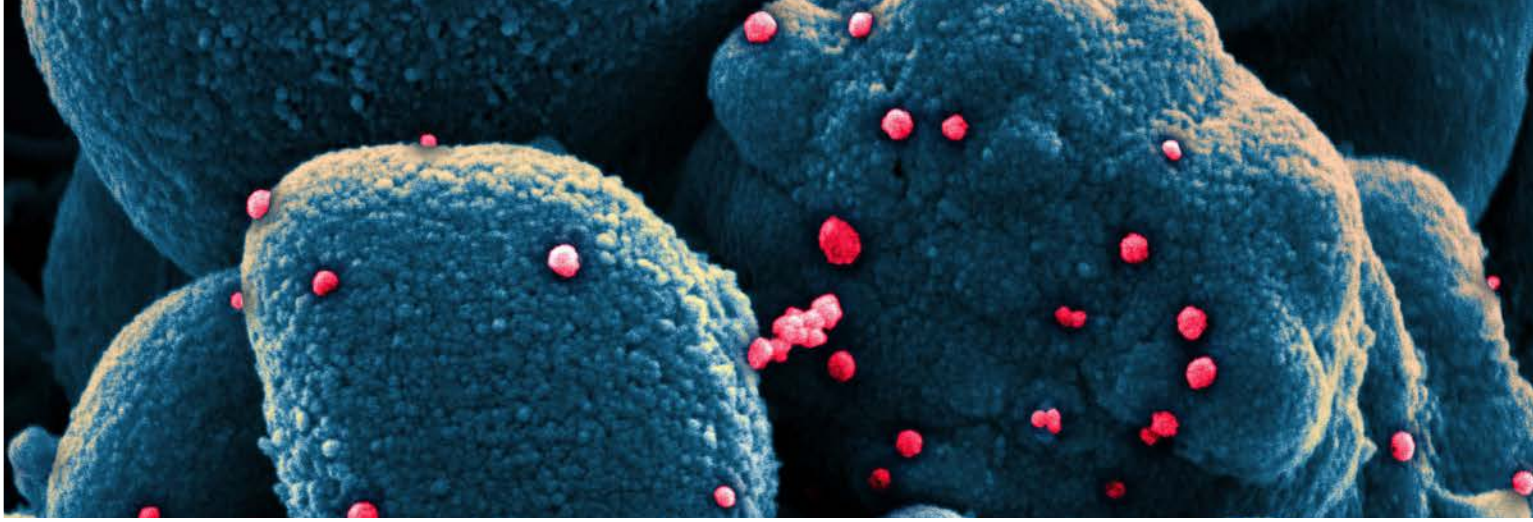

COVID-19:
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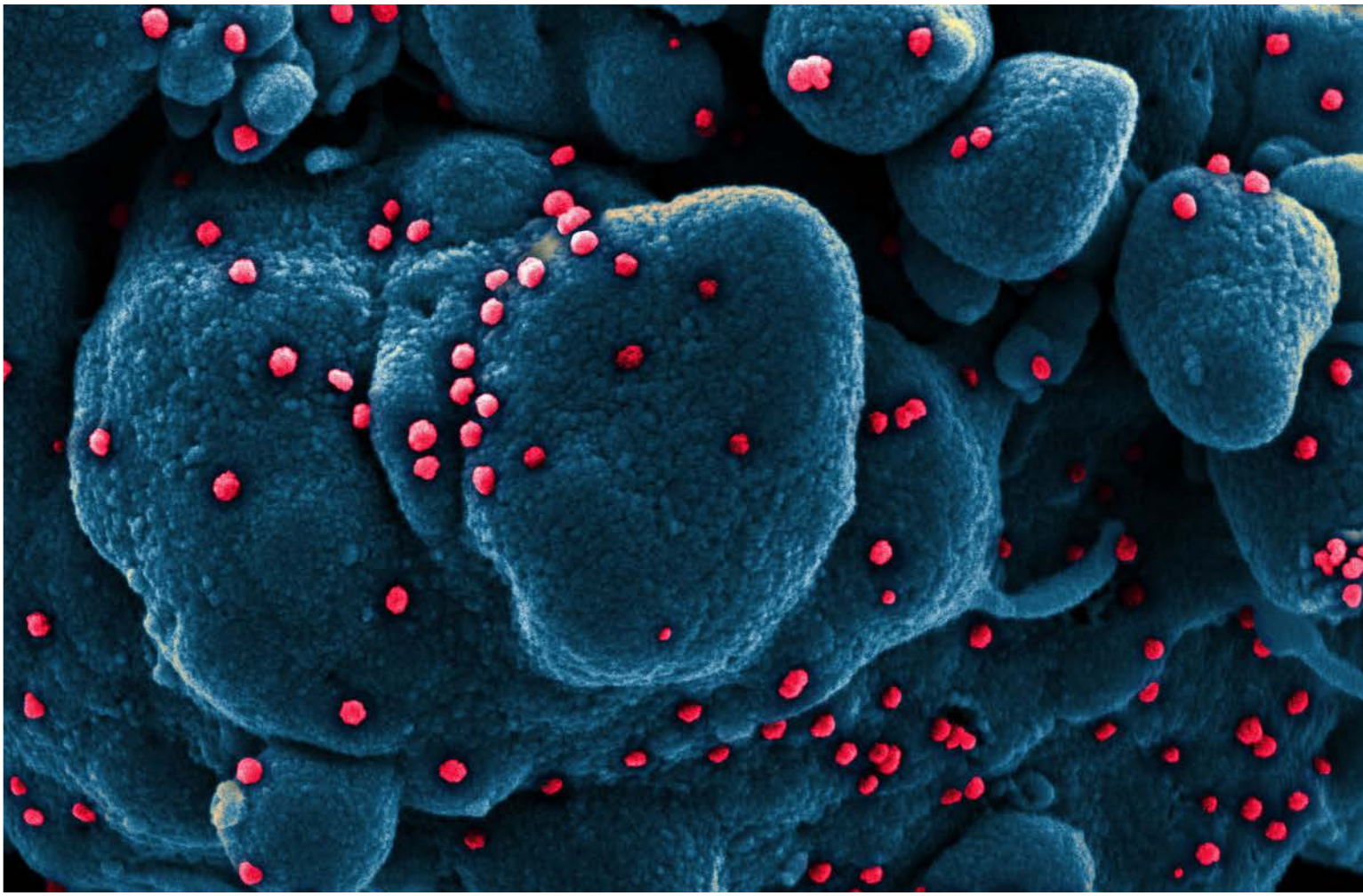

CIDRAP

COVID-19: The CIDRAP Viewpoint

April 30th, 2020

Part 1: The Future of the COVID-19 Pandemic: Lessons Learned from Pandemic Influenza

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CIDRAP, founded in 2001, is a global leader in addressing public health preparedness and emerging infectious disease response. Part of the Office of the Vice President for Research (OVPR) at the University of Minnesota, CIDRAP works to prevent illness and death from targeted infectious disease threats through research and the translation of scientific information into real-world, practical applications, policies, and solutions. For more information, visit: www.cidrap.umn.edu.

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Part 1: The Future of the COVID-19 Pandemic: Lessons from Pandemic Influenza

Preface

Welcome to "COVID-19: The CIDRAP Viewpoint." We appreciate that other expert groups have produced detailed plans for mitigating SARS-CoV-2 transmission and for reopening the country after stay-at-home orders and other important mitigation steps are eased. Our intent with the Viewpoint is to add key information and address issues that haven't garnered the attention they deserve and reflect the unique experience and expertise among the CIDRAP team and our expert consultants. We will address timely issues with straight talk and clarity. And the steps we will recommend will be based on our current reality and the best available data. Our goal is to help planners envision some of the situations that might present themselves later this year or next year so that they can take key steps now, while there's still time.

"COVID-19: The CIDRAP Viewpoint" will address such topics as pandemic scenarios going forward, crisis communication, testing, contact tracing, surveillance, supply chains, and epidemiology issues and key areas for research. We will release approximately one to two reports per week.

Our hope is that our effort can help you plan more effectively and understand the many aspects of this pandemic more clearly—and for you and your family, friends, and colleagues to be safer. Thank you.

– Michael T. Osterholm, PhD, MPH, CIDRAP Director

Introduction

When severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)—the virus that causes COVID-19—first emerged in Wuhan, China, in December 2019, even the most experienced international public health experts did not anticipate that it would rapidly spread to create the worst global public health crisis in over 100 years. By January 2020, a few public health officials began sounding the alarm, but it wasn't until March 11, 2020, that the World Health Organization declared a global pandemic.

The virus caught the global community off guard, and its future course is still highly unpredictable; there is no crystal ball to tell us what the future holds and what the "end game" for controlling this pandemic will be. The epidemiology of other serious coronaviruses (SARS-CoV-1, the virus that causes severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome coronavirus [MERS-CoV]) is substantially different from that of SARS-CoV-2; therefore, these pathogens do not provide useful models for predicting what to expect with this pandemic.

Alternatively, our best comparative model is pandemic influenza. Since the early 1700s, at least eight global influenza pandemics have occurred, and four of these occurred since 1900—in 1918-19, 1957, 1968, and 2009-10. We can potentially learn from past influenza pandemics as we attempt to determine a vision for the future of the COVID-19 pandemic. Identifying key similarities and differences in the epidemiology of COVID-19 and pandemic influenza can help envisioning several possible scenarios for the course of the COVID-19 pandemic.

The primary focus of these scenarios is on the temperate Northern Hemisphere, but similar patterns could occur in the Global South, as well. The lack of robust healthcare infrastructure (including a dearth of adequate personal protective equipment) and comorbidities such as other infections (eg, HIV, TB, malaria), malnutrition,

and chronic respiratory disease in certain areas of the Global South could result in the pandemic being even more severe in those areas, as was noted during the 1918-19 pandemic (Murray 2006).

Epidemiologic Similarities, Differences Between Covid-19 and Pandemic Influenza

Even though coronaviruses are very different from influenza viruses, the COVID-19 pandemic and pandemic influenza share several important similarities. First, SARS-CoV-2 and a pandemic influenza virus are novel viral pathogens to which the global population has little to no pre-existing immunity, thereby resulting in worldwide susceptibility. Second, SARS-CoV-2 and influenza viruses are predominantly spread via the respiratory route by large droplets, but also with a significant component of transmission by smaller aerosols. Asymptomatic transmission occurs with both viruses as well, thereby contributing to the spread of each. Finally, both types of viruses are capable of infecting millions of people and moving rapidly around the globe.

Pressing Issues

1. Because of a longer incubation period, more asymptomatic spread, and a higher R_0, COVID-19 appears to spread more easily than flu.
2. A higher R_0 means more people will need to get infected and become immune before the pandemic can end.
3. Based on the most recent flu pandemics, this outbreak will likely last 18 to 24 months.
4. It likely won't be halted until 60% to 70% of the population is immune.
5. Depending on control measures and other factors, cases may come in waves of different heights (with high waves signaling major impact) and in different intervals. We present 3 possibilities.

There are also important differences. The first is the incubation period; the average incubation period for influenza is 2 days (range, 1 to 4 days); whereas, the average incubation period for COVID-19 is 5 days (range, 2 to 14 days) (Lauer 2020). The longer incubation period for COVID-19 allowed the virus to move silently in different populations before being detected (Kahn 2020, Li 2020). This contributed to an initial environment of complacency before national governments became aware of the severity of the situation.

The second important factor is the asymptomatic fraction for the two infections. Although information is still being collected to definitively define the asymptomatic fraction for COVID-19, public health officials have stated that 25% of all cases may be asymptomatic (Rettner 2020) and better serologic studies may revise this percentage upward. A number of studies have explored the asymptomatic fraction for influenza; one review found a pooled mean for the asymptomatic fraction of 16% (range of 4% to 28%) (Leung 2015). Thus, while both viruses can lead to asymptomatic infections, the asymptomatic fraction appears to be somewhat higher for COVID-19 than for influenza.

Another consideration is the timeframe of presymptomatic viral shedding for people who fall ill. One recent study found that the SARS-CoV-2 viral load was highest at the time of symptom onset, suggesting that viral shedding may peak before symptoms occur, leading to substantial presymptomatic transmission (He 2020). A point-prevalence study of SARS-CoV-2 in nursing home residents showed that, for 27 residents who were asymptomatic at the time of testing, 24 developed symptoms a median of 4 days later (interquartile range, 3 to 5 days) (Arons 2020), supporting the potential for several days of presymptomatic shedding. For the H1N1 pandemic influenza A virus, one study showed that viral shedding peaks the first 1 to 2 days after symptom

onset, suggesting there may be less presymptomatic shedding for pandemic influenza A compared with SARS-CoV-2 (Ip 2016).

All of the above factors contribute to viral transmissibility. One way to quantify the transmissibility of a virus is to determine the basic reproductive number (R_0) for that virus. The R_0 is the average number of new infections that result from a single infected person in a wholly susceptible population (Delamater 2019). The R_0 can vary by factors that influence the contact rate between people, such as physical distancing strategies and lockdowns aimed at driving the R_0 below 1. An R_0 below 1 indicates that that an outbreak is shrinking rather than expanding, since each infected person is subsequently infecting less than 1 other person. While the R_0 is not influenced by herd immunity (which is the proportion of the population that is immune to a virus), either generated by natural infection or by vaccination, immunity in the population can influence the effective reproductive number (R_E), which is similar to the R_0 but does not depend on having a fully susceptible population (Delamater 2019). Immunity in the population can effectively diminish or end an outbreak by driving R_E below 1 (Fine 2011).

Recommendations

1. States, territories, and tribal health authorities should plan for the worst-case scenario (Scenario 2), including no vaccine availability or herd immunity.
2. Government agencies and healthcare delivery organizations should develop strategies to ensure adequate protection for healthcare workers when disease incidence surges.
3. Government officials should develop concrete plans, including triggers for reinstituting mitigation measures, for dealing with disease peaks when they occur.
4. Risk communication messaging from government officials should incorporate the concept that this pandemic will not be over soon and that people need to be prepared for possible periodic resurgences of disease over the next 2 years.

The R_0 for SARS-CoV-2 during the early course of the pandemic in China was estimated at 2.0 to 2.5 (Anderson 2020); however, the R_0 for SARS-CoV-2 is difficult to accurately determine in various geographic regions because of challenges in identifying and testing infected persons, and one study has suggested that the value may be considerably higher (Sanche 2020). Also, for SARS-CoV-2, the R_0 is not the same for each person; it can change based on natural variability in viral shedding by infected persons. Even the average value of R_0 is not a purely biological quantity—it depends on behavior and contacts. For example, some have speculated that the R_0 for SARS-CoV-2 may be higher in areas of denser population or more frequent contacts, such as large cities. In addition, some evidence indicates that some people are "super-spreaders," as was seen with MERS-CoV and SARS (Frieden 2020, Wong 2015). Some countries appear to have been able to drive their R_0 for SARS-CoV-2 below 1 with mitigation measures, although as the mitigation measures are lifted, the R_0 in any given area may creep back above 1, leading to disease resurgence over time.

The R_0 for pandemic influenza has varied by pandemic, but estimates have consistently been around or below 2, suggesting that even past severe influenza pandemic viruses have been less transmissible than SARS-CoV-2. A review article published after the 2009-10 pandemic examined a range of studies reporting R_0 values for the last four influenza pandemics. While the results varied, the highest median R_0 was associated with the 1918 and the 1968 influenza pandemics (both 1.8), followed by the 1957 pandemic (1.65), then the 2009-10 pandemic (1.46); by comparison, seasonal influenza epidemics have a median R_0 of 1.27 (Biggerstaff 2014).

Key Lessons From Past Influenza Pandemics

Of eight major pandemics that have occurred since the early 1700s, no clear seasonal pattern emerged for most. Two started in winter in the Northern Hemisphere, three in the spring, one in the summer, and two in the fall (Saunders-Hastings 2016).

Seven had an early peak that disappeared over the course of a few months without significant human intervention. Subsequently, each of those seven had a second substantial peak approximately 6 months afterfirst peak. Some pandemics showed smaller waves of cases over the course of 2 years after the initial wave. The only pandemic that followed a more traditional influenza-like seasonal pattern was the 1968 pandemic, which began with a late fall/winter wave in the Northern Hemisphere followed by a second wave the next winter (Viboud 2005). In some areas, particularly in Europe, pandemic-associated mortality was higher the second year.

The course of these pandemics was not substantially influenced by a vaccination campaign, except for the 2009-10 pandemic, during which vaccine initially became available in the United States about 6 months after the onset of the pandemic, although substantial quantities of vaccine were not available until after the pandemic had peaked in most parts of the country. One report estimated that the vaccination program prevented 700,000 to 1,500,000 clinical cases, 4,000 to 10,000 hospitalizations, and 200 to 500 deaths in the United States (Borse 2013).

Following three of the pandemics that have occurred since 1900, the pandemic influenza A strain gradually became more human-adapted and replaced the predominant seasonally circulating influenza virus to become the main seasonal influenza A strain identified each year. Following the 2009-10 pandemic, the pandemic influenza A H1N1 strain has been co-circulating seasonally along with influenza A H3N2.

Key points from observing the epidemiology of past influenza pandemics that may provide insight into the COVID-19 pandemic include the following. First, the length of the pandemic will likely be 18 to 24 months, as herd immunity gradually develops in the human population. This will take time, since limited serosurveillance data available to date suggest that a relatively small fraction of the population has been infected and infection rates likely vary substantially by geographic area. Given the transmissibility of SARS-CoV-2, 60% to 70% of the population may need to be immune to reach a critical threshold of herd immunity to halt the pandemic (Kwok 2020).

This may be complicated by the fact that we don't yet know the duration of immunity to natural SARS-CoV-2 infection (it could be as short as a few months or as long as several years). Based on seasonal coronaviruses, we can anticipate that even if immunity declines after exposure, there may still be some protection against disease severity and reduced contagiousness, but this remains to be assessed for SARS-CoV-2. The course of the pandemic also could be influenced by a vaccine; however, a vaccine will likely not be available until at least sometime in 2021. And we don't know what kinds of challenges could arise during vaccine development that could delay the timeline.

Second, there are several different scenarios for the future of the COVID-19 pandemic, and some of these are consistent with what occurred during past influenza pandemics. These can be summarized as follows and are illustrated in the figure below.

- *Scenario 1:* The first wave of COVID-19 in spring 2020 is followed by a series of repetitive smaller waves that occur through the summer and then consistently over a 1- to 2-year period, gradually diminishing sometime in 2021. The occurrence of these waves may vary geographically and may depend on what mitigation measures are in place and how they are eased. Depending on the height of the wave peaks, this scenario could require periodic reinstitution and subsequent relaxation of mitigation measures over the next 1 to 2 years.
- *Scenario 2:* The first wave of COVID-19 in spring 2020 is followed by a larger wave in the fall or winter of 2020 and one or more smaller subsequent waves in 2021. This pattern will require the reinstitution of mitigation measures in the fall in an attempt to drive down spread of infection and prevent healthcare systems from being overwhelmed. This pattern is similar to what was seen with the 1918-19 pandemic (CDC 2018). During that pandemic, a small wave began in March 1918 and subsided during the summer months. A much larger peak then occurred in the fall of 1918. A third peak occurred during the winter and spring of 1919; that wave subsided in the summer of 1919, signaling the end of the pandemic. The 1957-58 pandemic followed a similar pattern, with a smaller spring wave followed by a much larger fall wave (Saunders-Hastings 2016). Successive smaller waves continued to occur for several years (Miller 2009). The 2009-10 pandemic also followed a pattern of a spring wave followed by a larger fall wave (Saunders-Hastings 2016).

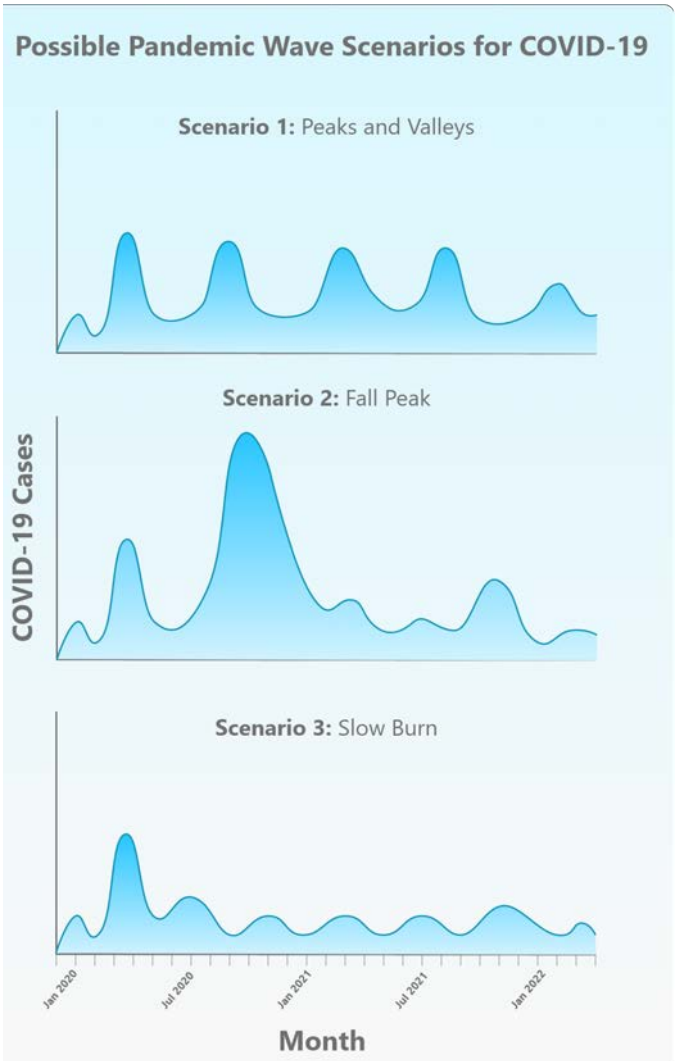

Figure 1

- *Scenario 3:* The first wave of COVID-19 in spring 2020 is followed by a "slow burn" of ongoing transmission and case occurrence, but without a clear wave pattern. Again, this pattern may vary somewhat geographically and may be influenced by the degree of mitigation measures in place in various areas. While this third pattern was not seen with past influenza pandemics, it remains a possibility for COVID-19. This third scenario likely would not require the reinstitution of mitigation measures, although cases and deaths will continue to occur.

Whichever scenario the pandemic follows (assuming at least some level of ongoing mitigation measures), we must be prepared for at least another 18 to 24 months of significant COVID-19 activity, with hot spots popping up periodically in diverse geographic areas. As the pandemic wanes, it is likely that SARS-CoV-2 will continue to circulate in the human population and will synchronize to a seasonal pattern with diminished severity over time, as with other less pathogenic coronaviruses, such as the betacoronaviruses OC43 and HKU1, (Kissler 2020) and past pandemic influenza viruses have done.

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