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Two worst pandemics- Spanish Flu and COVID-19: A review

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Abstract

1918 Spanish flu and COVID-19 can be considered as most hazardous pandemics earth has ever witnessed. They are results of what mayhems an organism not even visible with naked eye can cause. Causative agent for both the diseases is a virus but, they are not same. 1918 Spanish flu gave major indications that it has the existence of the new strain of flu and lasted for longer duration affecting lives in various ways. COVID-19 is again an indication of another emerging worst pandemic. Here, we have reviewed the overall factors that contributed to the severity of these two pandemics and comparison of the same. The main motive of this paper is to put together, compare and analyze versatility of both the pandemics and to discuss implications of the same.

Keywords: Pandemic; 1918 Spanish flu; COVID-19; Impacts; Comparison

1. Introduction

History suggests that, pandemics have caused widespread illness infecting millions of people worldwide, causing thousands of deaths. Feinleib [1] reviewed that pandemic can be defined as, an epidemic that occurs globally, or over a very extensive area crossing international boundaries and generally influencing large number of people. There are three criteria a virus must fulfill to cause pandemic: 1) no precedent immunity against it in population 2) the potential to cause illness in humans 3) contagious between humans [2]. All the three criteria mentioned above, for a virus to cause pandemic, are fulfilled by H1N1 virus and novel corona virus responsible for causing 1918 influenza and COVID-19 pandemic respectively [3]. Both the 1918 influenza which is referred as mother of all pandemics by Taubenberger and Morens [4] as well as COVID-19 referred as "once in a century health crisis", by WHO [5], has led to ruinous and scarring impacts on health and lives of people with the outcomes capable of remaining irreversible for a decennary or more. This review aims at gathering the essential information and to summarize findings on origin, epidemiology, clinical features, treatments and comparisons between Spanish flu and COVID-19.

2. The 1918 Spanish flu

In the military forts of the United States in March 1918 the "first wave" of the 1918 pandemic seems to arise [6]. The disease spread gradually in Europe. Reports about the ongoing spread of the disease were restricted due to wartime censorship by various countries. Spain being a neutral country conveyed all the horrid details of this pandemic and hence the disease came to known as the "Spanish flu" [7]. The virus was introduced into the human host before 1915 and is thought to have an avian ancestry from an unknown source which took place in three waves. Pandemic was caused by Influenza A virus of the H1N1 subtype [8]. It spread all-over the world in one deadly wave after another which evoked the word "flu". Approximately 1.8 billion were infected and more than 50 million died within short stretch of time. It is still unresolved what factor gave the 1918 virus the unmatched ability to pave way to successive pandemic

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waves. The effect of the pandemic is that the virus finds comparatively easy to enter into the host's respiratory system and replicates [9].

2.1. Origin and Epidemiology

Spanish flu pandemic was seemingly first originated in early March of 1918 [10]. It is still uncertain that where this pandemic began. Palese [11] reviewed the book by John M. Barry, which hypothesized that 1918 influenza pandemic is most likely to be originated in Haskell County, Kansas. Some researchers suggest that, it was originated in Asia, while others suggest it was originated in China or Vietnam, crossing U.S. [12]. According to Oxford [13], influenza virus first emerged in a British Army post in France.

The first wave of pandemic was mild but, the virus transmitted very rapidly through Western Europe and it reached Poland by July, 1918 and after that became more fatal by August, 1918. By winter of 1918, third wave arrived and reached more lethal stage by the spring, leading to 40-50 million deaths globally including 12.5 million in India and 550,000 in United States [10].

2.2. Virology

The molecular basis of each pathogen's structural properties, including infectivity, cell tropism, replication, immunogenicity, pathogenicity, and transmissibility is necessary to combat infectious diseases. Many pathogenic studies performed in animal models, showed both "gain-of-function" and "loss-of-function" using chimeric influenza viruses by carrying one or more 1918 viral genes of interest, expressed on less pathogenic viral "reference" backgrounds [14]. Several reverse genetics experiments indicated that the 1918 influenza virus exerts high pathogenicity and an interplay between different virulence factors, where a crucial role was played by the proteins which were encrypted by the polymerase gene and viral hemagglutinin (HA) segments [14, 15, 16, 17].

Influenza virus is usually spherical and at times can be referred as virion. Seventy- five percent proteins, one fourth percent ribonucleic acids (RNA) six and-a-half percent carbohydrate and eighteen percent lipids whole together make its structure. RNA is a genetic material present in nucleocaspid. It is related to nucleoprotein (NP) antigen which is used in further classification of influenza viruses into types A, B and C [18]. Nucleocaspid is surrounded by bilayers, an inner protein and an outer lipid membrane. Of which outer membrane have two types of spike-like projections namely hemagglutinin (H) and neuraminidase (N) which are glycoproteins [19]. This further indicates the fact that there are other minor protein substances present in the virus. To show its effect influenza virus enters into the human host cell to reproduce [18].

2.3. Transmission

Rate of transmission of influenza virus was observed to be very rapid. Transmission of virus was facilitated by wildly crowded military camps [20]. According to Britannica [10] number of cases went from 1 to 6,674 within six days at Camp Devens, Massachusetts, U.S. There are three widely accepted routes for human influenza virus transmission: 1) Droplets: Droplets released from mouth and nose, settle on mucus surface of upper respiratory tract as they are very large to reach lungs. 2) Aerosols: these are droplets nuclei that can also settle on mucus surface of upper respiratory tract but are also capable to reach lower respiratory tract as they are minute in size. 3) Person-person transmission: This occurs via close contact with infected person or contact with contaminated objects or surfaces [21].

2.4. Diagnosis

During 1918, there were no diagnostic tests available that could help in diagnosis of the disease. Even doctors were unaware about existence of influenza virus. At that time, it was believed by health experts that, 1918 pandemic was caused by a bacterium called "Pfeiffer's bacillus," which is now known as *Haemophilus influenzae* [22].

2.5. Clinical Manifestations

The initial signs and symptoms of Spanish influenza usually begin with cold, with sneezing and coughing with sudden attack. Canadian Medical Association published a report describing a typical case of influenza. According to that it began with instant weakness, pain and chills. Quantity of blood was also seen during coughing. Cyanosed face and fingers were also seen [23]. A medical report showed three distinct forms in which the influenza presented itself, though these forms co-presented in the majority of cases: (i) Nervous influenza: Very slow, intense cephalalgia, pain in eye orbits, joints and muscles. Symptoms ceased, strong dry cough accompanied by rubelliform and skin rash on arms, wrists and chest. Also, urticaria was observed. (ii) Pulmonary influenza: Shows pharyngeal, laryngeal and pulmonary symptoms. This form was deadliest of all. (iii) Gastric form: Characterized by digestive disease, vomiting diarrhoea, etc. [24].

A violent viral pneumonia also caused deaths often with either massive acute pulmonary haemorrhage or pulmonary edema. The disease course was less than 5 days [25].

2.6. Treatment

Earlier there were no such effective vaccines, antiviral drugs, or antibiotics available before the second half of the twentieth century as it was novel virus. The main strategy for treatment of influenza virus disease in 1918 was limited to supportive care [26]. So initially people were relying on the available remedies to reduce symptoms and the severity of the disease which included acetylsalicylic acid for reducing pain, fever or inflammation, anti-malarial drug such as quinine, ammonia, few drops of turpentine, water with salt, topical rubs for pain relief, inhaled substances for nasal congestion, and Bovril which is a thick, salty meat extract. Serum of patients which recovered from disease was collected by some physicians and this convalescent serum was injected into patients with active infection and according to meta-analysis of publications reporting this strategy, the patients which injected convalescent serum may have lower risk of death [20].

2.7. Vaccines

In attempts to control the spread of influenza virus, physicians developed and recommended non-standardized vaccines, as the medical community believed that influenza pandemic was caused by bacillus *Haemophilus influenzae*(named later), these vaccines were primarily recommended for protection against Pfeiffer's bacillus[20]. Firstly in 1943, killed vaccine was developed which was effective. Later from 1941, Fleming's penicillin was used to treat bacterial pneumonia. In 1963, amantadine came which was active against influenza and was tested in vivo, showing effectiveness in reducing the severity of symptoms and the length of the disease. In 1989, neuraminidase inhibitor, zanamivir (Relenza) came into the market. Later in 1993, antiviral drug called rimantadine was introduced and was reported for having severe side effects. Also, another neuraminidase inhibitor such as oseltamivir (Tamiflu), were developed commercially in 2005 and 2006 [26].

2.8. Post-Influenza Manifestations

Survivors of Spanish flu pandemic were reported to deal with sleeping disorders, depressive disorder, distractibility, hypotension and tiredness in daily life for a long time till several years, even after recovering from the disease [27]. Hepatitis, ear illnesses, deafness, blindness, and baldness were other after-effects that have been noticed in the persons linked to Spanish Influenza. After recovery from Spanish flu influenza, some patients have been reported to experience cardiac abnormalities, lung tuberculosis and kidney disorders in later life [28].

3. COVID-19

In December 2019, COVID-19 began with a sign of atypical pneumonia in Wuhan, Hubei, China [29]. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is found to be causative agent of COVID-19 pandemic [30]. Corona virus is a large family of viruses belonging to *Coronaviridae* family and order *Nidovirales* which have potential to cause illness in animals and humans [31]. Corona viruses can be divided into 4 genera- alpha (α), beta (β), gamma (γ) and delta (δ) but only alpha and beta have been known to be infectious to human beings [32]. It was observed that novel corona virus has similar symptoms to that of SARS-CoV in 2012 and both of them have same receptor- angiotensin converting enzyme 2 (ACE-2), therefore it was named as SARS-CoV-2 by WHO in February, 2020 [33]. Owing to devastating impacts of COVID-19 disease, WHO in January, 2020, declared it as Public Health Emergency of International concern [29].

3.1. Origin and Epidemiology

Human patients of COVID-19 were first found in December 2019, in Wuhan city of China, and most of the patients were reported to be stall owners, market employees and regular visitors of local Huanan Seafood wet market [34] and hence, market was shut down on 1st January, 2020 [35]. To identify origin of infection, a deep sequencing analysis of lower respiratory tract was carried out and samples showed that, the virus responsible for causing atypical pneumonia was novel SARS-CoV-2 and disease caused by it was named as COVID-19 on 11th February, 2020 by WHO Director-General, Dr. Tedros Adhanom Ghebreyesus [36]. The analysis of genetic sequences of SARS-CoV-2 from initial patients and those from later cases from china as well as other countries suggests that, SARS-CoV-2 is not artificial or lab-constructed virus but has an ecological origin in bat population [34]. Sheahan et al., [32] suggested that all corona viruses that infect humans are probably originated as zoonotic pathogens that have jumped from non-human animals to humans and number of corona virus pathogens causing SARS and MERS are observed to be present in bat reservoir species. Thus, it is assumed that source of origin of pandemic could be bats because the full genetic analysis points that coronavirus shares 88% sequence identity to Bat-CoV which lead to SARS, but it is found to be more distant [35, 37].

COVID-19 outbreak spread very rapidly and first case outside China was found on 13th January, 2020 in Bangkok, Thailand [35]. Within first six weeks, a large number of cases were found in more than 37 countries including USA, Japan, Iran and South Korea [38] and till March, 2020, it reached South-East Asia, affecting large number of people [39] and then, on 11th March, 2020, WHO declared COVID-19 as pandemic when it reached 114 countries including 118,000 cases and more than 4000 deaths [36]. According to weekly epidemiological update on COVID-19 by WHO, 14 September, 2021, was reported with 4 million new cases globally which represents first substantial reduction in weekly cases, whereas according to report on October 19, 2021, number of new cases decreased to 2.7 million [40, 41]. Currently, as of 20 October, 2021, globally, 241,411,380 confirmed cases and 4,912,112 deaths are recorded with 457,013 new cases and 8093 new deaths [42].

3.2. Virology

SARS-CoV-2 is microscopic, with diameter ranging from 60-140 nm and is enveloped with round or elliptical particles which are usually polymorphic [43]. SARS-CoV-2 virus is consists of 9-12 nm long crown like spikes on its surface [37]. The envelope encapsulates circular nucleocaspid proteins, inside which genome of corona virus i.e. large positive single stranded ribonucleic acid, containing 29891 nucleotides and 9860 amino acids [44] with size ranging from 26 to 32 kilobases in length, is present [43]. Genome of corona virus contains 10 open reading frames (ORF) with first ORF consisting of two thirds of viral RNA which codes for polyprotein 1a, polyprotein 1b and 1-16 non-structural proteins; whereas other ORFs encode for structural proteins like: 1) spike (S) protein having 2 subunits S1 and S2 that assist receptor binding and membrane fusion respectively 2) N protein which intensifies the viral entry 3) E protein which advances virion formation and pathogenicity and 4) M protein that structures ribonucleoproteins and provoke inflammatory response in host [44].

SARS-CoV-2 attacks epithelial cells of naso-bronchial region via spike proteins by binding to ACE-2 receptor, a membrane bound amino peptidase present between lungs and heart [45], and type 2 transmembrane serine protease (TMPRS S2) breaks down ACE-2, encouraging viral uptake, which results into activation of SARS-CoV-2 protein and mediates entry of virus in host cell [46]. While entering new human host, SARS-CoV-2 undergoes mutation forming mutant variants and several such variants are identified from onset of pandemic till now but, only few are considered as variants of concern. According to epidemiological update by WHO on June 22, 2021, SARS-CoV-2 variants found from start of pandemic which are considered as variants of concern are: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) [47].

3.3. Transmission

During onset of pandemic, a relation between origin of SARS-CoV-2 and Huanan market in Wuhan, China was observed [48] but findings suggest that there is a possibility that, at first SARS-CoV-2 was hosted by bat and it was passed on to human population through pangolin or any other wild animals, which are sold at wet market but, later it was spread potentially by person-person transmission [37]. SARS-CoV-2 can be transmitted via: 1) symptomatic carriers during close contact, droplets expelled from mouth and nose during breathing, talking, coughing and sneezing or through contact with infected surfaces 2) pre-symptomatic carriers, as during incubation period virus can be potentially transmitted 3) asymptomatic carriers, as even though they do not show symptoms but can be severely infected and are capable of transmission [49]. Chinese researchers observed SARS-CoV-2 in excreta of COVID positive patient, pointing the possibility of faeco-oral transmission [48]. Also, one of the studies showed positive results for COVID-19 on RTPCR in conjunctival swab, indicating the potential of transmission via eyes [35]. Li et al., [50] revealed that, a woman with SARS-CoV-2 infection delivered a baby, during her 35th week of pregnancy, which was tested negative for SARS-CoV-2 infection which suggests that transmission of virus from mother to child does not occurs.

3.4. Diagnosis

According to the recommendations issued by Centre of Disease Control and Prevention and World Health Organization, regarding the laboratory safety while diagnosis of corona virus suspected population specimens, the tests should be carried out in biosafety cabinets if there is possibility of splashes or generation of droplets or aerosols and only BL-3 laboratories should be used for isolation of virus [38].

The diagnosis for SARS-CoV-2 is done by using RTPCR, where a consensus E-region of beta corona virus or other specific regions like RdRp or N- region are targeted [35]. It is observed to show high false-negative test result rate in 27%-67% of infected people as it depends upon quality and timing of testing [46]. In addition to RTPCR, radiological examinations such as thin-slice chest CT as well as chest X-ray are used [35, 37]. Specimens for diagnosis of SARS-CoV-2 are collected in the form of sputum, branchioalveolar lavage fluid, nasopharyngeal swabs and oropharyngeal swabs [46]. According to Vieira et al., [48], SARS-CoV-2 can also be isolated from feces of infected person. Also, several serological assays such

as point-of-care assay and high throughput enzyme immunoassay can also be used in diagnosis but variation may be found in their performance, precision and validity [46].

3.5. Clinical Manifestations

Symptoms of COVID-19 are highly variable where the severity ranges from, asymptomatic to lethal [36]. The average incubation period of SARS-CoV-2 infection is 5.6 days [51] and period of active monitoring and development of symptoms is 14 days [52]. Initial symptoms during the onset of COVID-19 outbreak were recorded to be fever, dry cough, muscle pain, fatigue, shortness of breath or dyspnea and sputum production which were more common whereas, less common symptoms include nausea, vomiting, stomach-ache, diarrhoea, haemoptysis (coughing of blood from respiratory tract), pharyngitis and nasal congestion [48]. Other common symptoms include partial (anosmia) or total (hyposmia) loss of smell and partial (hypogeusia) or total (ageusia) loss of taste, which was considered as one of the characteristic feature of SARS-CoV-2 infection [53]. CT scans during initial mild pneumonia showed small, sub pleural, unilateral or bilateral frosted glass opacities in lower lobes which lead to complicated paving pattern and further consolidation [43]. A few neurological symptoms which include headache, dizziness, impaired balance and co-ordination, cerebral apoplexy, seizure disorder, visual impairment, nerve pain [33] and also, ocular symptoms such as conjunctivitis, epiphora (tear flow), eye irritation and conjunctival hyperemia [48] were observed in patients in later stages. After a week of appearance of symptoms, patients with severe infection may feel tightness in chest and shortness of breath [54].

According to available data, elderly population with more than or about 60 years of age and those with poor immunity with pre-existing diabetes, cardiovascular and respiratory conditions, malignancy, kidney and liver diseases are at more risk for SARS-CoV-2 infection than that of children [43] and are more susceptible to respiratory failure owing to severe alveolar damage [37]. Patients with fatal respiratory disease of corona virus may develop bilateral pneumonia, acute respiratory distress syndrome (ARDS) which may worsen in short period of time causing multiple organ failure, leading to death [45].

3.6. Treatment

During onset of pandemic, limited treatments were available to decrease rate of disease and mortality due to COVID-19 [55] but tremendous efforts of clinical researchers from all around the world resulted into availability variety of therapeutic options [47]. Initially, the focus was on providing symptomatic and supportive care, maintaining vitals, oxygen level and blood pressure and treating severe symptoms [35]. In comparison to onset of pandemic, now a considerable number of therapeutic options for controlling the disease are available some of them include: antiviral drugs such as ramdesivir; combination therapy of lopinavir-ritonavir also, hydroxychloroquine and chloroquine [47], β-D-N4-hydroxycytidine [33], ivermectin [55] are recommended. In addition to this, convalescent plasma therapy for patients with severe condition such as ARDS, can be used [48]. Anti-SARS-CoV-2 monoclonal antibodies such as Casirivimab, Imdevimab, Bamlanivimab, Etesevimab, Sotrovimab [47]; anti-inflammatory drugs such as dexamethasone and statins; immunomodulation agents such as tocilizumab, sarilumab, anakinra, ruxolitinib, baricitinib; anticoagulants like heparin and antibiotics like tyrosinekinase inhibitors are also used in management of COVID-19 symptoms and treatment [46]. In China, some of the traditional medicines such as decodation of Qing Fei Pai Du that include: *Ephedra herba, Gypsum fibrosum, Pinelliae rhizoma, Auranti fructus immaturus* and *Zingiberi rhizome recen* were used and was advised by state administration of Chinese medicine on 6th February, 2020, as it had been observed to be 90% effective in treatment of SARS-CoV-2 [43].

3.7. Vaccines

The vaccines generally require years of research and clinical trials, before reaching to clinics but, in order reduce the burden of increasing mortality rate, researchers are working continuously to develop safe and effective vaccine against SARS-CoV-2 [56]. As of September 28, 2021, a total of 6,136,962,861 vaccine doses have been recorded to be administered worldwide [42].

Table 1 Some leading vaccines against SARS-CoV-2 virus [56]

Sr. No.	Vaccine name	Developer	How it works	Status	Doses
1.	Comirnaty/ BNT162b2	Pfizer (Germany)	mRNA	Approved in U.S. and few other countries and authorized for emergency use in several countries.	2 doses 3 weeks apart
2.	Spikevax or Mrna-1273	Moderna (Boston)	mRNA	Approved in Switzerland, Emergency use in U.S. and other countries	2 doses 4 weeks apart
3.	Vaxzevria/ AZD1222 or Covishield in India	Oxford university and AstraZeneca	Adenovirus	Approved in Brazil and Emergency use in other countries.	2 doses
4.	Ad26.CoV.S	Johnson & Johnson	Adenovirus26	Authorized for emergency use in U.S. and other countries.	1 dose
5.	Sputnik-V/ Gam-Covid-Vac	Gamaleya, Russia	Adenovirus Ad5 & Ad26	Authorized for emergency use in Russia and several other countries.	2 doses 3 weeks apart
6.	NVX-CoV2327	Novavax	Protein	In phase 3	
7.	BBIBP-CorV	Sinopharm, China	Inactivated virus	Approved in China, U.A.E and Bahrain and for emergency use in other countries.	2 doss 3 weeks apart
8.	CoronaVac	Sinovac, China	Inactivated virus	Approved in China, Emergency use in other countries	2 doses 2 weeks apart
9.	Covaxin/ BBVI522	Bharat biotech, India	Inactivated virus	Emergency use in India and other countries.	2 doses 4 weeks apart

4. Post-COVID Manifestations

Atypical clinical parameters or symptoms were observed in patients of COVID-19 infection and they do not succeed to return to normal condition, are considered as abiding effects of the disease [57]. Some of such symptoms observed are as follows:

- Neurological abnormalities such as headache, complete loss of taste and smell, dizziness [58], loss of memory, thinking ability and decision making, obsessive compulsive disorder, generalized anxiety disorder, attention deficit hyperactivity disorder, depression [57] as well as in a case multiple sclerosis and acute myelitis that may affect cervical spinal cord were observed [39].
- Pulmonary manifestations such as reduced pulmonary diffusing capacity, cough, chest tightness and decreased respiratory muscle capacity were observed in a few patients after 3 months of recovery from COVID-19 [58].
- Cardiovascular manifestations such as cardiac arrhythmia and myocardial inflammation as well other symptoms such as hair loss and joint pain were recorded after SARS-CoV-2 infection recovery [57].
- During peak of second wave of COVID-19 disease, some countries especially India and nearby South-Asian countries were getting infected by a rare fungus of mucorales group [59], affecting body surface and internal organs such as brain, sinus, lungs, body tissue, eyes, bones, nerves and can be lethal if not treated and the disease is called black fungus or mucormycosis. During the peak i.e. in month of June 2021, India recorded 28,252 cases of black fungus among which 62.3% had been exposed to COVID-19 previously and researchers

revealed that Covid-19 patients are more favourable for this fungus because of humidity and moisture exposure during ventilation in ICU, which favours its growth [60].

5. Comparison between Spanish flu and covid-19

Table 2 Comparing Spanish flu and Covid-19

Sr. No.	Variable	1918 Spanish flu	COVID-19
1.	Source of emergence	Wild waterfowl (*Anseriformes*) [61]	Wild *Rhinolophus* bat [61]
2.	Infectious agent	H1N1 Influenza A virus [8]	SARS-CoV-2 [30]
3.	Origin and spread	Still uncertain but said to be originated in the military forts of the United States [6].	Wuhan, China [29].
4.	Age group affected	Younger populations were severely affected [62].	Elderly populations were severely affected [63].
5.	Transmission	Person-to-person transmission rate was low, but the infected patients faced more severe clinical problems [64].	Quite high rate of transmission from person to person, although the clinical problems were milder [65].
6.	Cell receptor	Binds to sialic acid receptors that are found on respiratory epithelial cells [66]. Within 10 hours these cells rupture, releasing approximately 10,000 viruses, each able to infect other cells.	Infects various cells of respiratory tract, gastrointestinal enterocytes, arterial and venous endothelial cells, as well as arterial smooth-muscle cells, by binding to ACE2 receptors [66].
7.	Symptoms	Headache, asthenia (weakness), joint pain, dry cough, high fever, cyanosis, neurological symptoms, bradycardia, haemorrhagic fever, primary influenza pneumonia and secondary pneumonia bacterial super infections [67].	High fever, cough, fatigue, neurological symptoms, lack of taste and smell, inflammation of conjunctivae of eye, gastrointestinal disturbances, and bilateral pneumonia [67].
8.	Clinical manifestations	ARDS can develop [68]. Need for intensive care and mechanical ventilator support higher [64]. Tissue damage mostly pulmonary [70] and pulmonary small-vessel thrombosis was prominent [71, 72]. Post mortem findings show severe pneumonias associated with DAD, hyaline membrane formation, and pulmonary edema. Enormous neutrophilic infiltrates in several [74].	Lung disease, such as pneumonia or ARDS, which may ultimately result in progressive respiratory failure [69]. Tissue damage in tissues and organ systemically [70] with neurological complications, and inflammatory syndromes [61]. Medium and small-vessel thrombosis reveal in autopsy studies of patients [73]. Post mortem findings show DAD including capillary congestion, pneumocyte necrosis, interstitial and alveolar edema with widespread thrombi [69]. Neutrophilic infiltrate infrequent [75].

9.	Complications	After-effects such as problems with sleeping, mental distractions, deafness, blindness, baldness, secondary bacterial pneumonia. In some heart problems, lung tuberculosis and kidney diseases later in life [27, 28, 76].	Not normally linked with secondary bacterial pneumonia. In some neurological abnormalities, pulmonary and cardiovascular manifestations, in some countries fungal infections reported causing mucormycosis (black fungus) [60, 76].
10.	Mortality	Mortality rate was statistically significant higher [64] with high mortality rate in young adults [77]. Death occurred after eight days of illness due to secondary bacterial infection [79].	Most deaths occurred in people over age of 70 years. Young children dying from infection are infrequent [78]. Patients died from hyperactive immune response which resulted in multiple organ failure [68].
11.	Treatment	Medical responses inadequate and people were unaware about the virus hence no such effective vaccines, antiviral drugs, or antibiotics available [80].	Plasma therapy, ICUs, antibiotic, antiviral, medical facilities and vaccines are available [56, 61].
12.	Impacts	Long term negative impacts on social aspects resulting into decrease in social trust [81] as well as negative impacts on economy [82] along with health of individuals are observed.	Widespread panic situation, negative impacts on the global economy, affecting international relations [83]. Mental distress leading to depression, anxiety and other mental health issues [84]. Positive impacts appear in environment such as decrease in pollution causes improvement in quality of air and water [85].

Note: DAD= Diffuse Alveolar Damage; ICU= Intensive Care Unit

6. Conclusion

COVID-19, due to its high mortality rate and quite high rate of transmission remind us of the first pandemic in the last century the 1918-19 influenza pandemic also known as Spanish Flu. Both are most devastating and lethal pandemics caused due to animal-human interface. Both diseases had shown massive global emergence via silent transmission by the respiratory route or by hands or fomites contaminated with respiratory secretions. Although they are respiratory diseases that can spread from person to person, there are some significant differences in their conditions, clinical course, and preventive measures. Influenza infects primarily by binding to sialic acid receptors that are found on respiratory epithelial cells, whereas SARS-CoV-2 infects various cells of the respiratory tract, gastrointestinal enterocytes, arterial and venous endothelial cells, as well arterial smooth-muscle cells. The speed of replication is much slower in COVID-19 as compared to H1N1, while both the diseases are generally associated with secondary fungal and bacterial infections. The mortality associated with COVID-19 is very different from H1N1, as it affected people with older age while in H1N1 younger populations were mostly affected. During Spanish flu pandemic, the medical knowledge was limited and hence there was unavailability of effective vaccines against the virus but now owing to advanced medical technologies, a large number of vaccines are under development, few of them are already approved and authorized for use. A few positive impacts on environment have been observed due to pandemic status but the negative impacts on physical as well as mental health caused by both the pandemics on lives of people globally remain wounding and irreversible for a long time.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that there is no conflict of interests.

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