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Immunity Markers in SARS-CoV-2 with Lessons Learned from H1N1 Flu Pandemic

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Abstract

A novel outbreak with global implications, COVID-19 can be compared with the 1918 Spanish flu in many aspects. Thus, preventive and therapeutic strategies that once proved to be effective in the containment of the old pandemic, such as self-isolation and convalescent plasma therapy, respectively, might once again come to our aid and prevent further outbreaks of the disease in the years to come. In our opinion, the COVID-19 pandemic can be harnessed in a way similar to the Spanish flu, provided that the preventive and therapeutic strategies are properly executed.

1. Introduction

In 1918, the H1N1 flu pandemic led to devastating consequences [1]. Starting in January 1918, the Spanish flu came in two major waves, with the latter ending in December 1920. The pandemic resulted in the infection of about 500 million, and the death of 50 million patients around the globe [2]. Mortality and morbidity of the 1918 flu pandemic were much greater than the corresponding figures in the 1889, 1957, and 1968 pandemics [3]; as illness severity incited severe systemic cytokine response in patients [4]. At that time, quarantine seemed to be the only option to decelerate transmission [5].

A study on individuals born prior to the pandemic has revealed evidence of strong seroactivity to the virus [6]. The aforementioned study reported cross-reaction between the antibodies and the genetically similar

hemagglutinin (HA) of the 1930 swine flu A (H1N1) virus. Obviously, the survivors of the flu pandemic in 1918 still retained mostly functional antibodies to the causative strain several decades after the first exposure [6].

Through the last century, passive antibody and plasma therapy have been experimentally used for the treatment of the Spanish flu, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) [7]. A meta-analysis on the results of eight non-randomized trials during the 1918 influenza pandemic reported case fatality rates of 16% and 37% among patients receiving the plasma and those in the control group, respectively [8].

Regarding humoral immunity, a portion of B cells responding to viruses can survive for many decades [9]. These long-lived plasma cells maintain a standing level of long-term immunity [10]. However, they remain dormant in the bone marrow [11, 12]. It is speculated that individuals who had previously been exposed to the H1N1 virus in 1889 or earlier, possessed antibodies still functional against the 1918 strain [13].

A previous study showed that immunization with the classical swine H1N1 virus and the 1918-equivalent vaccines can result in the production of antibodies against the 2009 swine H1N1 flu, and this conveys antigenic similarities between these strains. It can be inferred that a large fraction of the population possesses antibodies to the 1918 strain because of the 2009 H1N1 flu pandemic and notable vaccination measures. This is a reassuring finding in case of a resurgent H1N1 flu outbreak [13].

A cohort study on 93 participants with severe H1N1 flu reported lower mortality in subjects who received H1N1 convalescent plasma [14]. In following, it was suggested that transfusion of convalescent sera would serve as a promising approach in future outbreaks [15]. The idea was further supported by a clinical trial that confirmed the safety of convalescent plasma therapy (CPT) in terms of adverse effects [7]. This was further supported by another study [14] that emphasized the efficacy of CPT in treatment of severe flu. This study reported higher geometric mean titers of antibody against A/California/07/2009 in both vaccinated individuals and rehabilitated patients [16].

Today, large volumes of plasma are currently produced under the Food and Drug Administration (FDA) regulations [17]. A single donor could provide a weekly supply of H5N1 convalescent plasma. This is also a safe practice for donors, since the cellular components of blood are returned to the donor under sterile conditions. Convalescent plasma can also be exported to other regions in the form of frozen plasma [8].

In regard to the seasonal flu, several studies [18] have indicated that cross-protective immunity in individuals who developed flu in the early phase of the multi-wave H1N1 pandemic [19]. Hence, natural infection and/or vaccination in the early phase might prevent a more fatal resurgent outbreak. In 2009, scientists modeled the transmission patterns of two strains of flu viruses interacting through cross-immunity. Moreover, their results simulated two temporal waves of influenza outbreak and estimated the timing of between two waves. According to their findings, avoiding the second outbreak cannot be impossible because of an adequate level of cross-protection attained by either natural infection or vaccination in the first wave. Importantly, interventions for mitigation of the first wave might lead to a more virulent second wave of infection [18].

A cohort study in 2011 assessed herd immunity to swine flu in 28 paired serum samples from participants who had previously been infected with the 2009 H1N1 virus [18]. Their findings indicated that the participants had developed cross-reactive immunity to the more recent subtypes of H1 swine virus [20].

The COVID-19 pandemic has inspired lots of comparisons to the 1918 flu pandemic [5]. Figure 1 and Table 1 summarize the comparison of coronaviruses (COVs) [21].

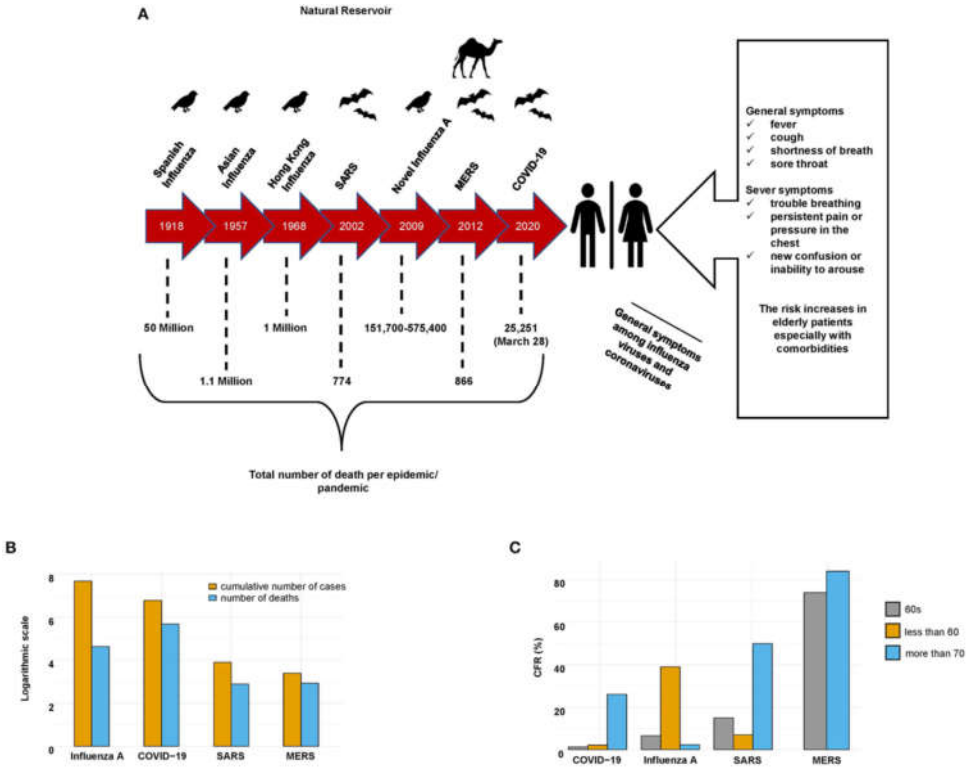

Figure 1. General features of MERS-CoV, SARS-CoV, SARS-CoV-2, and influenza A virus. (A) Characteristics of the outbreak caused by each strain. (B) Cumulative numbers of cases and deaths caused by each strain. While Influenza A virus has the greatest infectivity, SARS-CoV-2 managed to cause the highest number of deaths. (C) Case-fatality rate (CFR) of patients infected with each strain stratified based on age. (copied from an open access article [21])

Table 1. General characteristics of SARS-CoV-2, SARS-CoV, MERS-CoV, and influenza viruses [21]

Characteristic	Influenza A	SARS-CoV	MERS-CoV	SARS-CoV-2
Year and country of the first reported case	1918, United States	2002, China	2012, Middle East	2019, China
Natural reservoir and Intermediate host	Birds and Pigs	Bats and Cats	Camels	Bats and Debatable
Transmission mode	Contact, droplet, aerosol	Contact, droplet, aerosol	Contact, droplet, aerosol	Contact, droplet, aerosol
Incubation period (day)	2	2–7	2–14	2–14
Reproduction number (*R*0)	Median: 1.27; IQR: 1.19–1.37	Median: 0.58; IQR: 0.24–1.18	Mean: 0.69 (95% CI 0.50–0.92)	*R*0 = 3.1 (coefficient of determination, $r2 = 0.99$)
Host receptor	Molecules consist of Sialic acid	ACE2	DPP4	ACE2
Entry pathway	Receptor-mediated endocytosis	Endocytic pathway	Cell membrane fusion	Unclear
Blood tests	Lymphopenia, eosinopenia, hypoferremia, ↓↓ serum CO2-CP, ↑↑ serum CRP, ↑↑ serum CH50	Lymphopenia, thrombocytopenia, leukopenia	Leucocytosis, monocytosis, low CRP	Lymphopenia, thrombocytopenia, leukopenia, leucocytosis, monocytosis, low CRP
CFR	0.1%	~15%	34.4%	1–3%

CFR: Case fatality rate, CRP: C-reactive protein, CI: confidence interval, ACE2: Angiotensin-converting Enzyme 2, DPP4: Dipeptidyl peptidase-4 inhibitor, CO_2-CP, carbon dioxide, CH50: Total Complement Activity, IQR: interquartile range, MERS-CoV: Middle East respiratory syndrome-coronavirus, SARS-CoV: severe acute respiratory syndrome-coronavirus

Thus, in a similar way, strategies like public health education, quarantine, and vaccination as well as convalescent plasma therapy may act in concert to prevent resurgent outbreaks as far as 2023. For the time being, the website of the World Health Organization (WHO) provides valuable advice to raise the public knowledge by inviting people to wear face masks and observe social distancing [22].

2. Conclusions and Future Perspectives

Although the rather newly identified SARS-CoV-2 has shown far more aggressiveness than its predecessors, this should not be perceived as a reason for indefinite chronicity of the present outbreak, as our experience with comparatively devastating epidemics in the past, such as the 1918 Spanish flu outbreak, indicate that the situation with COVID-19 is likely to be placated by the natural dynamics governing the infectivity of a newly emerged viral strain throughout the time. Proved to be appreciably effective more than a century ago, self or patient-isolation and therapeutic interventions, such as convalescent plasma therapy will continue to contribute to containment of the current situation, as they did in the time of the Spanish flu.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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