



[4] COVID: testing for the virus and its antibodies, T-cell immune memory and impacts on survivors

Table of Contents:

- 1. Progression of the virus.....2**
- 2. PCR and Antigen testing.....3**
- 3. PCR testing caveats and shortfalls4**
- 4. Testing for antibodies5**
- 5. Tracking antibodies in COVID survivors.....7**
- 6. T-cells and COVID.....8**
- 7. How lethal is COVID?9**
- 8. Long term health issues for COVID survivors.....10**
- 9. Other discussion topics: eradication, multiple strains and asymptomatic transmission11**

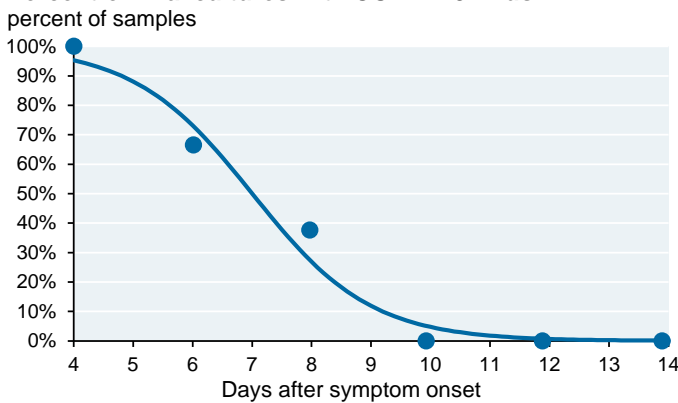


Progression of the virus

People that contract COVID-19 usually develop antibodies that most virologists believe will prevent them from getting sick again, although this assertion and the antibody levels required are still to be empirically proven. While other human coronaviruses that cause seasonal colds do not typically result in long-lasting immunity, SARS and MERS antibodies persisted for at least 2-3 years.

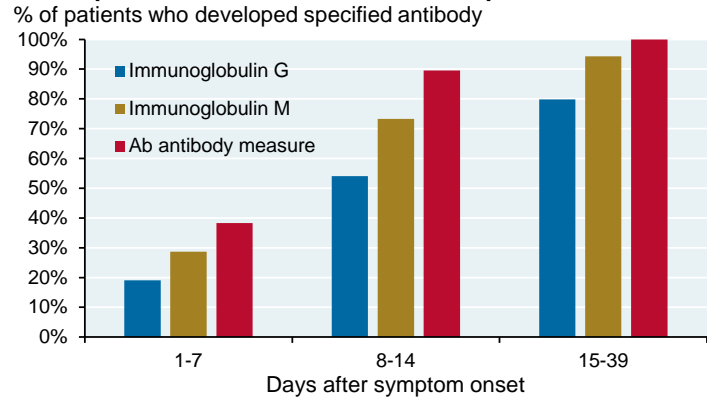
As shown on the left, by day 10, viral culture studies show that most people are no longer infectious. The viral decline is the direct result of the body’s immune response, part of which involves the appearance of virus-specific **antibodies (“seroconversion”)**. A March study from Shenzhen provides one assessment. Using **serology tests**, they measured the presence of general virus antibodies (Ab), early stage immune response antibodies (Immunoglobulin M) and antibodies for long-lived immunity (Immunoglobulin G). Some patients’ antibodies appeared during the first week; more showed up in the second week; and after 15 days, 80%-100% of patient samples contained one or more classes of antibodies. Overall, they found strong empirical support for routine application of serological testing in the diagnosis and management of COVID-19 patients.

Percent of viral cultures with COVID-19 virus



Source: Roman Wölfel et al, Bundeswehr Institute of Microbiology. 2020.

Development of antibodies in COVID-19 patients



Source: Juan-Juan Zhao et al, Shenzhen Third People’s Hospital. March 2020.

More recent studies confirm the appearance of antibodies and seroconversion. A July study from Harvard Medical School showed seroconversion after 11 days, and found that IgG antibodies were still detectable after 75 days.

Sources

“Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019”, Zhao et al, Institute of Hepatology, National Clinical Research Center for Infectious Disease, Shenzhen Third People’s Hospital, Shenzhen

“Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications”, Fan Wu et al, Shanghai Public Health Clinical Center, Fudan University, March 30, 2020

“Dynamics and significance of the antibody response to SARS-CoV-2 infection,” Iyer et al. Harvard Medical School, July 20, 2020



Testing for the presence of the virus

- The data we have seen on testing accuracy is divided into PCR test results and Rapid test (antigen) results
- Testing accuracy is typically measured by looking at its error rate, and there are two kinds of errors: false positives (people who aren't sick but who are TOLD they are) and false negatives (people who ARE sick who are told they are fine). The false positive error is a productivity problem: people told to stay home when they could come to work. The false negative problem is worse: these individuals spread the virus since they don't know they are ill.
- Neither PCR nor antigen tests have substantial false positive rates. That's the good news. However, there's a public health cost to rapid antigen tests since they have a much higher false negative rate than PCR tests
- The table below shows the false positive and false negative rates for both PCR and antigen tests. Ranges differ by manufacturer, and over time; more recent tests are presumably more accurate
- A false positive is different than a "high cycle" positive PCR test: in the former situation, someone isn't sick and is told they are infected. In the latter situation, a person has the virus but is at the tail end and is no longer infectious to others, but since the PCR test still picks up traces of genetic material, the test comes back as being positive. The test isn't wrong since they person had COVID, it's just that they are no longer infectious. I am not aware of PCR testing protocols that allow for identification of "high cycle" individuals
- As a reminder, none of the PCR or antigen tests have been certified for accuracy by the FDA. They have all been granted emergency use authorization due to the pandemic, but anyone tested should understand the risks inherent in the process.

| Diagnostic test | Method | Average "sensitivity": ability to detect virus in infected people (failures = false negatives) | Average "specificity": ability to confirm lack of infection in uninfected people (failures = false positives) | Indicative manufacturers |
|-----------------|--|---|---|---|
| PCR | Detect the virus genetic material | 98.9% (87.5%-100%) | 99.4% (92.3%-100%) | Abbott, Quidel, Roche, Thermo Fisher, LabCorp, Quest Diagnostics, Hologic |
| Antigen | Detect specific proteins on the surface of the virus | 90.4% (80%-97.6%) | 99.2% (96.6%-100%) | Abbott, Quidel, Becton Dickinson & Company, Access Bio, LumiraDx |

Source: John Hopkins University Center for Health Security, JPMAM. October 2020.



PCR testing caveats and shortfalls

A PCR test is not like a pregnancy test, which returns a simple yes/no result. PCR tests return a positive reading when a certain threshold of virus genetic material is found. And this is where it can get complicated: positive PCR (nasal swab) tests for the same person may differ depending on how “fine-tuned” the equipment is for evaluating them¹. As a result, reported infections could fall substantially if all equipment were calibrated similarly². Furthermore, some hospitalized individuals may be counted as COVID patients when they are in the hospital for other reasons. And finally, some people categorized as having died “from COVID” may have died “with COVID” instead (i.e., COVID was not a contributing cause of death).

All of this could be true, but people that strenuously push this narrative while excluding other factors remind me of someone I sat next to on Amtrak. His dog-eared copy of “**The Fountainhead**” made it clear he had read it too many times, limiting his ability to synthesize any information that contradicted his own, and preventing him from understanding why someone else would see things a different way.

- Yes, some PCR equipment is calibrated to levels that identify both present and past infections, resulting in an exaggerated measure of current infectiousness; PCR equipment should ideally be standardized to avoid unnecessary isolation and shutdowns. But PCR tests are the only way to easily monitor community spread³, and are useful as a policy indicator given their high correlation with hospitalizations (the median state correlation of reported COVID infections with COVID hospitalizations is 80%)
- While there may be some hospitalizations that are counted as COVID-related when they really aren’t, my contacts at Johns Hopkins tell me in practice, at a national level, that this is a very small number
- There are mortality errors in *both* directions: people who died from COVID and *weren’t* counted, and people who didn’t die from COVID and *were* counted that way. We can avoid debating mortality classification entirely by looking at “**excess deaths**”. As shown below, US mortality has been consistently higher than the excess death threshold, and daily US COVID deaths are still 15x-20x higher per person than in Europe
- Furthermore, for my benefit and for yours, **please do not focus solely on mortality risks**. There are well-documented long-term health risks that some COVID survivors face (see page 7) which should also affect public policy decisions. To exclude them from the narrative is disingenuous at best
- **Stop minimizing COVID risks by making too much out of a limited T-cell study from Sweden**. The number of people the authors found who appeared to recover from COVID without antibodies: 3. Yes, three. In other words, there is no robust evidence (yet) that T-cells can eradicate COVID on their own without the benefit of antibodies, nor is there evidence that individuals whose T-cells are responding to COVID are somehow not contagious, nor does anyone know if T-cells confer long-term immunity. The consensus is that T-cells may help shorten the course of the disease and its severity, which is good news on its own. Shane Crotty’s work at the La Jolla Institute of Immunology is the gold standard on this topic

¹ **Some equipment uses 35-40 cycles to determine PCR test positivity, which may pick up trace amounts of infection in people who are most likely not contagious any more, and at the tail end of infection.** Something like 30-32 cycles might make more sense if the goal is to identify currently contagious individuals. “High-cycle” PCR tests are best used when frequently testing the same individuals to monitor the progression of the disease, to confirm whether the patient is in the very early (infectious) or late (non-infectious) stage. However, in a recent paper from the UK health system, 8% of samples at cycles above 35 were still infectious.

² “Your coronavirus test is positive. Maybe it shouldn’t be”, NYT, August 29, 2020

³ Some universities measure virus content in dorm wastewater as an early warning signal, used in conjunction with testing, isolation and contact tracing. More widespread adoption of antigen testing in combination with PCR tests would also improve the process of identifying truly contagious individuals.



Testing for antibodies

Serology kits may differ on “**specificity**” (false anti-body positive) and “**sensitivity**” (false anti-body negative), in which case antibody presence could be misestimated⁴. A study from UC Berkeley analyzed 12 different serology tests, and provided some insight into these questions. The authors found “good to excellent sensitivity for all evaluated tests in hospitalized patients three or more weeks into their disease course”, and that their data “demonstrate specificity > 95% for the majority of tests evaluated, and > 99% for three of them”⁵. Roche announced that their serology test has 100% sensitivity and 99.8% specificity.

What do serology test results indicate in actual populations?

Research institutions and hospital systems around the world have released results of random serological tests for COVID-19 antibodies. Earlier this year, the results indicated much higher levels of COVID-19 exposure than were implied by reported case to population ratios. In simpler terms, serology results showed that there’s a **large number of unreported infections** due to people who couldn’t get a test, only had mild symptoms, were asymptomatic, etc. We used to show a table with these results, but they’re stale now since some countries have not released updates in several months and infections in many places have been surging.

In the US, the CDC is now working with commercial laboratories to conduct large-scale seroprevalence surveys. The table on the next page shows the CDC seroprevalence estimates based on samples taken in late July/early August. Using the seroprevalence estimates, we have calculated the estimated true infections to reported cases, the cumulative true number of infections, the case fatality ratio, and the true infection fatality ratio by state. The CDC plans to update the seroprevalence estimates every 2 weeks, but as you can see, there is a substantial lag involved of around 3 months due to the time it takes to process and aggregate the results.

⁴ The higher the disease prevalence, the lower the false positive problem. In addition, actual negatives are *much* larger than false positives, so as a policy approach, serology tests correctly identify the majority of susceptible people.

⁵ “*Test performance evaluation of SARS-CoV-2 serological assays*”, UCSF/UC Berkeley, April 2020.



| State | Seroprevalence (antibody presence) | Infection fatality rate based on seroprevalence | Reported case fatality rate | Seroprevalence cases divided by reported cases |
|-------|------------------------------------|---|-----------------------------|--|
| NY | 22.5% | 0.7% | 7.8% | 10.5x |
| NJ | 14.7% | 1.2% | 8.6% | 7.1x |
| LA | 10.8% | 0.9% | 3.2% | 3.8x |
| MD | 9.5% | 0.6% | 3.7% | 5.9x |
| PA | 8.9% | 0.6% | 6.1% | 9.5x |
| MS | 8.4% | 0.8% | 2.9% | 3.6x |
| AZ | 8.3% | 0.7% | 2.2% | 3.1x |
| NE | 7.9% | 0.2% | 1.2% | 5.2x |
| SC | 7.8% | 0.5% | 2.1% | 3.8x |
| IA | 7.8% | 0.4% | 1.9% | 4.9x |
| GA | 6.9% | 0.6% | 2.1% | 3.5x |
| ID | 6.5% | 0.2% | 1.0% | 4.3x |
| DE | 5.8% | 1.1% | 3.8% | 3.5x |
| TN | 5.8% | 0.3% | 1.1% | 3.2x |
| TX | 5.7% | 0.5% | 1.7% | 3.3x |
| CA | 5.6% | 0.4% | 1.8% | 4.1x |
| NV | 5.4% | 0.5% | 1.7% | 3.1x |
| AL | 5.4% | 0.7% | 1.8% | 2.5x |
| MA | 4.6% | 2.8% | 7.2% | 2.6x |
| AR | 4.3% | 0.4% | 1.2% | 2.6x |
| IL | 4.3% | 1.4% | 4.0% | 2.8x |
| FL | 4.1% | 0.8% | 1.5% | 1.7x |
| VA | 3.9% | 0.7% | 2.3% | 3.2x |
| MN | 3.9% | 0.8% | 2.8% | 3.5x |
| MI | 3.7% | 1.8% | 7.0% | 3.9x |
| CT | 3.3% | 3.8% | 8.9% | 2.4x |
| DC | 3.2% | 2.7% | 4.6% | 1.7x |
| UT | 3.1% | 0.4% | 0.8% | 2.1x |
| RI | 2.8% | 3.5% | 5.7% | 1.7x |
| MO | 2.8% | 0.8% | 2.2% | 2.8x |
| ND | 2.6% | 0.6% | 1.5% | 2.5x |
| OR | 2.5% | 0.4% | 1.7% | 4.7x |
| WA | 2.4% | 1.0% | 2.7% | 2.7x |
| NC | 2.3% | 0.9% | 1.6% | 1.7x |
| NM | 2.2% | 1.5% | 3.2% | 2.1x |
| OH | 2.2% | 1.4% | 3.6% | 2.5x |
| IN | 2.1% | 2.2% | 4.0% | 1.8x |
| KY | 2.1% | 0.8% | 2.1% | 2.5x |
| CO | 1.8% | 1.9% | 3.7% | 2.0x |
| WI | 1.5% | 1.2% | 1.6% | 1.4x |
| KS | 1.5% | 0.9% | 1.2% | 1.4x |
| OK | 1.5% | 1.0% | 1.4% | 1.5x |
| WV | 1.4% | 0.6% | 1.9% | 3.2x |
| NH | 0.9% | 3.5% | 6.1% | 1.8x |
| MT | 0.5% | 1.4% | 1.5% | 1.0x |
| VT | 0.5% | 1.9% | 4.0% | 2.1x |
| ME | 0.4% | 2.4% | 3.1% | 1.3x |
| AK | 0.4% | 0.9% | 0.7% | 0.8x |

Source: CDC Nationwide Commercial Laboratory Seroprevalence Survey. August 1, 2020. *No seroprevalence data for HI, SD and WY.



Serology tests: FDA caveats

There are over 50 companies that have informed the FDA of their intention to sell serology test kits in the US. Roche intends to ramp up production to the “high double digit” millions by June, which can be processed using their device with 300 results per hour. However, all kits are self-validated, and the FDA requires that the following disclosures be included:

- The tests have not been reviewed by the FDA
- Negative results do not rule out SARS-CoV-2 infection. Follow-up testing with a molecular diagnostic should be considered to rule out infection
- Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status
- Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains

These are strongly worded caveats, which some countries already appear prepared to disregard, or at least acknowledge as “acceptable” risk as the world focuses on getting back to work

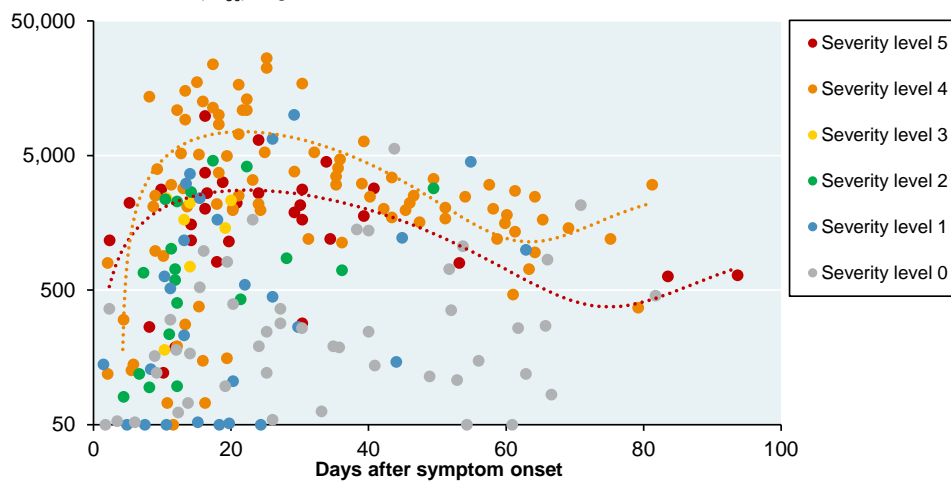
Tracking antibodies in COVID survivors

A recent study from King’s College in London found that antibody levels declined in COVID survivors. Some news reports concluded that these findings raise the risk of reinfection for survivors. However, that’s a very premature judgment to make without knowing the answer to any of the following questions:

- What antibody levels are required to prevent reinfection? Just because antibody levels decline doesn’t mean that they will be below the threshold required. Even if the blood plasma of recovered Covid-19 patients does not have high antibody levels, it has still proven to be sufficient to fend off the virus to some extent in vitro, and there is evidence that the body could produce more antibodies if needed⁶
- What antibody levels wouldn’t block reinfection, but would still reduce severity of the disease and render people asymptomatic? Again, another completely unknown quantity
- Could T-cell reactivity be enough when combined with modest levels of antibodies? See next page for a discussion of T-cell responses to disease

Duration of neutralizing antibodies by disease severity

Antibodies detected (ID₅₀), log scale



Source: Seow et al, “Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection”, King’s College London. July 11, 2020.

⁶ “The observation that plasma neutralizing activity is low in most convalescent individuals, but that recurrent anti-SARS-CoV-2 receptor binding domain (RBD) antibodies with potent neutralizing activity can be found in individuals with unexceptional plasma neutralizing activity suggests that humans are intrinsically capable of generating anti-RBD antibodies that potently neutralize SARS-CoV-2”. Source: “Convergent antibody responses to SARS-CoV-2 in convalescent individuals”, Robbiani et al, Rockefeller University. June 18, 2020.

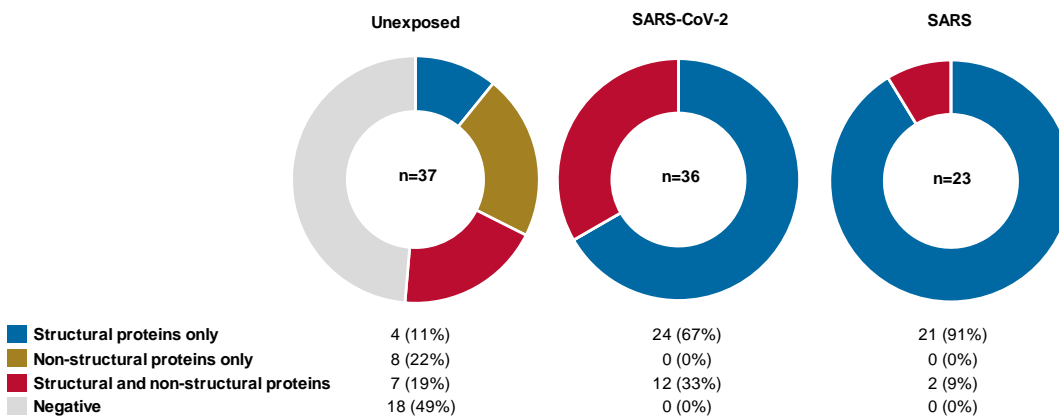


T-cells and COVID

Antibodies are not the only weapon the body uses to fight viruses; T-cells play a role as well, often through a process called “lysis” in which invading pathogens are killed or weakened (“killer” T cells destroy virus-infected cells, while “helper” T cells assist in antibody production). This research is early-stage, but scientists now believe that a subset of people have T-cells that recognize SARS-CoV-2 even though they’ve never been exposed to it. Known as cross-reactive T-cells, these cells may give the body a head start in fighting SARS-CoV-2.

- To be clear, T-cells provide **“cross reactive immune memory” rather than “immunity”**. **The distinction is critical; the latter implies iron-clad protection, while the former simply increases the prospects of less severe infection:** “T cells generally don’t completely prevent infections, they limit disease (make it shorter and/or less serious). Thus, wearing a mask is much more effective than hoping you and the people around you have pre-existing T cell memory”⁷
- Pre-existing T-cells that react to SARS-CoV-2 appear to result from past exposure to widely circulating “common cold” coronaviruses, and not from prior exposure to SARS-CoV-1, SARS-CoV-2 or MERS⁸.
- T-cells are analyzed to see if they secrete interferon-gamma after being exposed to SARS-CoV-2 viral proteins, which is how they respond when recognizing the specific antigen that activates them
- A multi-disciplinary team from Singapore writing in *Nature* magazine found that ~50% of a random unexposed group had T-cells that responded to SARS-CoV-2 viral proteins (in people that recovered from SARS-CoV-2 and SARS-CoV-1, 100% of patient T-cells did)⁹. Their results are similar to a May La Jolla Institute study finding T-cell reactivity in 50% of blood donor samples dating from 2015 – 2018¹⁰, and an April study from Berlin University finding T-cell reactivity in 34% of healthy blood donors¹¹
- After SARS-CoV-1, antibodies faded in some patients. However, their T-cell responses to SARS were still robust 17 years later. **This might explain the paradox of falling antibodies in recovering COVID patients and no reliable reports of reinfection.** In other words...”that would argue that there has been past zoonotic coronavirus transmission in humans, unknown viruses that apparently did not lead to serious disease, which have provided some people with a level of T-cell based protection to the current pandemic”¹²

Proportion of subjects with T-cell responses to SARS-CoV-2 structural and non-structural proteins



Source: SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls”, Bertoletti et al, Nature magazine, July 7, 2020.

⁷ Shane Crotty, Vaccine Discovery Division at La Jolla Institute for Immunology, August 11, 2020

⁸ “SARS-CoV-2-Reactive T Cells Found in Patients with Severe COVID-19”, Scientist.com, July 30, 2020

⁹ “SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS”, Bertoletti et al, Nature, July 7, 2020

¹⁰ “Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals”, Grifoni et al, La Jolla Institute for Immunology, May 14, 2020

¹¹ Presence of SARS-CoV-2 reactive T cells in COVID-19 patients and healthy donors”, Braun et al. Berlin University.

¹² “New Data on T Cells and the Coronavirus”, Derek Lowe, July 15, 2020

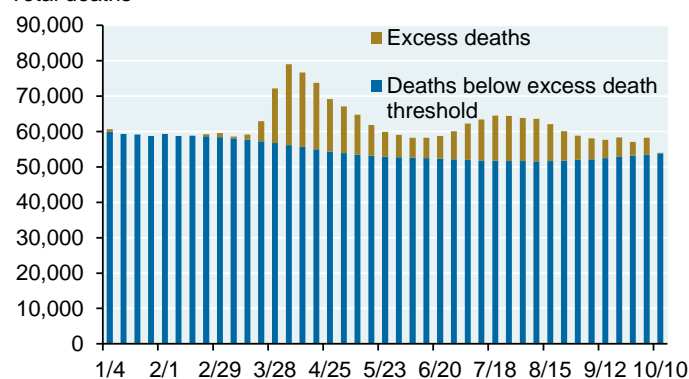


How lethal is COVID?

There's a lot of debate about the lethality of COVID vs the seasonal flu. A key statistical issue to keep in mind: the difference between case fatality rates (deaths as a % of reported cases) and true infection fatality rates (deaths as a % of all infected people, whether symptomatic or not). The latter can only be derived through a combination of antibody testing and other sampling methods involving molecular assessments of infection. The IFR of the seasonal flu is reported to be well below 0.1%, according to the CDC, with other estimates ranging from 0.02% to 0.04%. In contrast, the IFR for COVID has been estimated at 0.23% on a global basis by Stanford's Metaresearch Innovation Center, and at 0.6%-0.7% in the US by the CDC. So, no matter what IFR comparisons you use, COVID is significantly more lethal than the seasonal flu. A chart on "excess" (abnormal) death levels is another way to understand the incremental mortality impact of COVID.

US weekly deaths from all causes

Total deaths



Source: CDC. October 17, 2020.

What about younger people? While mortality rates for young people are much lower¹³, the risks are still substantial relative to other causes of death. An October 2020 Harvard Medical School study¹⁴ concluded that the mortality of COVID has been under-detected in this population:

- The study analyzes all-cause mortality among ~75,000 adults ages 25-44 in the US
- They define excess deaths as 2020 all-cause deaths minus 2019 all-cause deaths during the same period
- They found a 23% increase in all-cause deaths among 25-44 year olds vs the same period in 2019
- Despite the increase in all-cause deaths, only a small fraction of all-cause excess deaths have been attributed directly to COVID-19, which may be due to inadequate testing. Therefore, they conclude that the mortality of COVID has been under-detected in the younger adult population
- In 3 US regions, COVID deaths exceeded 2018 opioid overdose deaths during at least one month, making it the leading cause of death for people aged 25-44 during the periods

¹³ IFRs by age, from the CDC. For ages 0-19, 0.00003; for ages 20-49, 0.0002; for ages 50-69, 0.005; and for age 70+, 0.054.

¹⁴ "Mortality among adults ages 25-44 in the United States during the COVID-19 pandemic", Faust et al, Harvard Medical School, October 25, 2020

Long term health issues for COVID survivors

Lingering health consequences of COVID can be very debilitating for survivors of all ages: lung scarring, heart damage (cardiomyopathy and myocarditis), neurocognitive problems and abnormal blood clotting. While over 90% of influenza patients recovery fully within two weeks, COVID damage is apparently longer-lasting: CDC surveys show that 20% of those aged 18-34 experienced lasting symptoms. Furthermore,

Bottom line: you do not want to get this disease, no matter your age. Some recent after-effect studies are shown below; more detailed source information is available on request¹⁵.

Lung Scarring:

- A Chinese study of 70 hospitalized patients who were eventually discharged showed that 66 patients (94%) still had mild to substantial residual lung abnormalities on their last CT scans
- More than a third of 71 SARS patients infected in 2003 continued to have reduced lung capacity 15 years later in 2018
- MERS: 36% of patients continued to show signs of lung damage through abnormal chest radiographs
- COVID-19 scarring rates may end up being higher than SARS and MERS patients since those illnesses often attacked only one lung; COVID-19 appears to affect both lungs

Blood clots:

- A French study of 100 patients with severe COVID-19 showed 23% of patients with acute pulmonary embolus (blockage in the lungs as a result of a blood clots forming in other parts of the body).
- 2% to 4% of such survivors may have chronic pulmonary hypertension (shortness of breath, decreased exercise ability, heart failure)

Heart damage:

- An early study of 41 hospitalized patients in January from Wuhan, China found 12% of Covid-19 patients had signs of cardiovascular damage. Another study in Wuhan found that 19% of hospitalized COVID-19 patients showed signs of cardiac injury
- COVID-19 may cause long-lasting cardiac damage which could increase risk for heart attack and stroke

Neurological problems:

- Neurological symptoms were seen in 36% of Chinese patients. When looking only at severe cases the incidence of neurological symptoms increased to 46%. Symptoms included dizziness, headaches, nerve pain, impaired consciousness, and impaired taste/smell/vision
- Longer-term consequences of COVID-19 could include lower levels of attention, concentration, and memory, as well as dysfunction in peripheral nerves

Long term fatigue and breathlessness

- UK researchers examined 110 Covid-19 patients whose illnesses required hospital stays for a median of five days between March 30 and June 3. Twelve weeks after these patients were released from the hospital, 74% reported symptoms including breathlessness and excessive fatigue

¹⁵ American Heart Association, University of Texas Health Science Center, Columbia University Dep't of Neurology and Epidemiology, Tongji Medical College, Peking University People's Hospital, United Arab Emirates College of Medicine and Health Sciences, USC Keck School of Medicine, Johns Hopkins Medicine, Centre Hospitalier Universitaire de Besancon, Renmin Hospital of Wuhan University, North Bristol NHS Trust (UK)

Other discussion topics: eradication, multiple strains and asymptomatic transmission

When would we know if COVID were eradicated?

If at some point there are very few or no new cases reported in a given region, does that mean that COVID-19 has been eradicated? Not necessarily:

- It takes time to figure out if a virus is eradicated. The last smallpox case occurred in 1977, and the disease was not deemed to be eradicated until 1979
- COVID-19 (unlike SARS) can be transmitted by pre-symptomatic individuals, so the possibility exists that it could simmer undetected and re-emerge when conditions are more conducive to it spreading. This could produce periodic “flare-ups” of COVID-19 for several months even after the major waves now occurring subside. If that’s the case, COVID-19 could persist in humans until there’s a vaccine
- Even if COVID-19 disappeared from humans, it will not have disappeared from the animals from whom it “jumped” in the first place, so there’s always a possibility it could “jump” again. Not only that, but there’s always the risk of other zoonotic viruses appearing unless the world gets more serious about human-animal interfaces and the tools needed to accelerate vaccine development.

What about the issue of multiple COVID strains?

Some of my epidemiological contacts believe that different strains of COVID are minor variations of each other, that they have no real significance, and that they are better described as lineages rather than being immunologically distinct. Furthermore, most of my contacts believe that the polyclonal antibodies that confer immunity target specific parts of the COVID virus (the “viral antigens”) that are “conserved” (i.e., do not mutate), in which case each person’s antibody response would be sufficient to cover multiple strains. With the flu, mutations are much broader and require vaccines to be adapted to incorporate the mutations, but that is not the expected case with COVID. Since this is a new disease, this will have to be proven, but these are the operating assumptions so far.

What about the WHO statement on the lack of asymptomatic transmission?

- The WHO believes that it is rare for completely asymptomatic people to pass on the infection to others
- However, the WHO also believes that as many as 40%-60% of all infections are due to pre-symptomatic people....in other words, people that have the virus, don’t have a fever yet, are contagious and will develop a fever and/or other symptoms in 2-5 days
- I’m not sure exactly what kind of public policy approach or corporate policy approach would change based on the WHO findings. If you test people and they have the virus, they should self-isolate, since there is no way of determining if they are asymptomatic types, or pre-symptomatic types
- If you test people and they do not register as having the virus, they could still get the virus the very next day, or they could be one of the many people that the virus tests miss early in the infection period when they are still contagious (see page 2).
- As a result, a one-time test applied to a given population is kind of useless. You would have to continually test people in order to monitor the potential spread of infection in the workplace



IMPORTANT INFORMATION

The views, opinions and estimates expressed herein constitute Michael Cembalest's judgment based on current market conditions and are subject to change without notice. Information herein may differ from those expressed by other areas of J.P. Morgan. This information in no way constitutes J.P. Morgan Research and should not be treated as such.

The views contained herein are not to be taken as advice or a recommendation to buy or sell any investment in any jurisdiction, nor is it a commitment from J.P. Morgan or any of its subsidiaries to participate in any of the transactions mentioned herein. Any forecasts, figures, opinions or investment techniques and strategies set out are for information purposes only, based on certain assumptions and current market conditions and are subject to change without prior notice. All information presented herein is considered to be accurate at the time of production. This material does not contain sufficient information to support an investment decision and it should not be relied upon by you in evaluating the merits of investing in any securities or products. In addition, users should make an independent assessment of the legal, regulatory, tax, credit and accounting implications and determine, together with their own professional advisers, if any investment mentioned herein is believed to be suitable to their personal goals. Investors should ensure that they obtain all available relevant information before making any investment. It should be noted that investment involves risks, the value of investments and the income from them may fluctuate in accordance with market conditions and taxation agreements and investors may not get back the full amount invested. Both past performance and yields are not reliable indicators of current and future results.

Non-affiliated entities mentioned are for informational purposes only and should not be construed as an endorsement or sponsorship of J.P. Morgan Chase & Co. or its affiliates.

For J.P. Morgan Asset Management Clients:

J.P. Morgan Asset Management is the brand for the asset management business of JPMorgan Chase & Co. and its affiliates worldwide.

To the extent permitted by applicable law, we may record telephone calls and monitor electronic communications to comply with our legal and regulatory obligations and internal policies. Personal data will be collected, stored and processed by J.P. Morgan Asset Management in accordance with our privacy policies at <https://am.jpmorgan.com/global/privacy>.

ACCESSIBILITY

For U.S. only: If you are a person with a disability and need additional support in viewing the material, please call us at 1-800-343-1113 for assistance.

This communication is issued by the following entities:

In the United States, by J.P. Morgan Investment Management Inc. or J.P. Morgan Alternative Asset Management, Inc., both regulated by the Securities and Exchange Commission; in Latin America, for intended recipients' use only, by local J.P. Morgan entities, as the case may be.; in Canada, for institutional clients' use only, by JPMorgan Asset Management (Canada) Inc., which is a registered Portfolio Manager and Exempt Market Dealer in all Canadian provinces and territories except the Yukon and is also registered as an Investment Fund Manager in British Columbia, Ontario, Quebec and Newfoundland and Labrador. In the United Kingdom, by JPMorgan Asset Management (UK) Limited, which is authorized and regulated by the Financial Conduct Authority; in other European jurisdictions, by JPMorgan Asset Management (Europe) S.à r.l. In Asia Pacific ("APAC"), by the following issuing entities and in the respective jurisdictions in which they are primarily regulated: JPMorgan Asset Management (Asia Pacific) Limited, or JPMorgan Funds (Asia) Limited, or JPMorgan Asset Management Real Assets (Asia) Limited, each of which is regulated by the Securities and Futures Commission of Hong Kong; JPMorgan Asset Management (Singapore) Limited (Co. Reg. No. 197601586K), which this advertisement or publication has not been reviewed by the Monetary Authority of Singapore; JPMorgan Asset Management (Taiwan) Limited; JPMorgan Asset Management (Japan) Limited, which is a member of the Investment Trusts Association, Japan, the Japan Investment Advisers Association, Type II Financial Instruments Firms Association and the Japan Securities Dealers Association and is regulated by the Financial Services Agency (registration number "Kanto Local Finance Bureau (Financial Instruments Firm) No. 330"); in Australia, to wholesale clients only as defined in section 761A and 761G of the Corporations Act 2001 (Commonwealth), by JPMorgan Asset Management (Australia) Limited (ABN 55143832080) (AFSL 376919). For all other markets in APAC, to intended recipients only.

For J.P. Morgan Private Bank Clients:

ACCESSIBILITY

J.P. Morgan is committed to making our products and services accessible to meet the financial services needs of all our clients. Please direct any accessibility issues to the Private Bank Client Service Center at 1-866-265-1727.

LEGAL ENTITY, BRAND & REGULATORY INFORMATION

In the **United States**, bank deposit accounts and related services, such as checking, savings and bank lending, are offered by **JPMorgan Chase Bank, N.A.** Member FDIC. **JPMorgan Chase Bank, N.A.** and its affiliates (collectively "JPMCB") offer investment products, which may include bank-managed investment accounts and custody, as part of its trust and fiduciary services. Other investment products and services, such as brokerage and advisory accounts, are offered through **J.P. Morgan Securities LLC** ("JPMS"), a member of FINRA and SIPC. Annuities are made available through Chase Insurance Agency, Inc. (CIA), a licensed insurance agency, doing business as Chase Insurance Agency Services, Inc. in Florida. JPMCB, JPMS and CIA are affiliated companies under the common control of JPMorgan Chase & Co. Products not available in all states.

In **Luxembourg**, this material is issued by **J.P. Morgan Bank Luxembourg S.A. (JPMBL)**, with registered office at European Bank and Business Centre, 6 route de Treves, L-2633, Senningerberg, Luxembourg. R.C.S Luxembourg B10.958. Authorised and regulated by Commission de Surveillance du Secteur Financier (CSSF) and jointly supervised by the European Central Bank (ECB) and the CSSF. J.P. Morgan Bank Luxembourg S.A. is authorized as a credit institution in accordance with the Law of 5th April 1993. In the **United Kingdom**, this material is issued by **J.P. Morgan Bank Luxembourg S.A.– London Branch**. Prior to Brexit, (Brexit meaning that the UK leaves the European Union under Article 50 of the Treaty on European Union, or, if later, loses its ability to passport financial services between the UK and the remainder of the EEA), J.P. Morgan Bank Luxembourg S.A.– London Branch is subject to limited regulation by the Financial Conduct Authority and the Prudential Regulation Authority. Details about the extent of our regulation by the Financial Conduct Authority and the Prudential Regulation Authority are available from us on request. In the event of Brexit, in the UK, J.P. Morgan Bank Luxembourg S.A.– London Branch is authorised by the Prudential Regulation Authority, subject to regulation by the Financial Conduct Authority and limited regulation by the Prudential Regulation Authority. Details about the extent of our regulation by the Prudential Regulation Authority are available from us on request. In **Spain**, this material is distributed by **J.P. Morgan Bank Luxembourg S.A., Sucursal en España**, with registered office at Paseo de la Castellana, 31, 28046 Madrid, Spain. J.P. Morgan Bank Luxembourg S.A., Sucursal en España is registered under number 1516 within the administrative registry of the Bank of Spain and supervised by the Spanish Securities Market Commission (CNMV). In **Germany**, this material is distributed by **J.P. Morgan Bank Luxembourg S.A., Frankfurt Branch**, registered office at Taunustor 1 (TaunusTurm), 60310 Frankfurt, Germany, jointly supervised by the Commission de Surveillance du Secteur Financier (CSSF) and the European Central Bank (ECB), and in certain areas also supervised by the Bundesanstalt für Finanzdienstleistungsaufsicht (BaFin). In **Italy**, this material is distributed by **J.P. Morgan Bank Luxembourg S.A.– Milan Branch**, registered office at Via Catena Adalberto 4, Milan 20121, Italy and regulated by Bank of Italy and the Commissione Nazionale per le Società e la Borsa (CONSOB). In the **Netherlands**, this material is distributed by **J.P. Morgan Bank Luxembourg S.A., Amsterdam Branch**, with registered office at World Trade



Centre, Tower B, Strawinskykylaan 1135, 1077 XX, Amsterdam, The Netherlands. J.P. Morgan Bank Luxembourg S.A., Amsterdam Branch is authorised and regulated by the Commission de Surveillance du Secteur Financier (CSSF) and jointly supervised by the European Central Bank (ECB) and the CSSF in Luxembourg; J.P. Morgan Bank Luxembourg S.A., Amsterdam Branch is also authorised and supervised by De Nederlandsche Bank (DNB) and the Autoriteit Financiële Markten (AFM) in the Netherlands. Registered with the Kamer van Koophandel as a branch of J.P. Morgan Bank Luxembourg S.A. under registration number 71651845. In **Denmark**, this material is distributed by **J.P. Morgan Bank Luxembourg, Copenhagen Br**, filial af J.P. Morgan Bank Luxembourg S.A. with registered office at Kalvebod Brygge 39-41, 1560 København V, Denmark. J.P. Morgan Bank Luxembourg, Copenhagen Br, filial af J.P. Morgan Bank Luxembourg S.A. is authorised and regulated by Commission de Surveillance du Secteur Financier (CSSF) and jointly supervised by the European Central Bank (ECB) and the CSSF. J.P. Morgan Bank Luxembourg, Copenhagen Br, filial af J.P. Morgan Bank Luxembourg S.A. is also subject to the supervision of Finanstilsynet (Danish FSA) and registered with Finanstilsynet as a branch of J.P. Morgan Bank Luxembourg S.A. under code 29009. In **Sweden**, this material is distributed by **J.P. Morgan Bank Luxembourg S.A. - Stockholm Bankfilial**, with registered office at Hamngatan 15, Stockholm, 11147, Sweden. J.P. Morgan Bank Luxembourg S.A. - Stockholm Bankfilial is authorised and regulated by Commission de Surveillance du Secteur Financier (CSSF) and jointly supervised by the European Central Bank (ECB) and the CSSF. J.P. Morgan Bank Luxembourg S.A., Stockholm Branch is also subject to the supervision of Finansinspektionen (Swedish FSA). Registered with Finansinspektionen as a branch of J.P. Morgan Bank Luxembourg S.A.. In **France**, this material is distributed by **JPMorgan Chase Bank, N.A. ("JPMCB"), Paris branch**, which is regulated by the French banking authorities Autorité de Contrôle Prudentiel et de Résolution and Autorité des Marchés Financiers. In **Switzerland**, this material is distributed by **J.P. Morgan (Suisse) SA**, which is regulated in Switzerland by the Swiss Financial Market Supervisory Authority (FINMA).

In **Hong Kong**, this material is distributed by **JPMCB, Hong Kong branch**. JPMCB, Hong Kong branch is regulated by the Hong Kong Monetary Authority and the Securities and Futures Commission of Hong Kong. In Hong Kong, we will cease to use your personal data for our marketing purposes without charge if you so request. In **Singapore**, this material is distributed by **JPMCB, Singapore branch**. JPMCB, Singapore branch is regulated by the Monetary Authority of Singapore. Dealing and advisory services and discretionary investment management services are provided to you by JPMCB, Hong Kong/Singapore branch (as notified to you). Banking and custody services are provided to you by JPMCB Singapore Branch. The contents of this document have not been reviewed by any regulatory authority in Hong Kong, Singapore or any other jurisdictions. This advertisement has not been reviewed by the Monetary Authority of Singapore. JPMorgan Chase Bank, N.A., a national banking association chartered under the laws of the United States, and as a body corporate, its shareholder's liability is limited.

JPMorgan Chase Bank, N.A. (JPMCBNA) (ABN 43 074 112 011/AFS Licence No: 238367) is regulated by the Australian Securities and Investment Commission and the Australian Prudential Regulation Authority. Material provided by JPMCBNA in Australia is to "wholesale clients" only. For the purposes of this paragraph the term "wholesale client" has the meaning given in section 761G of the Corporations Act 2001 (Cth). Please inform us if you are not a Wholesale Client now or if you cease to be a Wholesale Client at any time in the future.

JPMS is a registered foreign company (overseas) (ARBN 109293610) incorporated in Delaware, U.S.A. Under Australian financial services licensing requirements, carrying on a financial services business in Australia requires a financial service provider, such as J.P. Morgan Securities LLC (JPMS), to hold an Australian Financial Services Licence (AFSL), unless an exemption applies. **JPMS is exempt from the requirement to hold an AFSL under the Corporations Act 2001 (Cth) (Act) in respect of financial services it provides to you, and is regulated by the SEC, FINRA and CFTC under US laws, which differ from Australian laws.** Material provided by JPMS in Australia is to "wholesale clients" only. The information provided in this material is not intended to be, and must not be, distributed or passed on, directly or indirectly, to any other class of persons in Australia. For the purposes of this paragraph the term "wholesale client" has the meaning given in section 761G of the Act. Please inform us immediately if you are not a Wholesale Client now or if you cease to be a Wholesale Client at any time in the future.

This material has not been prepared specifically for Australian investors. It:

- may contain references to dollar amounts which are not Australian dollars;
- may contain financial information which is not prepared in accordance with Australian law or practices;
- may not address risks associated with investment in foreign currency denominated investments; and
- does not address Australian tax issues.

With respect to countries in **Latin America**, the distribution of this material may be restricted in certain jurisdictions. We may offer and/or sell to you securities or other financial instruments which may not be registered under, and are not the subject of a public offering under, the securities or other financial regulatory laws of your home country. Such securities or instruments are offered and/or sold to you on a private basis only. Any communication by us to you regarding such securities or instruments, including without limitation the delivery of a prospectus, term sheet or other offering document, is not intended by us as an offer to sell or a solicitation of an offer to buy any securities or instruments in any jurisdiction in which such an offer or a solicitation is unlawful. Furthermore, such securities or instruments may be subject to certain regulatory and/or contractual restrictions on subsequent transfer by you, and you are solely responsible for ascertaining and complying with such restrictions. To the extent this content makes reference to a fund, the Fund may not be publicly offered in any Latin American country, without previous registration of such fund's securities in compliance with the laws of the corresponding jurisdiction. Public offering of any security, including the shares of the Fund, without previous registration at Brazilian Securities and Exchange Commission—CVM is completely prohibited. Some products or services contained in the materials might not be currently provided by the Brazilian and Mexican platforms.

References to "J.P. Morgan" are to JPM, its subsidiaries and affiliates worldwide. "J.P. Morgan Private Bank" is the brand name for the private banking business conducted by JPM.

This material is intended for your personal use and should not be circulated to or used by any other person, or duplicated for non-personal use, without our permission. If you have any questions or no longer wish to receive these communications, please contact your J.P. Morgan representative.

© 2020 JPMorgan Chase & Co. All rights reserved.