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The Corona Virus Disease-19 pandemic: Comparison with the 1918 Influenza Pandemic.

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Abstract

At the time of writing, the Corona virus disease-19 (COVID-19) is a raging global pandemic that is wreaking havoc on health systems and economies around the world. Most of the world's population have been asked the stay indoors to stop the disease transmission. More than 200 countries are affected and already over 2 million people have been confirmed as infected with over 150,000 people succombing to the disease. A similar situation existed during the Influenza virus pandemic over a 100 years ago during which, an estimated one third of the whole human population was infected and 50-100 million people died. Here, I give my perspectives on these two pandemics, highlighting the similarities and differences. I also describe the lacunae that still exist and need further investigation.

Introduction

WHO declared the outbreak of COVID-19 a pandemic on March 11, this year after tens of thousands of cases were reported across countries. An infectious disease that is extremely transmissible can spread across the world within a short time. If the virus is sufficiently novel, most people have no pre-exisitng immunity to fight the virus, allowing it to spread and eventually encompass almost the whole world. This is particularly so if the transmission is directly from human to human with no vector invloved in the viral life cycle. Moreover, the respiratory route provides the easiest means to acquire an infection since breathing is essential and the lungs easily accessible for the virus. These are typical features of both the Influenza and the Corona virus (SARC-CoV-2) pandemics.

Similarities between the two pandemics

Both Influenza and SARC-CoV-2 are enveloped RNA viruses. In Influenza, the genomic RNA is negative sense and consists of 8 individual single stranded segments whereas in SARC-CoV-2, it is a long stretch of single stranded positive sense RNA. Although Influenza types B and C have only humans as hosts, the virus which caused the 1918 pandemic, Influenza A, as well as well as SARC-CoV-2 have animal hosts in birds: for Influenza A, it is primarily chicken and for SARC-CoV-2, it is bats and pangolins. This animal/human transmission plays an important role in creating opportunities for emergence of novel viruses with increased virurence. For example, Severe acute respiratory syndrome (SARS) and Middle eastern respiratory syndrome (MERS) that occurred during 2003 and 2012, respectively were due to emergence of novel coronaviruses similar to SARC-CoV-2, although they did not assume pandemic proporions unlike the latter because they were likely less transmissible. For entering the human cells, SARS virus as well as the related SARC-CoV-2 use their spike porotein to bind its cellular receptor, angiotensin converting enzyme 2 (ACE2). Also for effective cellular entry, the spike protein needs to be cleaved by a cellular protease called furin. Compared to the SARS virius, the SARC-CoV-2 has 4 acquired mutaions in the receptor binding domain, as well as an additional furin cleavege site in the spike protein, probably by passage in pangolins and then in humans[1]. The receptor binding affinity increased by several fold due to these changes, resulting in extreme contagiousness to a level that enabled pandemic spread. In the case of the 1918 Influenza pandemic, the causative agent was not even known to be a virus. It was only later analyses which suggested that genetic resortments resulting in dramtic antigenic shift may have been the reason for the extreme susceptibility.

It is not known for sure as to where the Influenza pandemic began. The infection first made its appearance in Europe, America and areas of Asia before spreading to almost every country in the world. It was before the era of widespread air travel and large scale global cargo transport. However, during and after world war I, concentrations of soldiers moving around the world in crowded ships and trains may have helped to spread the killer virus. In case of SARC-CoV-2, the pandemic originated in Wuhan, China in Nov/Dec of 2019 and in about two months spread across the world due to the ease of human interactions facilitated by international travel and transport.

The Influenza pandemic occured in 3 waves: first in the spring of 1918, followed by a second and more deadly second wave (possibly due to mutations by passage in humans in the military troops) in the fall of 1918 and a third wave in the spring of 1919. Whether the COVID-19 pandemic follows a similar pattern is to be seen.

One of the simplest ways to prevent the spread of a contagion is to stop offering new hosts. Accordingly, social distancing was advocated in both pandemics, but practiced with varying degrees of efficiency and success in different countries as well regions within a country. Here the idea is simple – avoid the first person from transmitting to several others. The key to its success is the earliest start date after the first infected person is identified. Also, since the incubation period (as is believed in an acute infection such as Influenza and COVID-19) is expected to be short (upto 1-3 weeks), isolating people for 3-4 weeks should theoretically stop the spread effectively. Another important aspect of social distancing is that, by reducing the level of infection in the population, it tends to nullify the tendency of the pandemic to overwhelm the medical facility, staff and health supplies. One problem for successfully implementing the strategy is deciding when to start social distancing as so-called asymptomatic or pre-symptomatic individuals, who appear normal are transmitting the virus way before they are symptomatic. As well, the definitive identification of infection involves detection of the viral nucleic acid using sophisticated and time consuming tests such as polymerase chain reaction (PCR). In the US, robot-assisted machines are being used to test 1000's of samples at a time. Abbott Labs has also developed an isothermal RNA amplification kit that can give results in 15 minutes. Although these tests provide a means to definitively detect infection, one needs to be aware of the possibility of false negatives and false positives. Although false positives may be acceptable because it just results in unnecessary isolation, false negatives could be more dangerous since that person will likely spread disease.The key is to start social distancing as soon as even one confirmed case is detected during a pandemic or even start on an empirical basis just based on asumption during a pandemic. This is particularly important in resource poor developing and over crowed cities and countries, where the failure to contain can lead to a catastrophic outcome.

Social distancing was first started during the Influenza pandemic, particularly in the US. Its clear effect in preventing infections and death is obvious from a systamatic study of different states within the US[2]. For example, New York and St. Louis cities started quarantine measures very early - days before the death rate spiked. These cities had the lowest death rate of ~400 deaths /100,000. In contrast, Philadelphia waited for 8 days after peak before closing schools and banning gatherings and witnessed 750 deaths/100,000. In states where social distancing was relaxed immediately after death came down (San Fransisco), there was a stronger second death wave, resulting in an overall death rate of 673 deaths/100,000.

In the current COVID-19 pandemic, social distancing has been widely instituted across the world, although at different times after the infection appeared. But its positive effects is already in evidence in China, Italy, Spain and the US. How relaxing the lock down shapes the morbidity and mortality needs to be seen. Singapore, South Korea and Hong Kong have adopted another approach of fast identification of new infection, tracing and stringently isolating the contacts without entirely locking down the cities. It seems to have controlled the infection. This method likely needs to be robustly adopted after lifting the lockdown in countries where lock down is practiced. This basically needs widespread testing and ability to trace and isolate contacts. Failure to achieve this would likely result in deadly secondary and tertiary outbreaks.

Differences Between the Two Pandemics

There is a 100-year gap between the two pandemics. Correspondingly, the current pandemic has the advantages of scientific advancement over this time. Whereas during the Influenza pandemic, the causative agent was unknown (it was identified as a virus only in 1930), in the COVID-19 pandemic the virus was isolated and sequenced within two months after the infection was recognized. This led to a rapid development of PCR-based definitive diagnostic test that was used to effectively contain infection early on in countries such as Singapore and South Korea. However, extensive shortage of testing kits and medical supplies (personal protective equipment, such as gowns, masks etc) delayed the prompt institution of effective counter measures in the US, underscoring the importance of pandemic preparedness in advance. Improvements in hospital care and the use of ventilators is also an advantage for the COVID-19 pandemic as compared to the Influenza pandemic.

Within months into the pandemic, several clinical trials to test different treatment methods are underway. It is very likely the within 6 months to a year from now, some kind of effective treatment will be available. Preliminary studies already suggest that Remdesivir may be an effective treatment[3]. It is a nucleoside (adenosine) analog and inhibits RNA dependent RNA polymerase used

by Corona virus for its replication. It has also been effective for SARS and MERS in animal studies. Although much touted by some politicians, the hydroxyl chloroquine (anti-malaria drug) has been disappointing in preliminary studies[4].

A large number of vaccine candidates are already being tested or under development[5]. In addition to the conventional vaccines such as inactivated and attenuated vaccines, novel vaccine platforms such as mRNA vaccines (encoding the spike protein), subunit vaccines, adenoviral vaccines and dendritic cell-based vaccine are being tested. If any of them work, it will also provide a novel platform that may also be useful against other diseases. Another approach that is being tested is transfusion of convalescent plasma obtained from infected and recovered persons to critically ill patients. In preliminary studies, this has shown great benefits[6]. Since there already nearly 2 million infected and recovered persons in the world, this should provide an ample resource. Moreover, immunoglobulins can be isolated from pooled samples to broaden efficacy. As exuberant immune response, so-called cytokine storm has also been implicated for severe disease in some patients, drugs used for auto immune diseases are also being developed as therapies to inhibit such a response. With these positive developments, the ultimate death toll for the COVID-19 pandemic is likely to be much lower (orders of magnitude) than that during the Influenza pandemic.

One other difference between the two pandemics is that the black population was relatively protected during the Influenza pandemic[7], whereas during COVID-19 pandemic, the death rate in the blacks and Hispanics appear to be much enhanced. The exact reason for this is unclear. However, the life span in recent times is much higher than during the Influenza pandemic (80 vs 50 years) and with increasing age, pre-existing conditions such as heart disease, hypertension and diabetes (the rates of which are higher in the blacks) make COVID-19 more fatal. One other difference is that secondary bacterial pneumonia appears to be the common cause of death in Influenza pandemic and cytokine storm appear to be more in COVID-19 pandemic.

The end game

This brings us to an interesting question of how epidemics and pandemics end?. Common sense tells us that the only way that the virus gets eliminated from the population is by a robust level of herd immunity as was achieved with small pox vaccine and for the most part with polio vaccines. For COVID-19, the doubling rate R_0 has been estimated to be 3, which means that one person on an average, infectes 3 more and those will pass it to 9 more people and so on. On the basis of this, it has been calculated that the level of herd immunity needed to stop transmission to be around 70%[8]. Practically, this level of immunity has never been documented with any natural infection, whether acute or chronic. Moreover, social distancing, by reducing transmission, is also likely to delay the peak of infection (since isolated people previously exposed will continue to fall ill). This will also prevent the development of herd immunity – in fact, the level of immunity achieved is expected to be ~1% of polulation or less. Obviously this leaves the lurking virus to attack again after restriction is lifted.

Although nobody knows exactly how the Influenza pandemic ended, most scientists assume that either people died or were protected after infection. However, the best estimate of infection rates suggests a level of infection that does not surpass 30% of world population at that time. That leaves 70% of world population still susceptible for infection towards the end of the pandemic. Despite this, the virus disappeared. In fact, in Philadelphia, for example, 4,597 people died in the week ending 16 October 1918, but by 11 November, influenza had almost disappeared from the city[9]. This could surely not have been due to herd immunity. In this context, can anyone tell why the the Zika virus disappeared? Or why MERS or bird flu did not take off?. Going by the history of acute infections, although they may be devastating during their rein, they have to vacate one day and I am positive this will be the case with COVID-19 pandemic. Hopefully it will happen sooner than later.

Another theory holds that the 1918 virus mutated extremely rapidly to a less lethal strain, following the general knowledge-based concept that acute infections can not long last long unless they adapt to co-live together with their hosts for survival in the long term (like chronic diseases such as tuberculosis, leprosy and HIV). Whatever the reason, while everybody's wish is for the pandemic is to go away as soon as posssible, my contention is that we will never know for sure the scientific basis for the exit of the virus. And more importantly, once the problem ends it will be forgotten too soon to learn any durable leson for a future attack on a similar scale. In fact, one of my friends, a practicing doctor at the end of his week with COVID-19 patients asked me what if another similar virus emerges next year. I told him by next year we would have forgotten all about this issue, hopefully for the next 100 years. May I be right!.

Lacunae

Although great progress is being made on many fronts, including chemotherapy and vaccinology, unfortunately one thing we have not learned from many previous epidemics and pandemics is how to prevent an infected person from spreading the disease or to protect uninfected persons. Indeed, if we can prevent spreading without having to isolate people, the economic catastrophe we are seeing today can be totally prevented. For a respiratory virus, as easy it to acquire from breathing air, theoretically it should be as easy to prevent it from entering the airways. In my opinion, this is the most neglected aspect without enough research having been done. For example, why are methods to inactivate virus on the masks not investigated thoroughly? Why can we not make efforts to develop masks with safe equivalents of HEPA (high efficiency particulate air filters) filters or masks coated with virus adsorbing material? Interestingly a Danish company (ACT.Global), has developed a system called Premium Purity, with a spray-on film that allows surface to essentially clean itself for 12 continuous months. When the transparent coating is exposed to light, a photo-catalytic reaction occurs that kills microbes and purifies the air. According to the company, it has also tested effective against coronavirus strains. Such or similar such methods should be thoroughly investigated for coating on masks for example. Another possibility is to use some kind of thin layer of air curtain 3-4 inches away from nose using novel methods. The idea here is to create a positive pressure air-barrier in front of the nose, so that one does not get the virus from an infected individual even if he/she is in front of him. These ideas need a lot of experimentation and verification for sure, but if any of them work, it would be a major asset to combat future epidemics.

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