



REVIEW

COVID-19 and Spanish flu-18: review of medical and social parallelisms between two global pandemics

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Keywords

COVID-19 • Spanish flu • Pandemic • Influenza

Summary

The intrusion of infectious diseases in everyday life forces humans to reassess their attitudes. Indeed, pandemics are able to catalyze rapid transitions in scientific knowledge, politics, social behaviors, culture and arts. The current Coronavirus disease-19 (COVID-19) outbreak has driven an unprecedented interest toward the influenza pandemic of 1918. The issue is whether history can shed light on the best preventive response and future scenarios. The aim of this review is to highlight the parallelism between the two pandemics. Starting from epidemiology and clinical features, but further focusing on social and cultural issues, it is possible to unveil great similarities. Their outbreak pattern led to hypothesize a similar duration and death burden in absence of effective vaccines or innovative treatments for COVID-19. Thus, then as now, preventive

medicine represents the first and most effective tool to contain the course of the pandemic; being treatments available only supportive. At the same time, both pandemics shared the same pattern of narration (e.g. scapegoating) and the same impact on minorities in high-income countries. Furthermore, visual art responded to pandemic issues in 2020 in the form of Graffiti art, while similar role was ruled by Expressionism movement during the Spanish flu. Photography also was capable to document both catastrophic scenarios. Thus, it is possible to find a lot of clinical and social similarities between the two pandemics. Nevertheless, if the Spanish flu was not unforeseen, COVID-19 spillover was partially predictable and its global impact will hopefully not be overshadowed by a major crisis such as World War I.

Introduction

Among the numerous challenges that human health has faced, infectious diseases have stood out for their ability to profoundly impact multiple aspects of human life. In fact, there is an intimate connection between the spread of infectious agents and the complexity of human behavior. Pathogens directly reflect who we are, what we do, and how we live and interact with other people, animals, and the environment [1]. Furthermore, great pandemics and local epidemics have influenced the course of wars, determined the fates of nations and empires, and affected the progress of civilization. All in all, infections have been supporting actors in the drama of human history [2, 1]. This intrusion in everyday life forces humans, without social, national or gender distinction, to ask themselves existential questions and stimulate cultural progress. Pandemics are ubiquitous by definition and hence they lead us to re-think the socio-cultural issues of the communities we live in. This happened with the bubonic plague of the fourteenth century, which, according to historians represented a *primum movens* to transit from the dark Middle Ages towards Humanism and the Renaissance [3, 4]. Similarly, the appearance of syphilis in the fifteenth-sixteenth century changed the dogmatic beliefs of medicine and encouraged the investigation of experimental approaches and practices. More recently,

the XX Century has seen the advent of HIV, which led to a profound re-assessing of socio-cultural issues and impacted multiple aspects of everyday life [5]. Now, the XXI Century challenges us with a pandemic caused by a previously unknown virus. How deep will its socio-cultural impact be on humanity? How long will it last? Will it be different from previous pandemics? And importantly, can history help us to make predictions? The current worldwide COVID-19 outbreak has driven an unprecedented increase in the public and scientific interest toward the influenza outbreak of 1918. A first look at the Google search trends since 2004 (<https://trends.google.com>) revealed marked increases in searches for Spanish flu on the web and on media in March and April 2020. Furthermore, according to a non-systematic PubMed search using the tool PubMed by Year, the search terms Spanish flu or influenza 1918 in their abstract/title reached an all-time high in 2020 [6]. Many of these publications tried to identify similarities and differences between the two pandemics in order to learn some lessons from the past. We are still in a similar situation than then, as we still don't fully understand the new virus, the characteristics of its disease, and which drugs to use against it. As we write, our hopes are focused on the arrival of the vaccine, which in 2021 could change the natural history of this virus. Nevertheless, the socio-cultural impact that this experience has had on a global level has yet to be fully

comprehended. This paper aims to carry out analysis of the literature to verify the actual similarities between the Spanish flu pandemic and that of COVID-19.

Epidemiology

The most probable origin of 1918-20 Flu pandemic was the rural area of Texas with different reported cases of severe flu-like symptoms between January and February 1918. The disease disappeared rapidly only to strike with vengeance different US military camps on March. It seem to have travelled with soldiers into the battlefields of France and Belgium before spreading all over the world. The epidemic wave registered in autumn 1918 was the most destructive one; with even Eskimos decimated and twenty percent of Wester Samoans perished. 1918 Flu killed more people than any other disease in a period of similar duration in high-income countries [7, 8]. COVID-19 pandemic probably started in a Wet Market in Wuhan, China, in November 2019. When the first case of pneumonia of unknown origin was registered outside of the market it was evident that inter-human transmission was possible. The death toll is high: Spanish Flu killed 5 million (mln) people in 3 years; while up to Dicember 2020 COVID-19 death count was around 55.000 with 1,6 mln people infected [9]. Other waves of COVID-19 have been registered since than worldwide in the form of the so-called “second and third wave”, similar to the one of Autumn 1918 for Flu.

Both viruses had basic reproductive numbers ranging from 2 to 4 and similar patterns of viral shedding; thus presumably comparable generation intervals. Specifically, Petersen et al. reported a R0 of SARS-CoV-2 of 2,5 while the R0 for H1N1 pandemic influenza of 1918 was 2.0 [10]. A key difference is the fact that age was a protective factor for Flu deaths in 1918 (probably for a partial immunity caused by the less known Russian Flu), while it is strongly related to worse outcomes for COVID-19 [9].

The similarities of waves of recrudescence have brought some authors to overlap historical trends of Spanish Flu and recent COVID-19 outbreaks. Indeed, weekly numbers of COVID-19-associated pneumonia deaths up to May 2020 and Influenza deaths up to May 1919 in England and Wales show comparable trends [11]. Also, the devastating 1918 Spanish Flu saw a 10% increase in mortality in large coal-capacity cities from baseline flu-related mortality; meanwhile nowadays it is estimated that about 15% of deaths worldwide from COVID-19 could be attributed to long-term exposure to air pollution [12].

As emerged from afore mentioned analysis, SARS-CoV-2 and H1N1 showed similar transmission features and an overlapping pandemic pattern, with periodic waves of recrudescence. This assumption lead us to hypothesize a similar duration and death burden of COVID-19 in absence of effective vaccines or innovative treatments able to break SARS-CoV-2 transmission chain all over the world.

Clinical features of the two pandemics

From a virological point of view, SARS-CoV-2 and H1N1 virus, the causative agent of Spanish Flu, are extremely different; with the first being an Influenza A (IA) virus and the latter being the seventh coronavirus known to infect humans [13]. H1N1 etiology of Spanish flu was confirmed in 1936 thanks to sierological investigation using neutralizing antibodies for swine influenza virus in human serum [14].

IA caused onia “superinfection” [15]. As for H1N1 infection SARS-CoV-2 causes COVID-19, characterized by direct lung damage in the form of ARDS. The latter is also capable of triggering a strong immune response which cause cytokine storm syndrome, which is the main cause of respiratory insufficiency [16].

A few medicines were used to relieve IA symptoms and aid their recovery, but drugs were considered less important than factors like regular meals, warmth, and plenty of fresh air and sunlight [17]. Among the first advocates of what was later to become known as the “*open-air method*” was the English physician John Coakley Lettsom (1744-1815), who demonstrated its efficacy against tuberculosis. In 1919 the physiologist Sir Leonard Hill (1866-1952) wrote in the British Medical Journal that the best way to limit influenza infection was deep breathing of cool air and sleeping in the open. Thus, sun exposure may have kept infection rates down because ultraviolet radiation capacity to partially inactivate IA viruses. Another advantage of placing patients outside in the sun was that they synthesized vitamin D in their skin. Thus, it has been hypothesized that low levels of vitamin D may increase susceptibility to respiratory viruses such as H1N1. Interestingly close to 30 or studies have demonstrated that optimal 25(OH)-vitamin D blood levels reduces COVID-19 risk of infection as well, risk of severe disease and ameliorate the outcome; thus suggesting vitamin D3 4-5,000 IU for adults as oral integrator [18].

During Spanish Flu specific treatments were lacking. Noteworthy, the guidelines used at the time suggested a therapy that we now know to be dangerous. As a matter of fact, Aspirin was widely used to relief Flu symptoms and the high doses prescribed between 1918-20 could have indeed increased IA mortality rates. The loss of Bayer’s patent on aspirin in February 1917 opened the doors for many manufacturers into the lucrative aspirin market while ignorance of the nonlinear kinetics of salicylate (unknown until the 1960s) predisposed its overdosing. Indeed, the molecule is capable of inducing pulmonary vascular bed permeability to fluid and protein leading to pulmonary insufficiency when prescribed at dosages suggested for IA (reaching also 1000 mg per day) [15]. Since the start of COVID-19 pandemic, different drug trials have been carried out in order to discover the applicability of knew molecules in limiting SARS-CoV-2 infection and in reducing its morbidity and mortality. The first drugs investigated from the available arsenal have been: Lopinavir/ritonavir (LPV/RTV), Hydroxychloroquine and Azitromycin. LPV/RTV is an old generation boosted

protease inhibitor prescribed to control HIV infection, having antiretroviral efficacy. Such molecule was showed to be effective against SARS-CoV virus in 2003 [19] and hence it was suggested for treatment of SARS-CoV-2 pneumonia. Hydroxychloroquine and Azitromycin were utilized for COVID-19 admitted patients during the first months of pandemic for their anti-viral and anti-inflammatory activities; evidence reinforced in a small trial by Gautret and colleagues [20]. However, to date the hopes of success of these old drugs have been partially abandoned and none of such molecules have been recommended in COVID-19 guidelines. As a matter of fact, the only antiviral drug included in different guidelines on COVID-19 management is Remdesivir; a inhibitor of SARS-CoV-2 RNA polymerase. As for H1N1 in XX Century, nowadays the strongest scientific evidence is on supportive therapies rather than virus-targeted drugs. Indeed, oxygen supplement, heparin and dexamethasone are the pillars of COVID-19 hospitalized patients treatment [21].

So no effective virus-specific treatment was prescribed in the case of H1N1 pandemic, as well as SARS-CoV-2 pandemic. However, in XXI Century there is another weapon to limit bacteria and viruses, only partially developed in the first decades of XX Century; namely the “vaccine”. In the case of SARS-CoV-2, an efficacious vaccine might prevent infection, disease, or transmission. With different SARS-CoV-2 vaccine candidates in phase III trials already and others approved from regulatory international agencies, the situation can be described as cautiously optimistic. However, there are many unknowns moving forward; the first is the fact that phase III trials need to demonstrate effectiveness and safety in a very large population. To conclude, first months of 2021 will be crucial to discover if available vaccines will halve COVID-19 pandemic, a hope not existing for H1N1 during 1918-20 biennium. As a matter of fact, the causative agent of Spanish Flu was thought to be *Bacillus influenzae*, isolated from the first time from Pfeiffer during a previous Flu pandemic (Russian Flu 1989-90) [9].

Infection control and prevention attempts

The public health measures considered to control the COVID-19 infection in 2020 overlap more than any other the ones taken for Spanish flu [22]. Pasteur and Lister and the acceptance of the hygienic principles postulated by Semmelweis. Indeed, then as now, it is good habit to isolate the sick, avoid crowding, especially in communities, and disinfect the environments. For example, it was proposed to avoid contact with the sick and convalescents, as well to limit unnecessary crowds and travels. Specifically, was decided to close the taverns in the evening and the closure of the cinemas, suspend the funeral processions, and limit access to public transport. Moreover, it was widely recommended to wash hands several times a day to avoid the virus spread [23].

Of interest is the fact that in 1918 the systematic use of masks as protective equipment appeared for the first time in history. Initially, masks were widely used in hospitals in the United States, made with “*half a yard of gauze, folded like a triangular bandage, covering the nose, mouth and chin, and tied at the back of the head*”. Later, their use was extended to the general population (Figure 1) until they were imposed as in the case of the city of San Francisco. The Stanford University website reports contradicting results of two studies; the first, published in JAMA, reported a rapid decline in the number of cases of influenza among those wearing the mask, while the results of the latter did not show similar success in the Great Lakes region [24]. In fact, there was a small difference in the development of the disease between hospital staff who wore them and those who did not (8% vs 7.5%) in favour of the latter [24]. Contrary, some measures mirrored the misconceptions of past times. As a matter of fact, the BMJ on 2nd November 1918 published the suggestions of the Paris Medical Academy for the prophylaxis of influenza, giving importance to mildly disinfectant mouthwash [25].

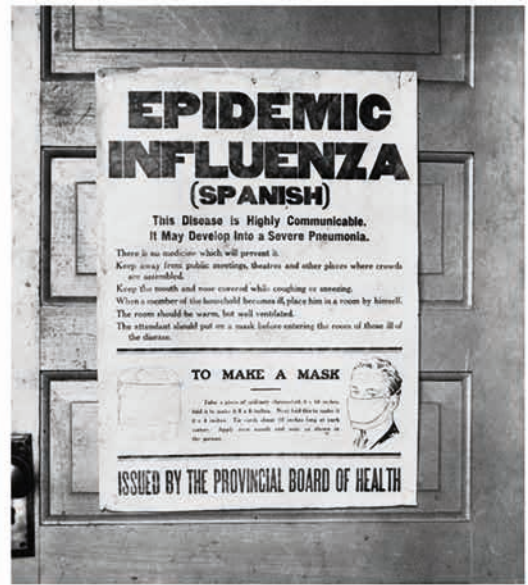
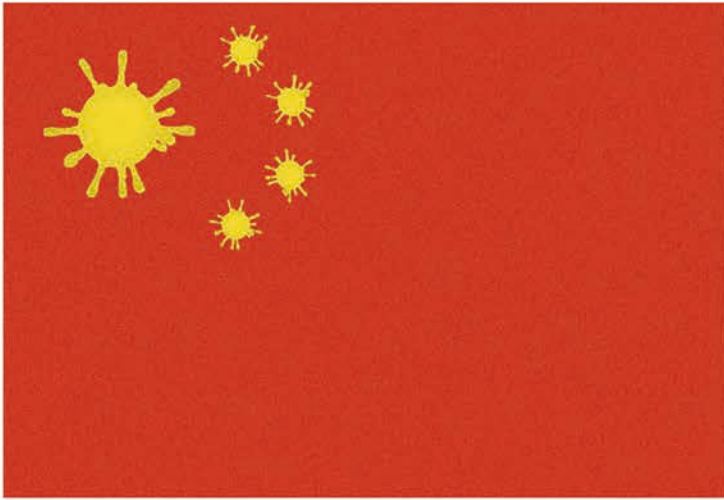
Preventive medicine, then as now, certainly represents the first and most effective tool to halve the course of a pandemic. Furthermore, nowadays we can take advantage of new technological possibilities to enhance hygiene measures, for example the contact tracing programs on smartphones.

Social implications of the two pandemics

Both pandemics have generated a big amount of myths behind their origins. Spanish Flu was believed to be a new weapon of war. Some stated that the germs causing it were inserted into aspirin made by the German drug company Bayer. Others believed that the plagued arrived in US on a camouflage German ship that had crept into Boston Harbor under cover of darkness and released the germs that seeded the city [7]. The most viral myth on COVID-19 origin is that SARS-CoV-2 was artificially created in a lab by a rogue government with an agenda; while seems to be demonstrated that it evolved from animal hosts [26].

Fear and frustration for both viruses led communities to identify *scapegoats* during their first months of pandemics. In the months since the coronavirus pandemic began, thousands of Asian Americans in the US have become targets of verbal assaults. As infection appeared, US politicians and citizenship repeatedly referred to COVID-19 as the “*China virus*” and “*Chinese flu*”; while also the term “*Kung flu*” was widely used to describe the syndrome [27]. Back to 1918 it is possible to use the nomenclature given to the pandemic—the Spanish flu—as a window into the role that xenophobia, stigmatization, and the scapegoating of vulnerable populations play in pandemic social responses. As Hoppe and colleagues explains, giving a disease the name of a foreign or minority community is inherently related to the desire to wall off those who are viewed as sources of contagion

Fig. 1. Example of a present and past ethnicisation of the pandemic. The National Flag of the People's Republic of China adapted with the SARS-CoV-2 shape, encountered on the web. A poster issued by Alberta's Provincial Board of Health alerting the public to the 1918 influenza epidemic, called Spanish as undertitled in the photo.



[28, 29]. As a matter of fact, Spain was the only country where, because of its neutrality in warfare, it was possible to advise the population against the new viruses while for the countries in war a strong censorship was the rule (Fig. 1). Nevertheless, unlike previous epidemics or pandemics, in 1918 only few cases of personal stigmatization were registered. Indeed, only 2 newspaper clips are available blaming Italian immigrants. Probably influenza spread so quickly across various levels of the population that it was hard to scapegoat anybody [7, 30].

Pandemics exact disproportionate toll on minority groups and magnify existing disparities. The broader context of the 1918 pandemic is critical for understanding the historical, as well as contemporaneous, landscape of health disparities. One interesting example is the fact that the few studies examining racial differences in the 1918 pandemic found that the population of African-Americans in US had lower influenza incidence but higher case fatality. Structural inequities have historically contributed and continue to compound disparate health outcomes in minority communities [31]. Recently, the Johns Hopkins University and American Community Survey showed that in US the infection rate and the death rate of COVID-19 in predominantly Black counties were respectively 3-fold higher and 6-fold higher than that in predominantly white counties [32]. One Century passed, but Black and Brown people continue to die at a disproportionate rates because of such viruses.

In both pandemics science and politics were entangled in complicated battles; at the point that in USA in some towns, cities and states, the act of wearing a mask became a statement of political allegiance in anticipation of presidential elections of November 2020. Back in 1918 wearing a mask was described as a wartime symbol of patriotism [33].

To conclude from false myths behind their origins, through scapegoating and political and ethnical implications both pandemics seem to share a similar pattern of narration and the same impact on minorities in high-income countries.

Mass culture

The COVID-19 pandemic is shaping the XXI Century from its beginning. How will this event be remembered by arts? How will paintings and pictures represent the human emotion and tragedy resulting from the suffering, death, and fears of an invisible enemy called SARS-CoV-2? To make such predictions it would be interesting to start analyzing how visual arts responded to Spanish Flu in 1918-20 period. The pain, the terror of illness, the fearful stress that gained people's minds were not an easy context for the flourishing of arts. It was a pandemic consisting of different personal tragedies and artists, as the general population, balanced their need to forget and the need to create some form of memories. Edvard Munch (1863-1944), a Norwegian painter, author of the well-known "*The Scream*"- 1893, painted two self-portraits after having contracted the disease. In the first canvas, "*Self-portrait with the Spanish Flu*"- 1919, Munch portrayed himself as a sick person in the middle of his room, while in the second "*Self-portrait after the Spanish Flu*"- 1919-20, the focus shifted on his sunken dark face: probably due to the lack of oxygenation because of bronchopulmonary complications [34, 35]. On 7th January 1918, the Austrian artist Egon Schiele (1890-1918) had to visit his mentor, the famous Gustav Klimt (1862-1918), in the Allgemeines Krankenhaus in Vienna. The day before, Klimt had died of a stroke that many

Fig. 2. a) Banksy new masterpiece “Game Changer” - 2020. The objective of his work is to replace fiction super-heroes with real superheroes, the ones working in NHS and facing day by day SARS-CoV-2. b) of the same opinion is the famous writer Fake who dedicated the “Super Nurse”- 2020 to healthcare workers in difficulties during COVID-19 management.



believe was a result of the flu, suffering simultaneously from pneumonia. The visit sadly resulted in three haunting drawings of a deceased Klimt's head, showing his face deformed from the stroke [36, 37]. As briefly reported above, the Expressionism seems to have been the most sensible art movement to return IA pandemic struggles in the form of visual art. The term *expressionism* refers to the art tendency of returning a reality distorted in order to make it expressive of the artist's inner feelings or ideas. As expressionism back in early XX Century was able to freely deliver author's thoughts to the audience, nowadays Graffiti permits feelings to be *expressed* without boundaries of space and age. Flourished thanks to hip hop culture, Graffiti art refers to images or text painted usually onto buildings, typically using spray paint [38]. During COVID-19 pandemic this movement, and in general street art, have striking works, creating temporally *mementos* in the urban context. The most famous examples came from Banksy (1974-) pens and stencils. On 6th May 2020 he donated a one meter by one meter work to the University Hospital of Southampton (UK). In the print, titled “*Game Changer*”- 2020 and showed in Figure 2a, a child is dressed in an onesie and next to him a basket contains abandoned Batman and Spider-Man puppets. The child holds, with his arm raised, his new super hero: a nurse with her arms in the classic posture of Superman in action. The artist desired to homage doctors, nurses, nursing staff, ambulance teams and in general people working in hospitals with grueling shifts. During the first months of the ongoing pandemic Healthcare Systems personnel was at the center of attention and its workers depicted as “*angels*”. Other gifts showing the love to healthcare workers are “*NHS Heroes*”- 2020 by John D’oh and “*Super Nurse*”- 2020 by Fake (Fig. 2b), both perfectly capturing the

heroism of the nurses on the pandemic frontline. Another image become a redundant topic in street art is the face mask and protective personal equipment (PPE) in general [39]. One example came again from Banksy and is the addition of a blue surgical face mask to the well-known “*Girl with a Pierced Eardrum*”- 2014, a take on Dutch artist Johannes Vermeer's painting but with a security alarm replacing the pearl.

Although the 1918 flu pandemic was a human disaster, its cultural legacy was overshadowed by that of the First World War and soon forgotten. Indeed, artists were more interested in depicting war than collapsing healthcare systems [35]; probably only the Expressionist movement left a portrait of the past suffering. By contrast, during the COVID-19 crisis, it is possible to denote an inner bond between arts; mainly modern tendencies and the struggle to contain the ongoing pandemic. Such images are being fixed in the world's collective consciousness owing to the pervasive capacity of the Internet. Will they last, or will they survive only until the struggle ends?

Ever since its invention, photography, like painting, has been used to document catastrophic scenarios. In this regard, photographic reports and masterpieces of visual art were produced both during the 20th century's most devastating pandemic and during the current COVID-19 outbreak.

The so-called “Spanish Flu” was the first major pandemic of the modern era; and it was also the first to be widely photographed. In army camps, in hospitals, in streets and in workplaces, photographers captured the struggle to deal with the crisis.

From the mundane to the grand, these photographs constitute a visual archive of people racked by the disease [40]. As shown in Figures 3 and 4, photography has documented clinical situations and moments of

Fig. 3. a) Paramedics with PPE transporting a corpse during the COVID-19 pandemic. b) The influenza ward at the Walter Reed Hospital in Washington, 1918. Simply-to-make protective masks were worn by healthcare workers.



daily life during both pandemics; in the light of the current pandemic, the concept of normality has been revised. Since the first COVID-19 lockdown, several cultural initiatives have featured photography. One example is the foundation of the Covid Photo Museum (CPM), the world's first virtual museum dedicated to the photography of the COVID-19 pandemic [41].

Conclusions

Emerging infectious diseases are a significant and growing threat to global health, the global economy and

global security. They mainly originate in wild animals, and their emergence often involves dynamic interactions among populations of wildlife, livestock and people within rapidly changing environments. The COVID-19 pandemic was fairly predictable. Bats are known to harbor zoonoses and, as recently reported by Deszak and colleagues, 13,000 coronaviruses are silently waiting for possible spillovers [42, 9].

Although only 0.1% of the 1,600,000 viruses capable of causing epidemics and/or pandemics are known, the 2020 pandemic was randomly forecast by Johns Hopkins Center for Health Security. Indeed, a model of an imminent pandemic was created and called CAPS

Fig. 4. a) Everyday life in 2020 means face mask adoptance in public places included flight. b) Football match audience wearing protective masks during the Spanish Flu epidemic of 1918.



– Coronavirus-Associated Pulmonary Syndrome. The setting was New York in October 2020, a couple of weeks before the first cases of COVID - Coronavirus Disease. This simulation correctly captured both the family of the virus which then caused the actual pandemics, and the circumstances of the spillover [9, 43].

By contrast, Spanish Flu was not predictable, for the simple reason that viruses were not known at the time. It was a destructive disease of unknown origin. Today, however, we are certainly to blame for ignoring the increasing risk of spillover caused by human exploitation of the biosphere. The risks of anthropization were not so deeply known during Spanish Flu pandemic. Thus, we had a whole century of training and scientific development in order to prepare for this latest pandemic. The question that arises is whether our society is ready to bear its responsibilities and learn from present errors. Indeed, as Rudolf Virchow (1821- 1902), the father of modern pathological anatomy, used to say: “An epidemic is a social phenomenon that has some medical aspects” [44]. As recently stated by a colleague, we, as physicians, “are uniquely positioned to discuss what is important to improving the health of our communities and [...] to recover from this pandemic and prepare for the next” [45]. Our best hope is to find ways to cure the patients affected worldwide and to repair the damage to society.

Availability of data

Figure 1 taken from <https://unsplash.com/>, created by visuals and from <https://commons.wikimedia.org/>. Figure 2a and 2b usage under the personal permission of the two authors. Figure 3a is an image of Isaac Quesada on <https://unsplash.com/>. Figure 3b is taken from Public domain CC0 pictures on <https://www.rawpixel.com/>. Figure 4a is an image of ismail mohamed - SoviLe on <https://unsplash.com/>. Figure 4b is taken from <https://commons.wikimedia.org/> and is of Public domain.

Acknowledgements

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

OS and EA designed and conceived the study; OS and EA drafted the manuscript; OS, MM and EA revised the manuscript, performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper.

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Received on April 27, 2021. Accepted on July 20, 2021.

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How to cite this article: Simonetti O, Martini M, Armocida E. Covid-19 and Spanish flu-18: review of medical and social parallelisms between two global pandemics. *J Prev Med Hyg* 2021;62:E613-620. <https://doi.org/10.15167/2421-4248/jpmh2021.62.3.2124>

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