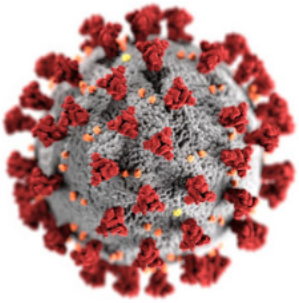

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: U.S. Cases Top 29m, Deaths 525,000

In the world as of March 8, 2021, 116,942,682 cases and 2,595,106 deaths have been confirmed. In the United States, there have been 29,000,012 cases, the most in the world followed in order by India, Brazil, Russia and the United Kingdom. China is now 84th in the world with 101,141 total reported cases. Deaths in the U.S. through March 8, 2021 have been estimated at 525,046.[1]

From March 10 through March 6, there have been 247,550 confirmed cases of Covid-19 reported from Dallas County with 3,122 deaths, about 22% of these from long-term care facilities.[2] More than 67% percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died, and 42% of the hospitalized cases have occurred in the Hispanic population. Specimens submitted for diagnosis of respiratory viruses in symptomatic persons show continuing positivity for SARS-CoV-2 with the latest result on 2/27/21 being 12.1%, down from an approximate peak value of 32% obtained during the first week of January, 2021. Two cases of influenza in symptomatic persons were reported during the week ending January 24, 2021. Otherwise, there have been no positive tests for influenza A and B and only four tests positive for RSV in specimens from the respiratory tract from 6/6/20 through 2/27/21. On the latter date, it was reported that there were 52 active LTCF outbreaks which cumulatively have resulted in 4,221 resident cases and 2,331 healthcare worker cases. There are 10 active outbreaks in congregate living facilities (homeless shelters, group homes and halfway houses).

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 3/8/21)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 3/6/21

New from CDC

Interim Recommendations for Fully Vaccinated People in Non-Healthcare Settings

On March 8, CDC released its first recommendations for fully vaccinated people.[1] They defined "fully vaccinated for COVID-19" as ≥2 weeks after they have received the second dose in a 2-dose series (Pfizer-BioNTech or Moderna), or ≥2 weeks after they have received a single-dose vaccine (Johnson and Johnson [J&J]/Janssen).

Fully vaccinated people can:

- Visit with other fully vaccinated people indoors without wearing masks or physical distancing
- Visit with unvaccinated people from a single household who are at low risk for severe COVID-19 disease indoors without wearing masks or physical distancing
- Refrain from quarantine and testing following a known exposure if asymptomatic

For now, fully vaccinated people should continue to:

- Take precautions in public like wearing a well-fitted mask and physical distancing
- Wear masks, practice physical distancing, and adhere to other prevention measures when visiting with unvaccinated people who are at increased risk for severe COVID-19 disease or who have an unvaccinated household member who is at increased risk for severe COVID-19 disease
- Wear masks, maintain physical distance, and practice other prevention measures when visiting with unvaccinated people from multiple households
- Avoid medium- and large-sized in-person gatherings
- Get tested if experiencing COVID-19 symptoms
- Follow guidance issued by individual employers
- Follow CDC and health department travel requirements and recommendations

Editor's note: As the number of fully vaccinated people begins rising rapidly in the coming weeks, these recommendations are becoming more vital. In general, their recommendations are pretty much as expected. The one recommendation that may not be adequately conveyed is that on travel. What appears to be a relatively common reaction after receiving the final vaccine dose is, "The first thing I am going to do now is book a flight to [favorite vacation spot]." However, the current CDC travel requirements and recommendations suggest not to travel at this time even if vaccinated. Since these recommendations are likely to be updated periodically, vaccinated individuals who are considering travel should continue to search CDC recommendations for the most current advice and consider postponing their celebratory travel until travel appears safer. Since travel regulations in other countries are likely to differ from those in the U.S. and may change significantly as infection rates fluctuate, international travel at this time is particularly uncertain.

References:

1. CDC. Interim Public Health Recommendations for Fully Vaccinated People. March 8, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated-guidance.html#anchor_1615143393075
2. CDC. Travel During COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html

Epi Corner

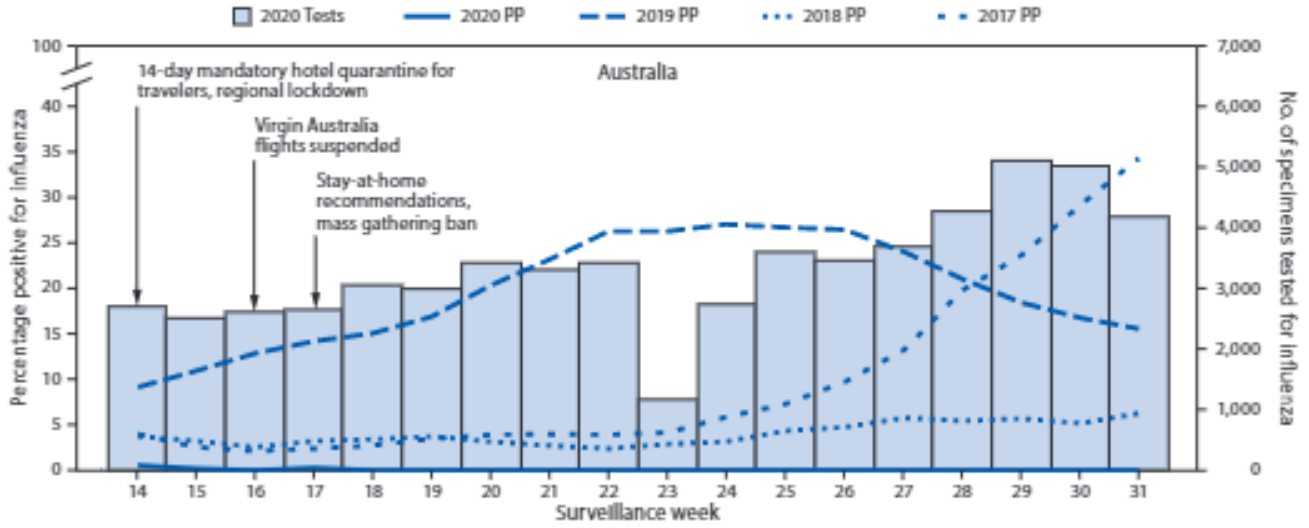
Influenza A and SARS-CoV-2 Infections: Recent Low Incidence of Influenza A Unexpected

The Covid-19 pandemic began in China in December 2019. It was predicted that the pandemic of viral respiratory infections might be at a maximum in the autumn of 2020 and continue through the winter because of the superimposition of SARS-CoV-19 and influenza A and B. Articles were written warning of the possibility of severe consequences of dual epidemics.[1]

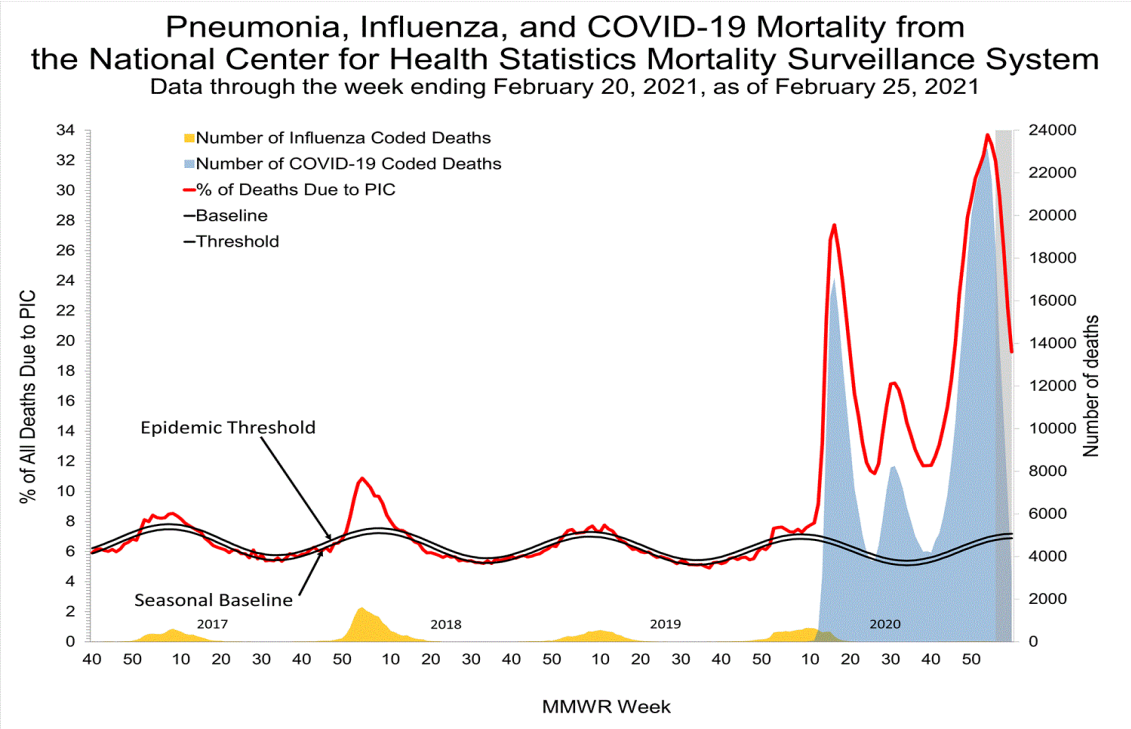
For example, a recent article from Wuhan, China, suggested that influenza infection might increase the infectivity and pathogenicity of SARS-CoV-2 virus.[2] The authors studied multiple cell types, pre-treated the cultures with influenza A virus and then added SARS-CoV-2 and measured its replication by determining the quantity of coronavirus nucleocapsid and envelope genes produced. Enhancement of SARS-CoV-2 virus replication occurred only after influenza A virus pre-treatment but not after respiratory syncytial virus, parainfluenza virus or a human rhinovirus. They were able to demonstrate enhanced replication of SARS-CoV-2 in mice by measuring nucleocapsid and envelope gene quantity and more pronounced pathological changes in animals that were pre-treated with Influenza A virus and subsequently challenged with SARS-CoV-2. The authors concluded that infection with influenza A virus produced a greater expression of ACE2, the known receptor for viral attachment on cell surfaces, allowing greater virus-cell attachment and subsequent replication.

In the summer of 2020, however, when the peak of influenza usually occurs in the southern hemisphere, e.g., Australia, Chile, South Africa, the opposite occurred, with a marked diminution of influenza A cases in the setting of widespread SARS-CoV-2 transmission. In Figure 2 below from the *MMWR*, the percentage of positive (PP) tests for influenza A in April-August 2020 (solid line) are barely visible in the graph, indicating little, if any, observable influenza activity in the Southern Hemisphere populations.[3] Note the comparison values for 2017, 2018 and 2019 (dotted and dashed lines) included in the figure. In the autumn of 2020, the identical pattern of a diminished occurrence of influenza A was also observed in the northern hemisphere (U.S. and Europe).

FIGURE 2. Number of specimens tested and percentage testing positive for influenza, by year — Australia, Chile, and South Africa, April–August (weeks 14–31), 2017–20



In the second figure to the right, note the absence of deaths due to influenza A in the latter part of 2020 and early 2021 in the U.S., indicating that this winter's increase in pneumonia, influenza and Covid-19 (PIC) mortality here has been due primarily to Covid-19 and not influenza. Cases of influenza A during this time have been far lower than usual, mirroring the changes seen in the southern hemisphere.



Because the synergy of concurrent influenza and Covid-19 epidemics might be unusually severe, it would be important to understand why this year's influenza A epidemic did not materialize concurrently with

the Covid-19 epidemic. The following five possible explanations have been advanced. For discussion, we will concentrate on influenza A since that is the major non-coronavirus respiratory pathogen.

First, does the decrease in influenza A infections result simply because we are at an expected low point of a usual transmission cycle where peaks and troughs of cases occur at a periodicity of 2-3 years?

Second, are we nearing the point where most of the population has immunity to influenza A viruses (H1N1, H3N2) presaging a period of about 5 years of diminished viral transmission before a new influenza virus enters the circulation causing a new pandemic? Such a period, termed "the salubrious interval," occurred in the five-year periods preceding the 1889, 1918 and 1957 major influenza pandemics.[4]

Third, are vaccines and antiviral drugs having an effect in lowering transmission of influenza A, and has that effect been sufficient to influence case occurrence? It has been estimated that as many as 193 million of the 328 million persons in the U.S. were immunized against influenza A this fall. Antiviral drugs such as oseltamivir, zanamivir, peramivir and beloxavir may lower case occurrence and influence virus transmission. Use of antiviral drugs might be particularly more effective in influenza where the R_0 approximates 1 and is less than that for SARS-CoV-19 where that value may be as high as 2 or 3.[5]

Fourth, are there virological factors that could be operative in the apparent diminution of influenza A cases during the present pandemic?

Fifth, are present mitigation efforts being undertaken to prevent SARS-CoV-2 transmission actually working to decrease the spread of influenza A as well? These efforts include masking, social distancing, avoidance of crowds assembled under inadequate ventilation conditions, working at home, limiting travel, and hand washing. Could these measures be working even better for influenza than for Covid-19?

At present, there is no definitive information to decide which of these potential explanations is playing the major role. We suspect that the extraordinary mitigation measures being practiced by the majority of the world's population are having the biggest effect. Studies to decide this question would be important to support new, more effective approaches to mitigating future epidemics of viral respiratory infection.

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1. Ding Q, Lu P, Fan Y et al. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol* 2020; 92(9): 1549-1555. https://doi.org/10.1002/jmv.25781.
2. Bai L, Zhao J, Liang S et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. *Cell Res* 2021; 0: 1-9. https://doi.org/10.1038/s41422-021-00473-1.
3. Olsen SJ, Azziz-Baumgartner E, Budd AB et al. Decreased influenza activity during the Covid-19 pandemic- United States, Australia, Chile and South Africa. *MMWR* 2020; 69(37): 1305-1309.
4. Langmuir AD, Henderson DA, Serfling RE. The epidemiological basis for the control of influenza. *Am J Public Health* 1964;54 (4): 563-571.
5. COVIDView. *A Weekly Surveillance Summary of U.S. Covid-19 Activity. Week ending November 28, 2020*. CDC Report prepared February 4, 2021. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/past-reports/12042020.html

Clinical Advance

Colchicine Treatment of Ambulatory Patients with Covid-19

A recent study has been published, but not yet peer reviewed, assessing the role of colchicine in the treatment of ambulatory patients with Covid-19. Colchicine has a history extending back more than 200 years in the treatment of gouty or crystal arthritis. It acts by inhibition of tubulin polymerization with effects on the inflammasome, cellular adhesion molecules and inflammatory cytokines. It is relatively non-toxic and inexpensive.[1]

In this study, investigators tested colchicine at 0.5 mg BID for 3 days followed by 0.5 mg once a day for an additional 27 days in a double-blind, placebo controlled clinical trial.[2] Initial entrants into the study were enrolled on the basis of a positive PCR test but also by epidemiological and clinical criteria. Later in the study, all included patients had to have PCR documentation of Covid-19. This review of the study will only include those patients with laboratory-documented disease. The study was multi-center, begun in March 2020 and completed

in December 2020. The primary composite endpoint was hospitalization or death with a secondary endpoint of the need for mechanical ventilation.

In PCR documented cases (4,159 patients), the rates of the primary endpoint were 4.6% and 6.0% in the colchicine and placebo groups, respectively (odds ratio 0.75; 95% confidence interval, 0.57 to 0.99; P = 0.04). The absolute percent reduction for the composite endpoint was 6.0% - 4.6% = 1.4%. The number needed to treat (NNT) to prevent one case of hospitalization or death was 70. Diarrhea, the most frequent and troublesome adverse event, was reported in 13.7% of the colchicine group and 7.3% of placebo recipients. Limitations of the study included short duration of follow-up of 30 days. Patients needing hospitalization when first seen were excluded from the study. The authors concluded that "among non-hospitalized patients with confirmed Covid-19, colchicine led to a lower rate of the composite of death or hospitalization than placebo." Additional studies evaluating the roll of colchicine in the treatment of Covid-19 are in progress.

References:

1. Reyes AZ, Hu KA, Teperman J et al. Anti-inflammatory therapy for Covid-19 infection: the case for colchicine. *Ann Rheum Dis* 2020;0:1-8. doi:1136/annrheumdis-2020-219174

2.Tardiff J-C, Bousbdallaoui N, L'AllierPL et al. Efficacy of colchicine in non-hospitalized patients with Covid-19. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1

From the Editors

The aim of this biweekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.