

## **BRIEF19**

*A daily review of covid-19 research and policy.*

### **RESEARCH BRIEFING**

#### **Mask mandates associated with fewer hospitalizations in the weeks after implementation.**

Spoiler: a new study has found that [mask mandates made a difference](#), especially in preventing covid-19-related hospitalizations, especially among middle-aged adults.

But let's focus on methods for a moment. Testing the effects of “non-pharmacologic interventions,” or NPIs, meant to curb the covid-19 pandemic has been tricky business. It's not so easy as measuring case counts before and after a particular government policy goes into effect. Why? Because often, the implementing of a particular policy occurs around the same time that the general population has become sufficiently alarmed so as to modify their behavior willingly. Therefore, what is being measured is not the effect of a policy, but the rational behavior of a populace. Many behaviors changes occur over the period of a few weeks. This means that drawing a line at the moment an official government policy goes into effect and assessing before versus after can produce misleading results. In addition, using something seemingly reasonable like coronavirus case counts can also pose a problem. If the number of tests increases around the same time as a policy like a mask mandate or shelter-in-place goes into effect, case counts will rise, even if the rates are really dropping. That's why many researchers have chosen test positivity (the percent of tests that are positive) as the metric of choice. Of course if testing increases rapidly, that too can muddy the findings, as suddenly lower rates are detected as a result of that rollout, rather than the true number of cases in a community. Deaths are a reasonable metric to study, but they are a lagging indicator and are likely to miss significant disease burden in younger persons, a noticeable fraction of whom might become sick enough to miss work or even need hospitalization, but who fortunately die at far lower rates. Long story short? Hospitalization rates are perhaps the perfect outcome measure for testing the effect of something like a mask mandate. These events reflect the prevalence of serious disease in a way that is agnostic to testing policies. People either need to be hospitalized or they do not.

The [new study](#) published in the US Centers for Disease Control and Prevention's journal *Morbidity and Mortality Weekly Report (MMWR)*, reports on precisely this. Researchers followed trends in hospitalization in areas where mask mandates went into effect. Rather than a strict before-and-after analysis, the researchers broke things down into four time periods: 4 weeks or more before a mask mandate, the 27 days leading up to the mask mandate, the 20 weeks after the mandate, and the period 3 weeks or more after the mandate. They also broke the population up into three age groups (adults 18-39, 40-64, and 65 or older). Mask mandates were associated with statistically relevant declines in covid-19-related hospitalization growth among adults ages 40-64 in the 20 days following the mask mandate. For adults ages 18-64, that effect was seen only 3 weeks or more after the enacting of the policy. Of note, the policies were *not* observed to have a significant impact on adults 65 and older, a finding that the authors chalk up to the fact that mask wearing was already known to be high in this demographic in many regions regardless of mandates. As always, the implication of such results much be taken in context. If one were to read these data and conclude that masks do not help people older than 65, that would be an incorrect interpretation. Rather, persons over 65 are leading the way on masks, and the rest of us would be wise to learn from them. [8 February 2021](#). —*Jeremy Samuel Faust, MD MS*

#### **Exposure to other coronaviruses does not give immunity against SARS-CoV-2.**

There are many coronaviruses. Most cause symptoms of the common cold. Occasionally, a nasty one, like SARS and SAR-CoV-2 causes far worse illness. Coronaviruses are actually common causes of the common cold. Therefore, many people are in fact walking around with antibodies from previous infections of run-of-the-mill coronaviruses. The question has therefore arisen: might antibodies from previous common coronavirus infections help people fight off the novel SARS-CoV-2 coronavirus? The idea is all the more enticing because some of these antibodies can indeed cross-react with parts of SARS-CoV-2.

The authors of [a new study](#) appearing in the journal *Cell* tested the blood collected back in 2017 from 263 children (under 18 years of age) and 168 adults as part of the Penn Medicine Biobank at the University of Pennsylvania. The scientists tested the blood for any ability to bind to the entire SARS-CoV-2 Spike protein, the receptor binding domain, and the nucleocapsid protein. The Moderna and Pfizer vaccines are directed against the spike protein, making it an attractive target. The receptor binding domain is the portion of the novel

virus that is most unique to SARS-CoV-2, and it is believed to account for its virulence and, possibly, its potential to elicit counterproductive inflammation, including so-called cytokine storms. For its part, the nucleocapsid protein provides a resting place, tethered to the inner barrier of the virus for the viral genome to nestle in.

Of the samples tested, 4.2 reacted to the SARS-CoV-2 full length spike protein, 0.93 percent to the receptor binding domain, and 16.2 percent to the SARS-CoV-2 nucleocapsid protein. But binding to these proteins is *not* the same as inactivating them. These pre-existing antibodies that bound to SARS-CoV-2 did not stop the virus from infecting cells when put to the test in laboratory experiments, nor did people who had antibodies to other milder coronaviruses experience less severe illness than those without evidence of cross-reactive antibodies.

The bottom line is that antibodies against old and novel coronavirus infections may cross-react, but this cross-reactivity provides no direct clinical protection. The only mildly reduced efficacy of vaccines in the face of the British and South American variants suggests that the response to vaccines will be at least somewhat effective against other variants of SARS-CoV-2, though, unless those variants dramatically alter the structure of function of the receptor binding domain. If that happens, a race to tweak the viruses will intensify.  
*12 February 2021.* —Michael Chary, MD PhD

### **The frozen fish theory thaws. Understanding the WHO investigation and its limitations.**

A theory has been going around that frozen fish delivered to China was the original source of SARS-CoV-2. While to date, no transmission has been linked to food packaging despite multiple shipments of frozen food in multiple countries testing positive for the presence of SARS-CoV-2 genetic material, it is understandable why what otherwise sounds like a far-fetched theory was not dismissed outright. The reality is that SARS-CoV-2, and therefore covid-19, likely came from a small mammal. But we truly do not know for sure.

This was the backdrop for the [World Health Organization's mission](#) to Wuhan which concluded earlier this week. At its conclusion, the team left open the possibility that the virus *may* have been transmitted to humans through frozen food. While this scenario is highly unlikely, this investigation occurred in an extremely complex political and diplomatic landscape.

Determining a virus' [origin](#), whatever that may be, could be an extremely long process. It can take decades and sometimes definitive answers never emerge. So, pinning down the origin of SARS-CoV-2 was never going to happen in two weeks. The WHO's mission was the start of a much longer process that will likely take years.

Ebola has been around for 40+ years and while we think it circulates in bats, we still haven't proved it by isolating infectious virus. We've only just sequenced a full genome from a bat. This isn't a movie, like *Outbreak*, where scientists find the host monkey instantly end the pandemic. Nor is the WHO a law enforcement agency. They cannot simply show up to a country with a warrant and demand access to every relevant archive.

The purpose of the WHO mission is to lay the groundwork for a much longer collaboration. If the international community wants to be part of these origin studies, there must be a collaborative relationship with scientists in China and with the Chinese government. Building long-term productive collaborations requires diplomacy and trust, and the building and maintaining of productive relationships. That also requires compromise. Like it or not, China does not have to allow any investigation at all. The WHO team is there at the pleasure of the Chinese government and cannot conduct the type of forensic investigation that many inexperienced onlookers from afar have demanded. They are also not detectives by profession or hobby; rather, they are a bunch of microbiologists. In fact, these particular experts are not qualified to conduct an audit of the Wuhan Institute of Virology. If the WHO is going to investigate the lab origin hypothesis, far-fetched though it may be, they will need to assemble a team compromised actual forensic investigative skills. What this WHO mission can do, however, is to continue to study both natural zoonotic origin and the “frozen fish” theory. That is within their skill set. And as implausible as the frozen fish theory might be, investigating it might be a condition of investigating other origins as well. *12 February 2021.*

—Angela Rasmussen, PhD ([Brief19 Thread-of-the-Week](#))

## **French study finds daycare does not increase spread of covid-19 in young children.**

For working parents of young children, the covid-19 pandemic has not been kind from a [productivity](#) standpoint. Reliable, affordable childcare is something of a myth in the United States, and the pandemic strained what limited options existed before. Daycares closed at the start of the United States outbreak, out of fear that children would be efficient viral vectors. Since then, a mounting body of evidence has found that children are in fact less commonly associated with viral spread, at least in some settings (as [covered in Brief19](#) as early as May of last year). But less is known about SARS-CoV-2 transmission in daycare or preschool settings, precisely because fears around the disease led most such facilities to close, and in many instances stay closed for months at a time. In short, because of covid-19 fears, there have been few opportunities to study this question rigorously. However, a new French study has shown such fears have not in fact been borne out.

At the end of the first coronavirus stay-at-home period last June, [researchers](#) in France wanted to know how many young children between 3 months old and 5 years of age who attended daycares had evidence of *prior* SARS-CoV-2 infection. They focused their efforts on 22 daycare centers in three major cities in France: Annecy, Rouen and Paris. They also studied daycare staff for signs of previous infection.

At the time of the study, nearly 10 percent of the Parisian population was estimated to have been affected by covid-19. (Rouen is a two-hour drive and Annecy is approximately 7-hours drive from Paris, respectively. *Editor's note: Annecy [looks absolutely beautiful](#) and the Brief19 team would quite like to visit the area when this is all over*). The researchers examined blood samples from 327 children along with 197 daycare staff in an effort to detect antibodies which would indicate a previous infection. Fourteen of the children (accounting for four percent) were found to have evidence of active covid-19 (based on particular antibodies that arise early in the disease, rather than the nasal PCR testing that most health officials and researchers use to track active or recent infection). According to information gathered from their parents, 43 percent of those children were asymptomatic. The cases were spread across 13 daycares, so no clusters of positivity were identified. There was, however, a correlation between adults testing positive in their homes beforehand. Furthermore, roughly seven percent of daycare staff were exposed to covid-19 across eight different daycares, two of which had small clusters of infection.

Ultimately, the researchers concluded that young children are more likely to get covid-19 at home than at daycare, adding to a growing body of evidence asserting that congregant settings for children such as daycare or preschools have not responsible for the majority of community spread so far.

On the other hand, the spread of any infectious disease increases when people are together for longer, so it could be that these data reflect the simple fact that despite daycares being a destination for these French children, they still spend a majority of their time at home.

Nevertheless, these data may be helpful in the push to reopen childcare and learning centers across the country and the globe in areas where it is otherwise safe to do so and the proper safety mechanism are in place.

It should be noted, however, that this study was conducted in June, prior to the introduction of new, more infectious variants. It is possible that children could be more effective spreaders of the viral variants currently in circulation. But if these data hold up, given what we know about the importance getting children socialized and educated and how difficult it is to accomplish the latter in remote learning environments, it may be both safe and advisable to get the little ones [back to in-person learning settings](#), whenever possible. [10 February 2021](#).  
—Joanna Parga-Belinkie, MD

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