

I hope everyone had a wonderful weekend. Lots to share today.

Under COVID-19 News I start with the “big” news on resuming J&J vaccinations. See my comments below. Next is an update on influenza versus COVID-19. The last is a few updates from the NIH.

Under Journal Review I selected an article from the VA dataset on long term sequelae from a veteran who survived SARS-CoV-2 infection. The next article looks at the difference between influenza and COVID-19 invasive aspergillosis. The last article is an interesting simulation on impact of testing of children and transmission.

Have a great Monday

Ed

COVID-19 News

J&J Vaccine Update

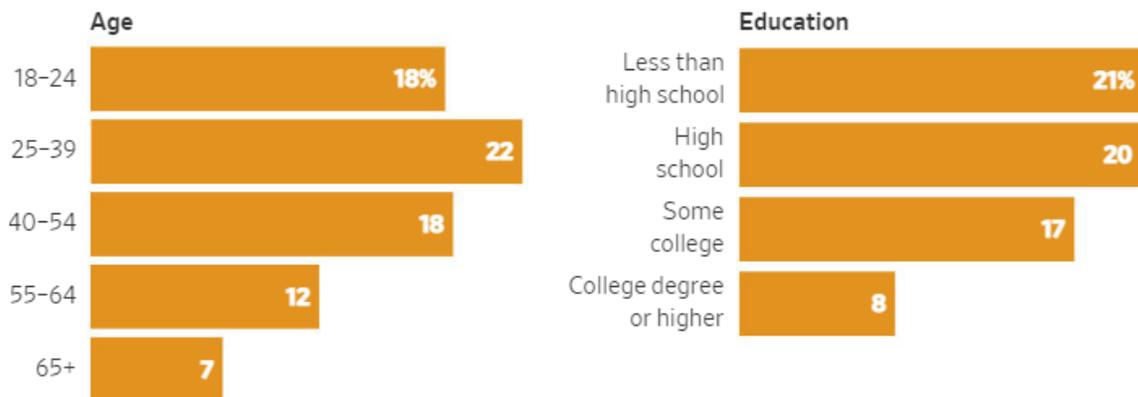
On Friday April 23rd, the ACIP recommended that the J&J COVID-19 vaccine be reinstated in the United States' vaccination campaign in a 10 to 4 vote. One member abstained from voting because of a conflict of interest. The Immunization Safety Office at the CDC shared that the agency has now detected a total of 15 thrombosis with thrombocytopenia syndrome (TTS) cases, including 3 fatalities, up from 6 when the pause was first instated. All 15 of the cases were women, and all but 2 were under the age of 50. Seven of the 16 cases were in women ages 30 to 39. Seven of the 15 cases were in obese women, and two women were taking oral contraceptives. None had known blood clotting disorders. Of the 15 cases, 3 women died, 5 were recovered or recovering at home, and 7 remained hospitalized, including 4 in the intensive care unit. All women experienced symptom onset no sooner than 6 days post vaccination, but no later than day 15, and all reported headache, fatigue, and abdominal pain. No TTS has been documented in recipients of the Moderna or Pfizer vaccines, the two mRNA vaccines authorized for COVID-19 in the United States. [Moderna has had 3 cases but with normal platelet levels] J&J said the company had agreed on warning language with the FDA, which will say the vaccine has, in rare instances, caused TSS in women under the age of 50.

Comment: The vaccine has been tested in South America and South Africa and was highly effective in protecting against severe disease despite the presence of circulating variant strains in those locations. In the US, the J&J vaccine was 85% effective in preventing symptomatic illness in clinical trials, and 100% effective in preventing death. The fact that the J&J vaccine offers a high level of protection against variants, and the benefits of single dose regimen cannot be overstated. The benefits clearly outweigh the risks, though there are differences in age groups, and particularly for women less than 50 years of age. Vaccinating 1 million adults with the J&J vaccine in the U.S. is estimated to lead to 2100 fewer COVID-19-related deaths and roughly 6000 fewer COVID-19 hospitalizations. The risk of blood clots is much higher with COVID-19 disease than from vaccination. The J&J vaccine is an important tool in both in the US and in the global fight against COVID-19. It can be especially useful in vaccinating people who are hard to reach such as the homeless, homebound, persons needle averse [only 1 shot] and people who live in remote areas. Going forward, additional information should be provided to healthcare professionals, instructing them on how to properly diagnosis and treat TTS when symptoms are seen in those who have received the vaccine. If you are a pre-menopausal woman, you may prefer taking an mRNA vaccine.

The recent signs indicate a slowing of vaccinations. Many have not returned for their second dose. This is not good news. Supply may become greater than demand in some areas of the US. Nationally, demographic divides persist in Americans' willingness to get vaccinated. While surveys earlier this year found racial and ethnic splits in vaccine hesitancy, those gaps have narrowed. [but still present especially in the African American community] What remains are gaps between younger and older Americans, and those with and without college degrees. Internationally we need more vaccines which is why getting J&J back in circulation is so important. Global shortages of vaccines especially in poorer countries will only lead to more deaths, prolonging the pandemic. [look at India]

Bottom line: Vaccination not only protects you, but also your community. I believe people have a moral obligation to get vaccinated. If vaccination falls short of necessary uptake, we may **not** achieve herd immunity and/or community control.

Percentage who say they definitely or probably won't get a Covid-19 vaccine



Source: U.S. Census Bureau Household Pulse Survey conducted March 17-29

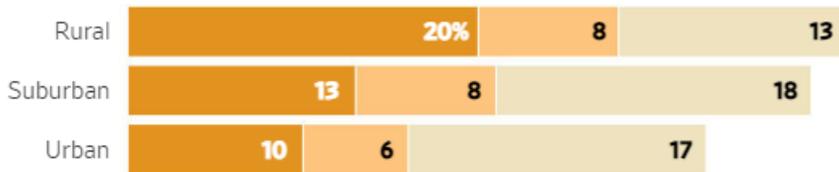
Percentage who say they are hesitant about getting the Covid-19 vaccine

■ Definitely won't get vaccine ■ Only if required ■ Wait and see

By party identification

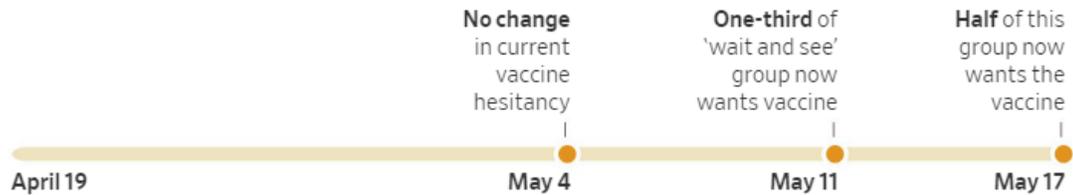


By type of area



Source: Kaiser Family Foundation survey of 1,862 adults conducted March 15-22

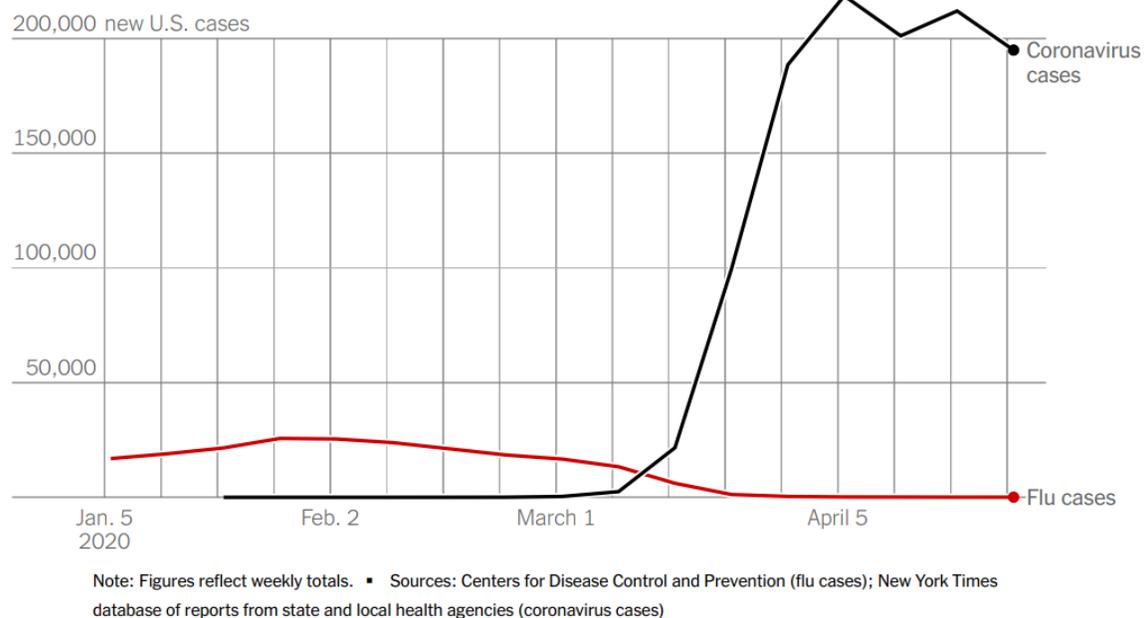
Estimated number of days it would take to reach all adults in the U.S. who want a Covid-19 vaccine with at least one dose



Source: Kaiser Family Foundation calculations based on CDC estimates of U.S. Covid-19 vaccinations

Influenza 2020/2021

There have been fewer influenza cases in the United States this flu season than in any on record. About 2,000 cases have been recorded since late September, according to data from the CDC. In recent years, the average number of cases over the same period was about 206,000. As measures to stop the spread of the coronavirus were implemented around the country in March 2020, influenza quickly disappeared, and it still has not returned.



Comment: Experts are uncertain about what will happen when the flu does return. Experts do not yet know which public health measures were most effective in eradicating the flu this season, but if behaviors like the 3 Ws after the pandemic are relaxed, we could have both SARS-CoV-2 and influenza circulating this fall and winter. Much also depends on the latest flu vaccines, their effectiveness and the public's willingness to get them. The recent drop in cases, however, will make it difficult for experts to decide which flu strains to protect against in those vaccines. It is harder to predict which strains will be circulating later, they say, when so few are circulating now.

The CDC estimates that the flu has killed 12,000 to 61,000 people a year since 2010. There is another hard-to-predict factor that could play a significant role when the flu comes back: whether society will carry on behaviors learned in the pandemic that benefit public health. Will mask-wearing become the norm? History has shown that the last time Americans had a chance to make those behaviors they did not.

NIH Updates COVID-19 Treatment Guidelines

April 21, 2021

- Based on the results of a large, randomized, placebo-controlled trial in outpatients with COVID-19, the Panel has determined that there are insufficient data to recommend either for or against the use of colchicine in non-hospitalized patients with COVID-19. For hospitalized patients, colchicine is not recommended.
- Based on the results of a small randomized controlled trial and an observational study, the Panel has determined that there are insufficient data to recommend either for or against the use of flvoxamine for the treatment of COVID-19.

Comment: The NIH has continued to regularly update their guidance in real-time as new evidence becomes available. Organizations like NIH, IDSA and SCCM just to name a few have provided an invaluable service to the medical community.

Journal Review

High-Dimensional Characterization of Post-Acute Sequelae of COVID-19

Nature published online April 22, 2021.

[doi.org/10.1038/s41586-021-03553-9\(2021\)](https://doi.org/10.1038/s41586-021-03553-9(2021))

The investigators used the national healthcare databases of the US Department of Veterans Affairs to systematically and comprehensively identify 6-month incident sequelae including diagnoses, medication use, and laboratory abnormalities in 30-day survivors of COVID-19. They showed that beyond the first 30 days of illness, people with COVID-19 exhibit higher risk of death and health resource utilization. This approach identified incident sequelae in the respiratory system and several others including nervous system and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, musculoskeletal pain, and anemia. They demonstrated increased use of several therapeutics including pain medications (opioids and non-opioids), antidepressants, anxiolytics, antihypertensives, and oral hypoglycemics and evidence of laboratory abnormalities in multiple organ systems. Analysis of an array of pre-specified outcomes reveals a risk gradient that increased across severity of the acute COVID-19 infection (non-hospitalized, hospitalized, admitted to intensive care). The findings showed that beyond the acute illness, substantial burden of health loss — spanning pulmonary and several extrapulmonary organ systems — is experienced by many COVID-19 survivors. [sounds like sepsis]



Comment: The findings showed that beyond the acute illness, substantial burden of health loss — spanning pulmonary and several extrapulmonary organ systems — is experienced by many COVID-19 survivors. While this study identified post-acute sequelae of COVID-19, it does not distinguish if they are a direct or indirect effect from COVID-19. Since this was a VA dataset there was a male predominance.

The results should stimulate the development of multidisciplinary care strategies to reduce chronic health loss among COVID-19 survivors.

Navigating the Uncertainties of COVID-19 Associated Aspergillosis (CAPA): A Comparison with Influenza Associated Aspergillosis (IAPA)

J Infect Dis published online April 21, 2021

[doi/10.1093/infdis/jiab163/6189669](https://doi.org/10.1093/infdis/jiab163/6189669)

Invasive pulmonary aspergillosis (IPA) is increasingly recognized as a life-threatening superinfection of severe respiratory viral infections, such as influenza. The pandemic of COVID-19 due to emerging SARS-CoV-2 raised concern about not only secondary bacterial infections but also IPA complicating COVID-19 in ICU mechanically ventilated patients. While the association between severe influenza and IPA has been demonstrated, it remains unclear whether SARS-CoV-2 infection represents a specific risk factor for IPA. [there have been observational reports] In this article the authors compare these two entities on three levels of consideration: i) epidemiology, ii) clinical characteristics and iii) pathogenesis. In particular, the authors discuss the similarities and differences between influenza-associated pulmonary aspergillosis (IAPA) and SARS-CoV-2 associated aspergillosis (CAPA). Compared to IAPA, the majority of CAPA cases have been classified as presumed rather than proven/probable IPA, in the absence of +galactomannan or histopath evidence. Discrimination between colonization and CAPA can be difficult. Distinct physiopathology and cytokine profiles of influenzas and COVID-19 may help explain the differences.

	IAPA	CAPA
Incidence	Variable (10 – 30%)	Variable (4 – 35%)
Baseline characteristics of patients	Approximately 25-30% immunocompromised ¹	<10% immunocompromised ¹ Predominantly males Obesity, hypertension, diabetes
Timing	Early (usually within 3-7 days from ICU admission)	Variable (from 3 to >14 days from ICU admission)
Mycological findings	Positive serum galactomannan in 50-70% cases Bronchoscopy and BAL findings in most cases	Positive serum galactomannan in <10% cases Unfrequent use of bronchoscopy, diagnosis relying on non-BAL respiratory samples in some cases
Type of IPA classification²	Majority of probable/proven cases (≥60%) Important proportion of tracheobronchitis (30%)	Majority of putative cases (>90%) Unknown proportion of tracheobronchitis
Inflammatory response to viral infection	Potential deleterious role of high IL-10	Potential protective role of high TNF-alpha/IFN-gamma
Bacterial superinfections	Frequent pneumonia due to community-acquired pathogens Nosocomial pneumonia in 10-20% of Influenza ICU cases	Rare pneumonia due to community-acquired pathogens Nosocomial pneumonia in 10-20% of COVID-19 ICU cases
Role of corticosteroids	Deleterious impact on both overall influenza mortality and IAPA incidence	Benefit for overall COVID-19 survival, unknown impact on CAPA incidence
Impact on outcome	Overall mortality 50-60% Association of IAPA with increased mortality in some studies [3, 16]	Overall mortality 60-70% Association of CAPA with increased mortality demonstrated in some but not all studies [5, 44]

Comment: Whether CAPA represents a unique entity is still under discussion. Other important questions remain such as what the true incidence is, what are the predisposing role of steroids or immunomodulatory drugs, how do we differentiate colonization versus invasive disease, and what are the clinical indications for antifungal therapy.

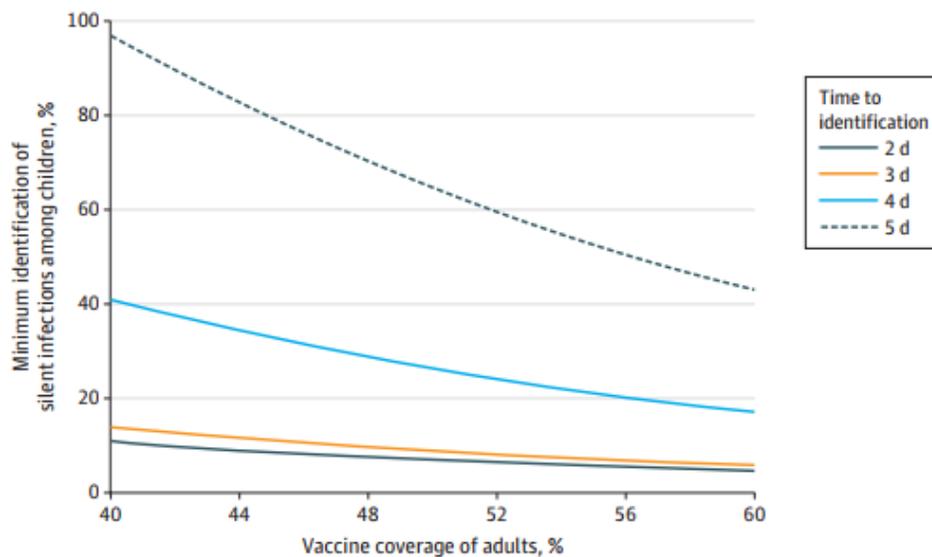
Simulated Identification of Silent COVID-19 Infections Among Children and Estimated Future Infection Rates with Vaccination

JAMA Netw Open published online April 23, 2021

doi:10.1001/jamanetworkopen.2021.7097

The investigators tried to estimate the benefits of identifying silent infections among children as a proxy for their vaccination. This study used an age-structured disease transmission model, parameterized with census data, and estimates from published literature, to simulate the estimated synergistic effect of interventions in reducing attack rates during the course of 1 year among a synthetic population representative of the US demographic composition. The population included 6 age groups of 0 to 4, 5 to 10, 11 to 18, 19 to 49, 50 to 64, and 65 years or older based on US census data. Data were analyzed from December 12, 2020, to February 26, 2021. In addition to the isolation of symptomatic cases within 24 hours of symptom onset, vaccination of adults was implemented to reach a 40% to 60% coverage during 1 year with an efficacy of 95% against symptomatic and severe COVID-19. In the base-case scenarios with an effective reproduction number $Re = 1.2$ [assume NPI], a targeted approach that identifies 11% of silent infections among children within 2 days and 14% within 3 days after infection would bring attack rates to less than 5% with 40% vaccination coverage of adults. If silent infections among children remained undetected, achieving the same attack rates would require an unrealistically high vaccination coverage (81%) of this age group, in addition to 40% vaccination coverage of adults. [adult vaccination rates are already higher—at least 1 dose] The estimated effect of identifying silent infections was robust in sensitivity analyses with respect to vaccine efficacy against infection and reduced susceptibility of children to infection.

Figure 3. Required Identification of Silent Infections Among Children to Reduce Attack Rates to Less Than 5% With Vaccination of Adults



Comment: it is unlikely that the next academic year will start with classrooms of fully vaccinated children because vaccine trials are just now commencing for elementary school-age children. It is likely that many children will not be offered vaccination until 2022, but children 12 and up should be vaccinated before the next academic year. [FDA has been silent to date on the Pfizer application on adding children 12-15] This analysis considers the value of frequent testing of schoolchildren in reducing community transmission rates. Certainly, the US and many countries find themselves in a stronger position than they were in 2020. In the US, the pace of vaccinations is increasing [slowing recently], and hospitalizations are now declining in most regions.

They did not include the effects of nonpharmaceutical interventions, but instead calibrated the model to current estimates of the effective reproduction number that implicitly accounts for these effects. Relaxation of such measures would increase the need for vigilant contact tracing among unvaccinated populations. Sensitivities of different tests were not included.

The lower risk of severe disease in children and adolescents, and increasing protection of older individuals, will likely make decisions about the next academic year easier. I anticipate that the next academic year will return our children to normal full-time in-person instruction, even if not all will be vaccinated. The authors estimate that detecting only 10% to 20% of infections in schoolchildren within the first 3 days after onset of infection may be enough to prevent widespread community transmission, assuming that most adults are vaccinated in the area. This study demonstrates the potential benefit of using school-based testing, even in the face of widespread adult vaccination, to minimize risk to communities as schools repopulate following the COVID-19 pandemic.