 2016**). (Figure 1).

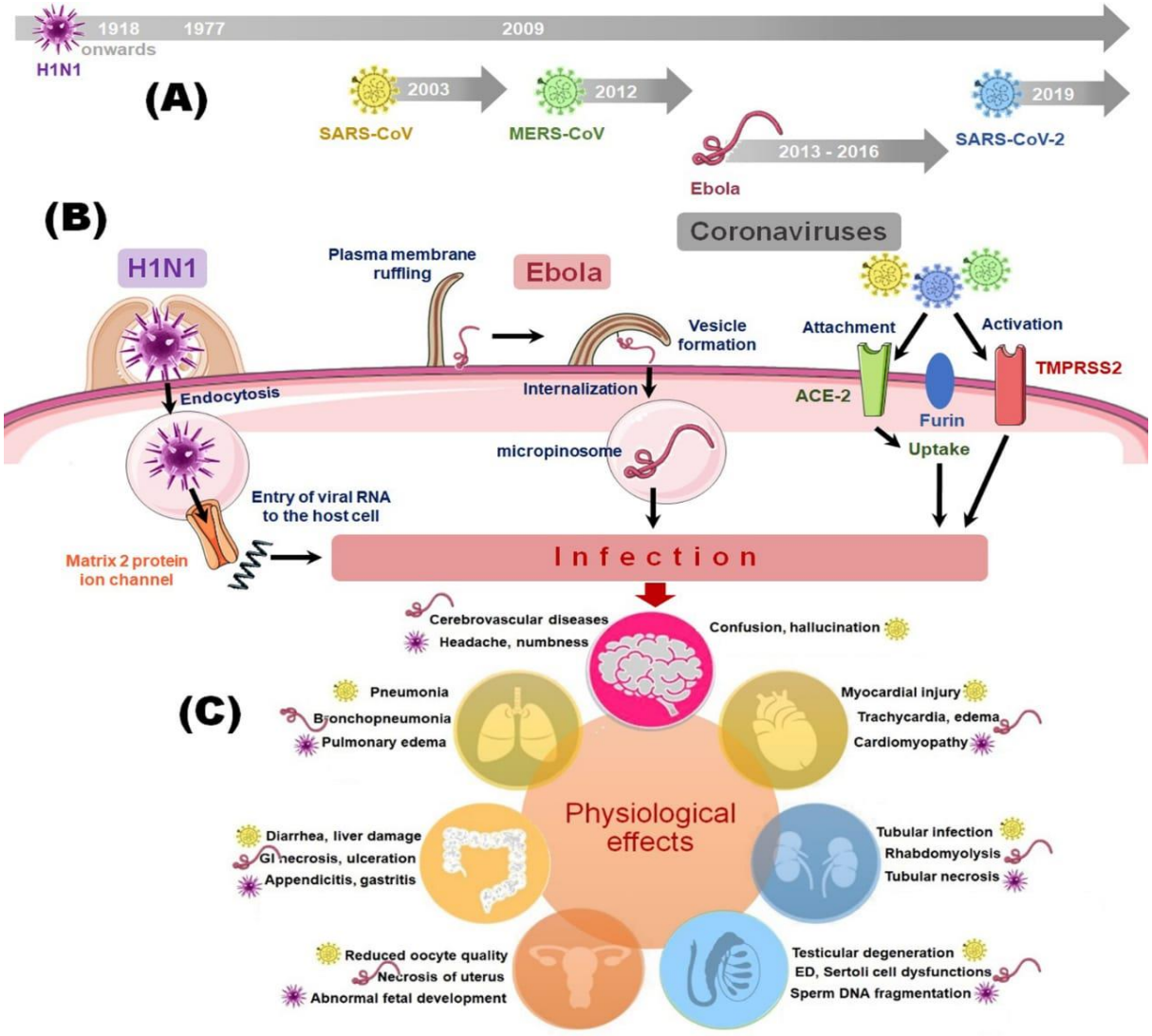

Figure 1 Schematic representation of the (A) history of pandemics in 21st century, (B) the mechanism of invasion of these deadly organisms and (C) their physiological effects. (H1N1: influenza A virus subtype H1N1, SARS-CoV: severe acute respiratory syndrome coronavirus, MERS-CoV: Middle-East respiratory syndrome coronavirus, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ACE2: angiotensin-converting enzyme, TMPRSS2: transmembrane prot ease serine subtype 2, ED: erectile dysfunction).

EFFECTS ON MAJOR PHYSIOLOGICAL PROCESSES

The respiratory system is a prime target of all these viruses. H1N1 causes acute respiratory disease along with excessive production of pro-inflammatory cytokines, which leads to development of conditions such as pulmonary edema, acute bronchopneumonia, alveolar hemorrhage and acute respiratory distress syndrome (**Zaragoulidis et al., 2011**). The respiratory complications of Ebola virus include tachypnea with increased vascular leakage, which leads to pulmonary edema (**Wolf et al., 2015**). The major effects of SARS-CoV include alveolar collapse, desquamated alveoli, alveolar hyperplasia and damage to bronchial epithelial cells (**Gu et al., 2005**). MERS-CoV causes ground-glass opacities, pleural thickening and fibrosis in patients with moderate frequency (**Ramadan and Shaib, 2019**). SARS-CoV-2 induces mild to moderate pneumonia in patients with severe inflammatory response that affect the host cells (**Mohanty et al., 2020**). It results in tissue damage and microvascular pulmonary thrombosis (**Ciceri et al., 2020**). (Figure 1).

H1N1-infected patients are found to be severely affected by active inflammation and necrosis in myocardial tissue, which later gives rise to dilated cardiomyopathy, myocarditis, acute myocardial infarction, chronic ischemic heart disease and stroke (**Richardson et al., 1996; Onitsuka et al., 2001; Golabchi and Sarrafzadegan, 2010**). Ebola infected patients develop tachycardia with progressive hypotension, decreased ventricular inotropy and decreased contractility of the heart due to the virus-induced cytokine circulation (**Kortepeter et al., 2011**). Cardiovascular complications are also common in SARS-CoV-infected patients, which include tachycardia, brachycardia, cardiac arrhythmia and cardiomegaly (**Yu et al., 2006**). MERS-CoV is also known to cause chronic cardiac disease in moderate frequency (**Assiri et al., 2013**). Patients infected by SARS-CoV-2 have high possibility of experiencing circulatory symptoms such as palpitations, chest tightness and shortness of breath as initial symptoms (**Huang et al., 2020**). (Figure 1).

H1N1 influenza virus can induce severe gastrointestinal (GI) complications such as acute appendicitis, abdominal pain and hemorrhagic gastritis in severe cases, especially in children (**Landi and Coleman, 2008; Adalja and Henderson, 2010**). Ebola- infected patients experience GI necrosis and hemorrhage, which is often accompanied by ulceration in GI tract (**Reisler et al., 2018**). Diarrhea, vomiting, nausea and abdominal pain are the initial symptoms in the early phases of infection in SARS-CoV patients which are followed by regional hemorrhage and lymphocytic infiltration in the gut wall (**Zhang, 2003**). The intestinal epithelial tissue of MERS-CoV- infected patients often shows degeneration and inflammation due to increased viral load (**Zhou et al., 2017**). The effects of SARS-CoV-2 on GI tract is less severe with primary symptoms that include diarrhea, nausea, vomiting and abdominal pain (**Hajifathalian et al., 2020**). (Figure 1).

Severe neurological complications in H1N1-infecetd patients include seizures, acute inflammatory demyelinating polyneuropathy, acute disseminated

encephalomyelitis and alterations in the level of consciousness, ranging from lethargy to coma (**Sulkava et al., 1981; Asadi-Pooya et al., 2011**). Ebola causes infrequent neurologic disorders with severe effects being electrolyte imbalance, shock and coma (**West and von Saint Andre-von Arnim, 2014**). People infected by SARS-CoV developed neurologic symptoms such as seizures, myopathy and rhabdomyolysis [53]. In case of MERS-CoV, infected patients experience neuropathy, delirium and acute cerebrovascular disease (**Kim et al., 2017**). Typical neurological symptoms of SARS-CoV-2-infected patients include headache, epilepsy and confusion, and some patients have a high risk of intracranial hemorrhage, with potential destruction of blood-brain barrier (**Mao et al., 2020**) (Figure 1).

H1N1 influenza virus is known to infect the kidneys, with predominant effect including acute tubular necrosis, myoglobin pigmentation and disseminated intravascular coagulation (**Watanabe, 2013**). Ebola-infected patients frequently experience kidney injury due to increased cytokine production (**Prasad et al., 2019**). SARS-CoV-infected patients often develop acute renal failure in association with indirect causes such as pre-renal factors, hypotension, rhabdomyolysis (**Huang et al., 2005**). Patients infected with MERS-CoV are at risk of developing progressive renal function impairment with most of them are likely to suffer from proteinuria (**Memish et al., 2013**). The most frequent kidney dysfunction in SARS-CoV-2-infected patients is mild to moderate proteinuria, along with disrupted glomerular filtration barrier which results in the increased filtration of plasmatic proteins (**Martinez-Rojas et al., 2020**). (Figure 1).

H1N1 imparts various deleterious effects on the reproductive system of the patient, which include disruption of sperm DNA integrity and production of abnormal sperm with increased risk of infertility in men (**Sergerie et al., 2007**). There is no well-documented effect of Ebola on human reproductive system, but it was found to cause inflammation and necrosis in the uterus of guinea pig model (**Connolly et al., 1999**). The direct effect of SARS-CoV on male reproductive system include marked decrease in serum testosterone levels, along with a significant reduction in the ratio of testosterone to luteinizing hormone (LH) and the ratio of follicle-stimulating hormone (FSH) to LH (**Ma et al., 2020**). SARS-CoV-2-induced oxidative damage may lead to membrane lipid peroxidation and sperm DNA fragmentation, which negatively impacts spermatogenesis and spermiogenesis. Furthermore, sperm count and seminal volume are lowered, which may adversely affect reproductive outcomes and ultimately lead to infertility in males (**Sengupta and Dutta, 2020**). (Figure 1).

VACCINE DEVELOPMENT

Vaccines against SARS-CoV-2 are being developed at an unprecedented speed (**Roychoudhury et al., 2020**). As of 29th December 2020, 172 vaccine candidates are in pre-clinical development and 60 vaccine candidates are in clinical trial phases, 11 of which are in phase 3 clinical trial stage (**WHO, 2020**). An adenovirus vector vaccine 'Sputnik V' developed by The Gamaleya National Center for Epidemiology and Microbiology, which is currently undergoing a phase 3 clinical became the first registered SARS-CoV-2 vaccine on 11 August 2020 (**National Geographic, 2020**). Subsequently, an mRNA vaccine 'BNT162b2' developed by Pfizer and BioNTech currently undergoing phase 3 trials received temporary authorization from the UK Medicines and Healthcare products Regulatory Agency on 2nd December 2020 and a week later on 8th December 2020, Margaret Keenan, a 90 years old woman became the first person to receive a vaccine against SARS-CoV-2 (**Roychoudhury et al., 2020; BBC, 2020**). Pfizer is expecting to produce globally up to 1.3 billion doses of vaccine in 2021 with the help of its extensive US and European manufacturing networks (**Pfizer, 2020**). The Pfizer/BioNTech vaccine has also become the first vaccine to get emergency validation from the World Health Organization (WHO) paving way for countries worldwide to quickly approve its import and distribution (**France 24, 2020**). As of 3rd January 2021, more than 12 million vaccine doses have already been administered in 30 countries with the USA leading the tally with 4.28 million doses (**Bloomberg, 2021**). The University of Oxford and AstraZeneca have developed a non-replicating viral vector designated 'ChAdOx1 nCoV-19', which is also under a phase 3 clinical trial [66]. An Indian company called Bharat Biotech has prepared an inactivated viral vaccine which is undergoing phase 3 trials (**National Geographic, 2020**). On 3rd January 2021, the drugs regulatory authority in India have approved the emergency use of two coronavirus vaccines developed by the AstraZeneca with Oxford University and by Bharat Biotech (**BBC, 2021**). Three American companies, Moderna Therapeutics, Johnson and Johnson and Novavax has independently developed three vaccine candidates namely 'mRNA-1273', 'JNJ-78436735' and 'NVX-CoV2373' respectively, all of which are currently undergoing phase 3 trials (**National Geographic, 2020**). The USA is managing state allocations of Pfizer/BioNTech vaccine as well as Moderna's shot, with the goal of getting 20 million doses distributed by early January (**Bloomberg, 2021**). Four Chinese companies, Sinovac, Cansino Biologics, Anhui Zhifei Longcom Biopharmaceutical Company and Sinopharm has independently developed four vaccine candidates which are also in phase 3 clinical trials (**National Geographic, 2020**). All these vaccine candidates have shown potent immune response in previous trial phases (**National Geographic, 2020**).

During the development of SARS-CoV vaccine, live-attenuated virus, live-attenuated recombinant virus, recombinant modified vaccinia virus Ankara, recombinant non-replicating adenovirus, virus-like particles and a combination of DNA, recombinant viral vector and viral peptides were used but the process was later decelerated owing to the lack of suitable animal models for testing (**Orellama, 2004; Tang et al., 2004; Sutton and Subbarao, 2015**). Similar cases were seen during the development of MERS-CoV vaccine, where the animals developed immunological response but exhibited limited viral replication and clinical manifestation of the disease (**Sutton and Subbarao, 2015**). However, protein-based vaccines and a combination of DNA and protein-based vaccines have shown some degree of long-term protection in mice and macaques (**Zhao et al., 2017**). Two types of vaccines have been available for H1N1 influenza, which included trivalent inactivated vaccine and live attenuated influenza vaccine with the latter being more effective in children over 2 years (**CDC, 2020**). On 19th December 2019, the Ebola virus vaccine 'Ervebo' was announced by the US Food and Drug Administration (FDA), which is a recombinant, replication-competent vaccine (**FDA, 2019**).

LESSONS LEARNED FROM THE VIRAL EPIDEMICS

The above-mentioned viral outbreaks that took place during the twenty-first century so far have made it clear that the global population needs to be prepared for such emergencies to act appropriately and to restore both the health and economic sector of the affected countries. By analyzing the impacts and by taking lessons from these epidemics, mankind can reduce the magnitude of damages for future outbreaks (**Heymann and Rodier, 2004**).

One of the most important lessons learned from the outbreaks was the need of early detection and prompt reporting of cases of any disease with a potential of international spread. During the SARS-CoV epidemic, a resolution was passed by the WHO requesting the affected countries to report cases promptly so that the international spread could be stopped (**Heymann and Rodier, 2004**). Similar approach was critical for the control of MERS-CoV spread as well (**Saeed et al., 2017**). Centers for Disease Control and Prevention (CDC) has adopted aggressive measures to stop the spread of SARS-CoV-2 by identifying the early cases arriving in the USA from affected countries (**Patel and Jernigan, 2020**). During H1N1 epidemic, early incident rates were not properly reported by the officials in Mexico which resulted in steep increase in infected cases during the latter part of the year (**WHO, 2009; Chong et al., 2014**). Similar situation arose during Ebola outbreak when national and international shortcomings of early disease detection fueled the emergence of public health crisis (**Woolhouse et al., 2015**).

In the wake of a global health crisis, international collaborations hold immense importance to contain the outbreak. During SARS-CoV outbreak, long-term international collaborations helped to understand the mode of transmission of the virus and the clinical spectrum of the disease (**Heymann and Rodier, 2004**). As a result of collaborative research during MERS-CoV epidemic, prioritization of the search for an appropriate vaccine as well as effective medications for the treatment was demonstrated (**Zyoud, 2016**). To eradicate the ongoing SARS-CoV-2 pandemic, global efforts are now focused on understanding its properties and etiopathology to develop interventions, including vaccines and specific treatments (**Frazer, 2020**). During H1N1 outbreak also, various institutions worked collectively in response to the global pandemic which led to its end after a year of its emergence (**People.cn, 2020**). The clinical trials of Ebola vaccine were supported by improved coordination among international stakeholders, researchers and regulators (**Keusch et al., 2017**).

A strong healthcare system is a prerequisite for a country to tackle an epidemic large magnitude. The SARS-CoV epidemic exposed weakened health facilities with problems, such as requirements for isolation wards, long periods of intensive care, mass screening, contact tracing, active surveillance and quarantine facilities (**Heymann and Rodier, 2004**). The ongoing SARS-CoV-2 epidemic has stretched the carrying capacity of healthcare systems to the extreme extent, which made it clear that much more efficient healthcare facilities are to be established, especially by the developing countries to contain a pandemic of such magnitude in future (**Kretchy et al., 2021**). The H1N1 pandemic substantially impacted healthcare systems of the world, particularly through an increased burden on the emergency departments of hospitals, which experienced a high surge in inpatient admissions (**Rubinson et al., 2013**). During Ebola epidemic, lack of robust healthcare facility was one of the prime reasons behind the failure of early containment of the epidemic in West Africa (**Dentico, 2014**).

Effective application of proper interventions, the burden on healthcare system can be substantially lowered during the time of pandemic. Standard public health intervention strategies were followed during SARS and MERS-CoV outbreak, which included treating patients with antiviral drugs, following social distancing norms and implementing quarantine measures (**Heymann and Rodier, 2004**). Although the vaccines for SARS-CoV-2 have already been registered, non-vaccine interventions such as remdesivir and dexamethasone are being tested, until the commencement of large-scale immunization programs (**Dong et al., 2020**). During the H1N1 pandemic, both pharmaceutical and social distancing interventions were recommended by the WHO and other countries, which slowed the rate of transmission (**Halder et al., 2010**). Similarly, a combined action of

several intervention strategies was responsible for preventing the spread of Ebola (**Kirsch et al., 2017**).

CONCLUSION

Emergence and reemergence of infectious viral diseases pose serious threats to both global public health and economy. All the previous epidemics and the ongoing SARS-CoV-2 pandemic has caused deleterious consequences for health, social and economic aspects of low as well as high- income countries. The global approach should focus on stopping the spread of the disease while an effective vaccine is developed, which calls for global collaboration.

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