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Responses against infectious disease pandemics: a narrative review on COVID-19

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ABSTRACT

Currently, the world is facing the coronavirus disease 2019 (COVID-19) pandemic. With this, an emerging infectious disease pandemic in the absence of effective antiviral agents and vaccines for a novel virus is no different from the 1918 influenza pandemic, which became a great disaster for humankind. We also experienced a global lockdown with a stringent implementation of social distancing, which is a first for mankind living in the present day, and has led to enormous economic damage and restrictions on individual freedom. The microorganism that will cause the next pandemic may be a highly fatal avian influenza virus, another coronavirus, or a completely different microorganism. This COVID-19 pandemic is an enormous lesson for humankind and is tantamount to a vaccine in preparation for the next pandemic. Important and urgent undertakings were given to each country in terms of complementing laws and regulations for a stronger and more resilient healthcare system, such as investment in research and development for new rapid diagnostic technologies, vaccines, new therapeutic agents, among others.

Keywords: Coronavirus; COVID-19; Disease outbreaks; Emergency preparedness; Influenza, human

INTRODUCTION

In the past, infectious diseases were a great threat to mankind, and the infant mortality rate was exorbitantly high that in Asia, celebrations were held to celebrate the 100th day and 1st year after birth. Epidemics of infectious diseases such as plague killed more than a third of the European population during the 5 years of the Middle Ages [1], and the emergence of various infectious diseases such as smallpox from Europe had a significant impact on the decline of the Native American population [2].

In the past 150 years, great advances have been made in the prevention and treatment of infectious diseases due to advances in medicine, improvement of personal hygiene, and development of vaccines and antimicrobial agents; however, emerging infectious diseases continue to pose a threat to humans. In particular, it has been emphasized that a pandemic caused by

emerging infectious diseases can cause serious disasters to mankind at any time; therefore, it is necessary to prepare for it. However, it is true that preparations were not sufficient, and this coronavirus disease 2019 (COVID-19) pandemic clearly revealed it. This paper intends to suggest how to prepare for the next pandemic by comparing and reviewing the recent pandemics experienced from the 1918 influenza pandemic to COVID-19.

THE 1918 INFLUENZA PANDEMIC AND THE RESPONSES

It is estimated that the pandemic caused by the influenza A (H1N1) virus, which lasted for about 2 years from February 1918, infected more than 500 million people out of a population of 1.8 billion at that time, resulting in more than 50 million deaths [3-5]. At this time, the disease was thought to be transmitted through the respiratory route, but the causative microorganism was not identified, and, of course, there was no accurate diagnostic method, no antiviral agent, or available vaccine. In addition, antibiotics to treat secondary bacterial pneumonia have not yet been developed. Overall, the medical care for influenza and its complications is very limited. Advanced organ supportive technologies did not exist, and intensive care units were not available until the 1950s [6].

The only way to fight this pandemic was to wear a mask and implement social distancing. Community mitigation measures included the mandatory isolation of sick persons and quarantine of their contacts, school closures, and bans on public gatherings [7]. In fact, efforts to stop the spread of infection through social distancing and isolation of infected persons were attempted when the Black Death epidemic in medieval Europe killed many people. The term “quarantine” was also derived from a policy that mandated a 40-day observation period before disembarking from a ship arriving in Venice, Italy [8]. The social picture of that time, when human relationships were devastated by avoiding meeting between close friends and even family members, is well described in the work “The Decameron” by Giovanni Boccaccio (1313 to 1375), a literary writer at the time.

RESPONSES AGAINST THE 1957 AND 1968 INFLUENZA PANDEMICS

Compared to the influenza A (H1N1) pandemic of 1918, the damage caused by the influenza A (H2N2) pandemic of 1957 and the influenza A (H3N2) pandemic of 1968 were relatively small (Fig. 1) [9-11]. The reason may be that at that time, unlike in 1918, there were powerful weapons that could counteract them. After the first successful isolation of influenza A virus in 1933, a live attenuated monovalent vaccine was developed, and an inactivated bivalent vaccine was also developed and used following the isolation of influenza B in 1940 [12]. As soon as the pandemic influenza virus strain was identified, vaccines targeting this new strain could be produced within months. Although its therapeutic effect was not strong, amantadine, the first antiviral agent against influenza virus, was developed in 1964 [13]. In addition, following the discovery of sulfa drugs in the late 1920s, penicillin ushered in the antibiotic era since 1940.

PREPAREDNESS FOR POSSIBLE NEXT INFLUENZA PANDEMIC IN THE EARLY TO MID 2000S

All three respiratory virus pandemics in the last 100 years of the 20th century were caused by the influenza virus and the emergence of human infection by the highly pathogenic avian influenza virus since the late 1990s influenced the national strategies to prepare for the next pandemic crisis in the early to mid 2000s. In particular, there was a high awareness that the time had come for a new influenza pandemic to occur after the last influenza pandemic in 1968. At that time, the most important tool in preparedness guidelines was to immediately start the development of a vaccine targeting the new pandemic virus strain in the event of a novel influenza pandemic and secure vaccine-manufacturing facilities to produce enough amount to vaccinate the entire population [14-16]. The second was to stockpile antiviral drugs such as oseltamivir, an effective therapeutic agent for influenza, developed in 1996, in an amount that can be administered to more than 25% of the total population so that they can be used during a pandemic [15]. As such, the most important weapons in response to the novel influenza pandemic are vaccines and antiviral drugs, which can be used immediately, so the importance of non-pharmaceutical measures such as social distancing could be considered as relatively low.

RESPONSES AGAINST THE 2009 INFLUENZA A (H1N1) PANDEMIC

The 2009 influenza A (H1N1) pandemic was a pandemic that had been anticipated to some extent like this, and diagnostic technology for viral infection had already greatly advanced,

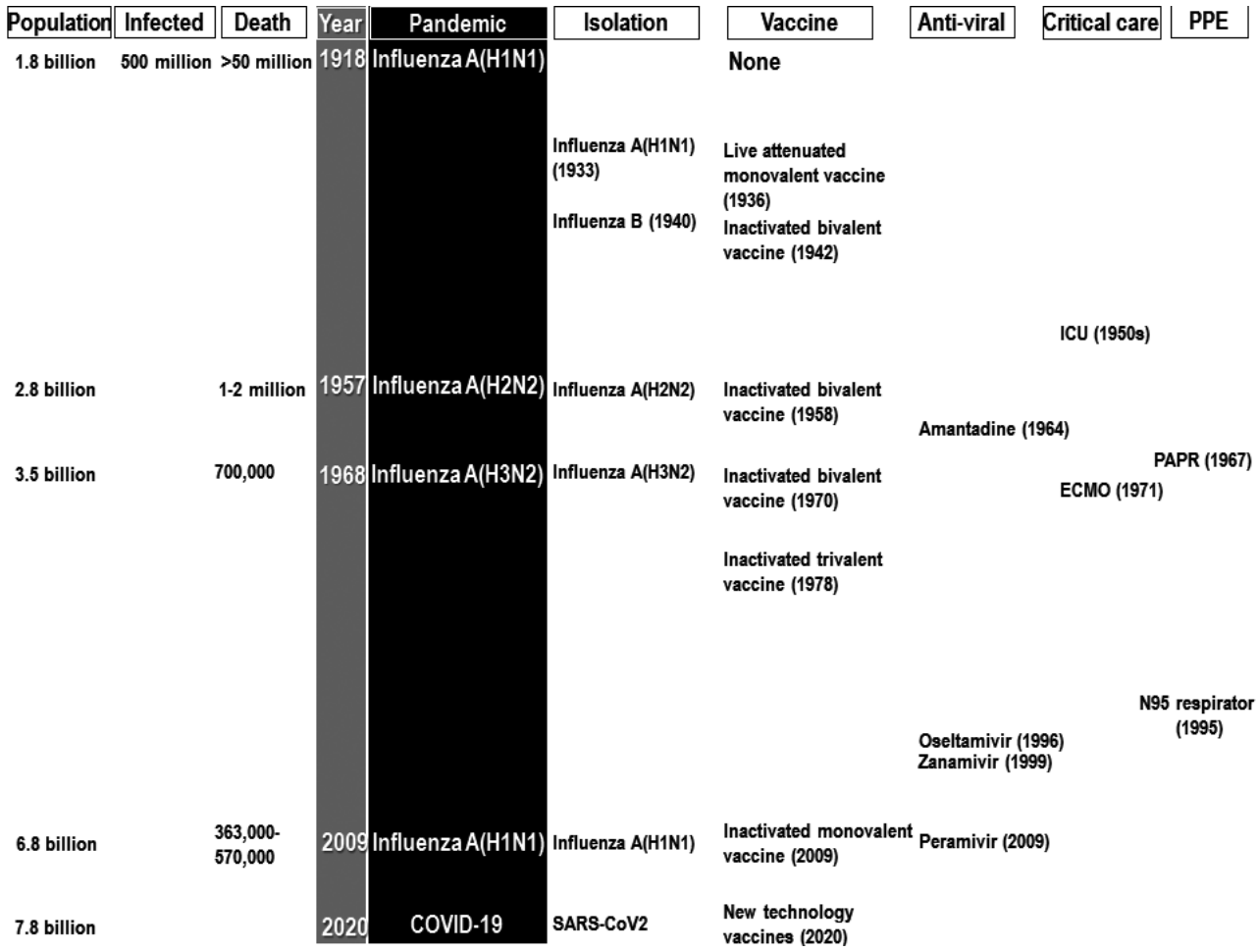

Fig. 1. Comparison of the magnitude of outbreaks and availability of vaccines and antiviral agents between the pandemics since 1900. PPE, personal protective equipment; ICU, intensive care unit; PAPR, powered air purifying respirator; ECMO, extracorporeal membrane oxygenation; COVID-19, coronavirus disease 2019.

and the nucleic acid detection-based technology such as the real-time reverse transcriptase-polymerase chain reaction method was utilized very efficiently [17]. Crisis response capabilities differed by country. Although some developed countries were able to respond better according to preparedness guidelines, vaccine production capacity and stockpiles of antiviral drugs varied greatly between countries, which made it particularly difficult to respond to the crisis in countries where there was a shortage of antiviral agents for months before the vaccine was available [18]. However, fortunately, 2009 influenza A (H1N1) did not show a high fatality rate; therefore, it was only at a level similar to that of seasonal influenza, and the damage caused by this pandemic was not as great as initially feared [19].

GLOBAL RESPONSES AGAINST SEVERE ACUTE RESPIRATORY SYNDROME

Prior to the 2009 influenza pandemic, many countries experienced a public health threat due to the epidemic, which was caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) that emerged in late 2002. The SARS-CoV was the first strain capable of causing a global outbreak in recent human history, with a strong transmission and a high fatality rate; however, it faded out due to intense public health mitigation measures and international cooperation. The SARS outbreak ceased in June 2003, with a total of 8,096 reported cases and 774 deaths (case fatality rate 9.6%), with most cases being acquired nosocomially [20]. Although an effective vaccine against SARS-CoV was not available at that time, the SARS epidemic could be controlled by the successful implementation of various non-pharmaceutical measures. The re-

sponse to the SARS epidemics in Asian countries, including China, Hong Kong, Taiwan, and Singapore, as well as other countries such as Canada, could serve as an opportunity to strengthen their response system for highly infectious disease crises [21-25].

RESPONSES TO THE CURRENT COVID-19 PANDEMIC

Following the epidemic caused by SARS-CoV in 2002 and the novel influenza A (H1N1) pandemic in 2009, the pandemic that has come as a threat to all countries in the world for 10 years was a new CoV, not the influenza virus that mankind has anticipated and has been preparing for, which has made it difficult to control at the beginning of the pandemic. This is the first CoV that has caused a pandemic in recent human history. CoVs have repeatedly crossed species barriers, and some well-known examples are SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses likely originated from bats and then jumped into another mammalian host before crossing species barriers to infect humans: the Himalayan palm civet for SARS-CoV and the dromedary camel for MERS-CoV [26].

Because influenza virus is a respiratory virus that continues to cause seasonal epidemics around the world, there is an established infrastructure for global surveillance, prevention, and treatment that can be applied to any new pandemic strain. Vaccine-manufacturing companies can produce a vaccine for a pandemic in a few months in collaboration with the public health sector, which actually occurred during the 2009 influenza pandemic. In contrast, there are no existing vaccines or effective antiviral agents for coronavirus. Unlike the influenza pandemic, in order to develop a vaccine with proven efficacy and safety, vaccine candidates had to start with phase 1 clinical trials [27]. However, fortunately, SARS-CoV-2 has a high genetic similarity to SARS-CoV [28], as the name suggests, and so previous studies on virulence factors of SARS-CoV and some experiences in the early stages of vaccine development against SARS-CoV helped speed up vaccine development to some extent during this pandemic by SARS-CoV-2 [29-33].

The increase in international flight traffic from China during the past decades has accelerated the initial spread of this virus between countries to a more rapid pace [34,35]. In addition, in contrast to SARS-CoV, it has been difficult to contain the spread of infection because patients with COVID-19 begin viral shedding and transmit the virus even before symptoms develop [20]. At the beginning of this pandemic, we experienced that SARS-CoV-2 caused significant morbidity and mortality in the elderly, and that a sudden increase in the number of severe cases of COVID-19 caused the collapse of the nation's healthcare system [36-39].

Until an effective vaccine was available, non-vaccine preventive measures, including wearing a mask, were very important [40-42]. Policies of various regulating strengths, from a nationwide lockdown to targeted social distancing, have been applied differently in each country and even within each country depending on the epidemic situation [43,44]. In addition, policies that prohibit entry from countries with large outbreaks or that apply a 2-week quarantine to those arriving from abroad have been widely implemented. Efforts to prevent the spread of infection included mandatory quarantine, people wearing masks both indoors and outdoors, school closures, sports stadiums with empty spectators, business closures, prohibition of large-scale private and public gatherings, international travel restrictions, conferences or seminars held in virtual meetings, and so on. Such interventions have also resulted in global economic disruptions [45,46]. These multifaceted public health interventions would seem as if we had returned to the 1918 influenza pandemic situation; however, it was an unavoidable and a very important preventive measure during the first year of this pandemic in the absence of a vaccine.

Some countries, such as Sweden, have minimized the lockdown policy and adopted the herd immunity strategy at an early stage of this pandemic with the expectation that herd immunity would be reached faster to minimize further waves of transmission [47]. However, this strategy failed because an increasing number of patients with severe COVID-19 exceeding the surge capacity resulted in increased deaths and disruption of the healthcare system. It should be stated that this is not a realistic approach for many countries as it works best when a country has a certain age demographic like younger and healthier populations and a healthcare system capable of handling a large number of cases [48].

To alleviate social distancing or lockdown policies that caused great inconvenience to life and took a toll on the economy, the successful development and mass production of effective and safe vaccines are urgently needed. Initially, there was no guarantee that vaccine development would be successful in 12 to 18 months [49,50]. However, fortunately, the vaccine was successfully developed, and vaccination began less than a year after it was declared a Public Health Emergency of International Concern on January 30, 2020 by the World Health Organization

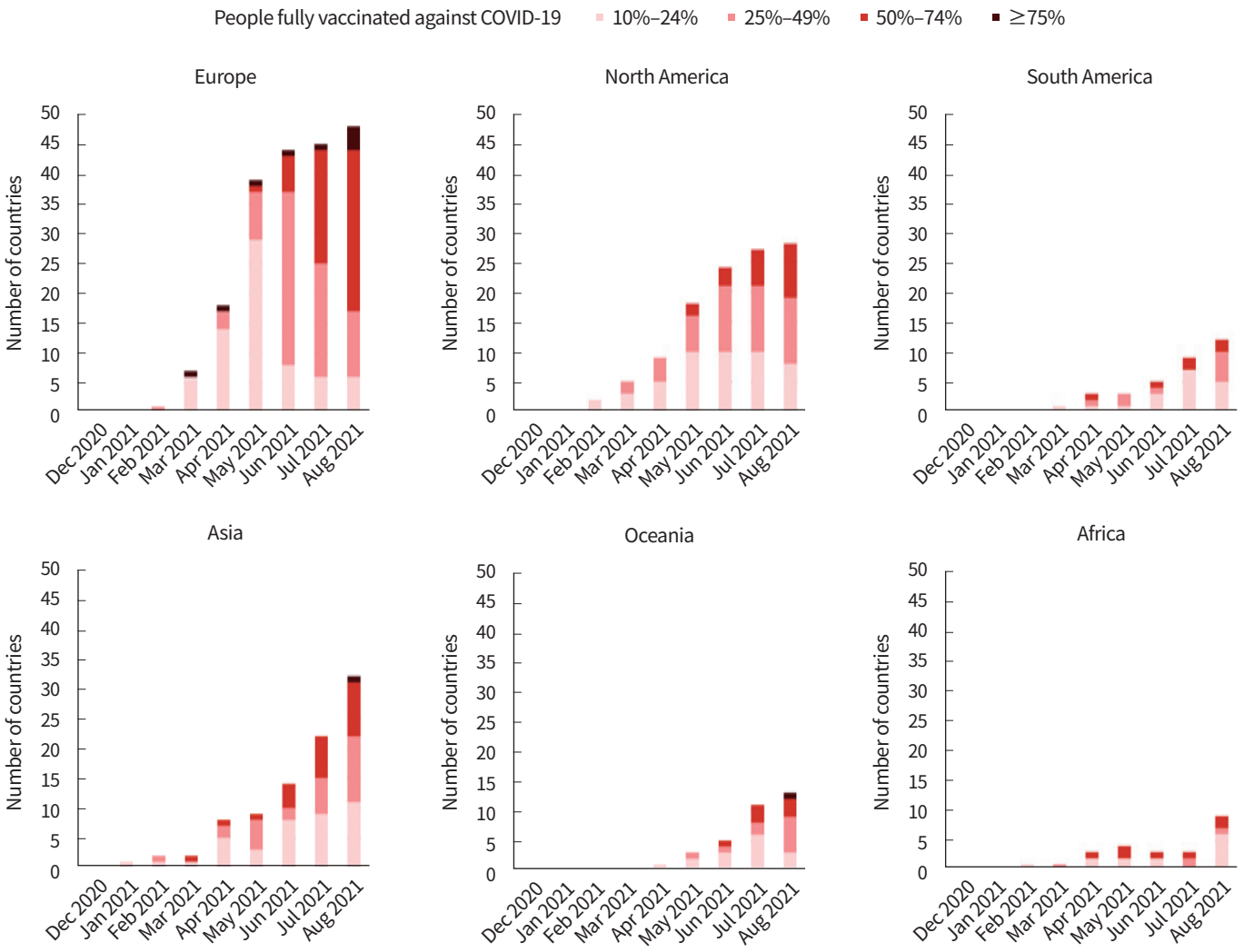

Fig. 2. **Intercontinental comparison of coronavirus disease 2019 (COVID-19) vaccination completion rates by country. These charts were created using the data provided by "Our World in Data" website as a source [52].**

(WHO) and later declared a pandemic [51]. Currently, there are multiple different platforms of vaccines being administered in many countries, although there are large differences in vaccination rates from country to country (Fig. 2) [52].

Unlike in the past, which mainly depended on live attenuated virus vaccines or inactivated virus vaccines, new technology vaccines have been successfully developed and used during this pandemic, including nucleic acid vaccines, viral vector vaccines, and protein-based vaccine [53-55]. In particular, nucleic acid vaccines and non-replicating viral vector vaccines are important weapons that give hope to end the current pandemic as the first antiviral vaccines successfully developed and licensed in human history. As of September 17, 2021, there are 22 approved vaccines, seven of which have been approved by the WHO [56]. There were 193 countries with approved vaccines. Vaccine candidates in clinical trials included 37 vaccines in phase 3 clinical trials, 66 vaccines in phase 2 clinical trials, and 37 vaccines in phase 1 clinical trials [56].

Monoclonal antibodies and immunomodulating agents have been mainly used for the treatment of COVID-19; however, new antiviral agents have been developed and started to be used in clinical practices in some countries. Dissemination through mass production of effective antiviral agents is essential for the control of the pandemic.

PREPAREDNESS AGAINST THE NEXT PANDEMIC

As soon as this SARS-CoV-2 pandemic can be contained, we

need to prepare for the next pandemic that can come at any time. It may be a novel influenza virus, it may be another novel CoV, or it may be a completely different species of virus. More than 100 years have passed since the 1918 influenza pandemic, and we are more prepared for the next influenza pandemic, with global influenza surveillance, advanced molecular diagnostics, influenza vaccines, vaccines for some respiratory bacterial infections, antiviral and antibacterial agents, improved infection control, and advanced intensive care with ventilator support [6].

One of the worst-case scenarios is a pandemic caused by a highly pathogenic avian influenza virus. Highly pathogenic avian influenza viruses of subtypes H5N1 and H7N9 have the potential to cause a pandemic in humans and is of great concern because the mortality rate of human infection is very high [9]. From January 2003 to June 2021, 862 human infections of H5N1 avian influenza have been diagnosed in 15 countries, and 455 deaths have been reported, with a mortality rate of 52.8% [57]. In addition, 1,568 people were diagnosed with H7N9 avian influenza in China from the beginning of 2013, and 616 people died (mortality rate, 39.3%) [58]. Although human-to-human transmission of avian influenza has seldom occurred, the risk of having a pandemic potential through mutation exists. If the highly pathogenic avian influenza virus that causes human infection with a fatality rate of more than 60% mutates and causes a pandemic by making it easier to transmit from person to person, the impact would be considerable even if antiviral agents exist and vaccine production is possible within a few months [3].

In the event of a pandemic caused by a virus that is more deadly than the current or previous pandemics, the damage to mankind could be very serious. In 1918, the world's population was only about 1.8 billion, and most people lived in rural areas. At present, the human population has quadrupled to more than 7.2 billion, and far more people live in densely populated metropolitan areas, posing a greater risk of infectious disease transmission [59]. Furthermore, the growing number of international travel makes the global spread of infectious diseases much easier.

In response to the pandemic initiated by an emerging infectious disease, the following are important: early recognition of an emerging infectious disease, rapid identification of causative microorganisms, rapid communication and cooperation between countries, technologies for rapid diagnosis, identification of viral virulence factors and rapid vaccine development, facilities for mass production of new technology vaccines, and successful public health interventions with public cooperation until the vaccine is available, and cooperation between the public and private health sectors. To prepare for the next pandemic, it is necessary to improve the healthcare system and invest in research and development for diagnostic technology, vaccines, and therapeutics.

CONCLUSION

Having suffered the first pandemic caused by the coronavirus in the past century, we have tried to stop the spread through a global lockdown, including stringent social distancing measures without a vaccine for the first year, and now we are in the stage of overcoming the pandemic through widespread vaccination. Unlike the influenza pandemic, which we could respond to from the beginning with effective antiviral agents and vaccines, we experienced that a pandemic caused by a novel virus without existing effective antiviral agents and vaccines could be disastrous for humankind. More importantly, we need to prepare for the next pandemic. We are well aware of our vulnerabilities as we have been through the COVID-19 pandemic.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: DRC.
Acquisition, analysis, or interpretation of data: DRC.
Drafting the work or revision: DRC.
Final approval of the manuscript: DRC.

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