



[4] COVID: reinfection, antibodies, T-cell immune memory and survivor impacts

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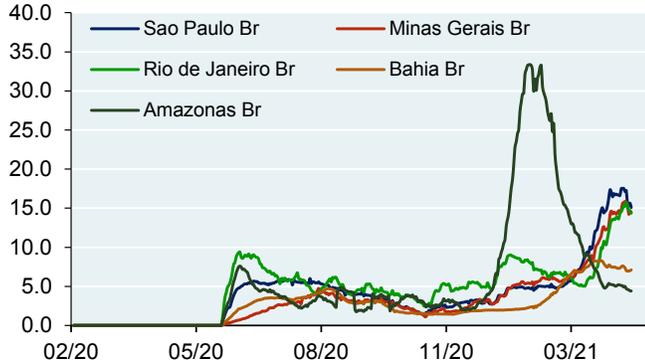


Reinfection risks in previously infected individuals

There has been a spike in mortality and infection in the Amazon (Brazil), which is a concern since last year the region was believed to have reached herd immunity through community spread.

Brazil states

Daily deaths, # per mm, smoothing = 14 days



Source: Johns Hopkins University, IMF, JPMAM. Apr 25, 2021.

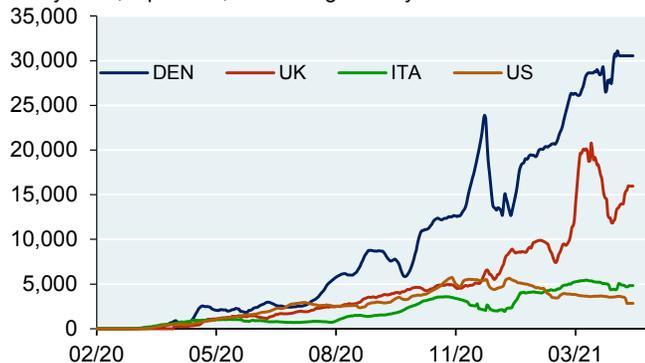
As for the developed world, a March 2021 study in *The Lancet* analyzed reinfection risk in Denmark, which has continued to provide PCR tests to large segments of its population despite a sharp decline in infections. The Statens Serum Institute found that from September to December 2020, **0.65% of a population of previously infected individuals experienced reinfection**, which was 80% below the 3.3% infection rate in individuals who had not been infected before. However, these results were skewed by age group. For those 65 and over, the infection rate for previously infected individuals was just 50% below the infection rate in the first-time infected population. The Denmark results are similar to other reinfection studies from the US and UK. The study did not comment on the *severity* of reinfection; only that it was confirmed through PCR testing.

Key takeaways:

- Naturally occurring antibodies provide protection against reinfection, but not for everyone
- Reinfection rates have ranged from 0.5% to 1.0% of previously infection populations; in Denmark, reinfection rates were ~80% below infection rates among first-time infected groups. Protection was lower for people over 65, whose reinfection rates were only 50% below first-time infection rates
- **This highlights the importance of vaccinating people who have had COVID, particularly those > 65**
- Some of my contacts believe that **reinfection rates may be lower in vaccinated populations**, given the possibility of more robust antibody and T-cell responses to the vaccine’s spike protein; although this will have to be empirically proven over time

Testing

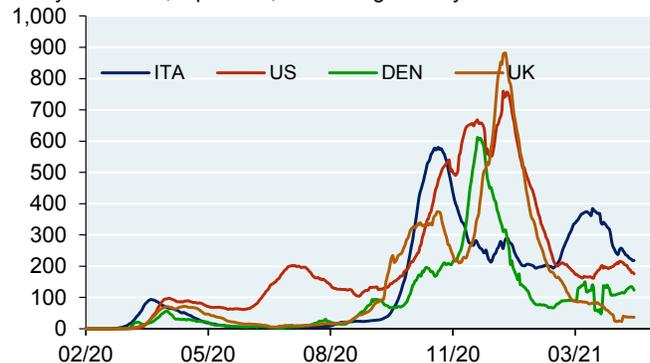
Daily tests, # per mm, smoothing = 1 days



Source: Johns Hopkins University, IMF, JPMAM. Apr 25, 2021.

Infections

Daily infections, # per mm, smoothing = 7 days



Source: Johns Hopkins University, IMF, JPMAM. Apr 25, 2021.

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 request¹.

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 had 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
- A study of 62,000 COVID patients showed that 20% later developed a new mental illness such as anxiety, depression and insomnia

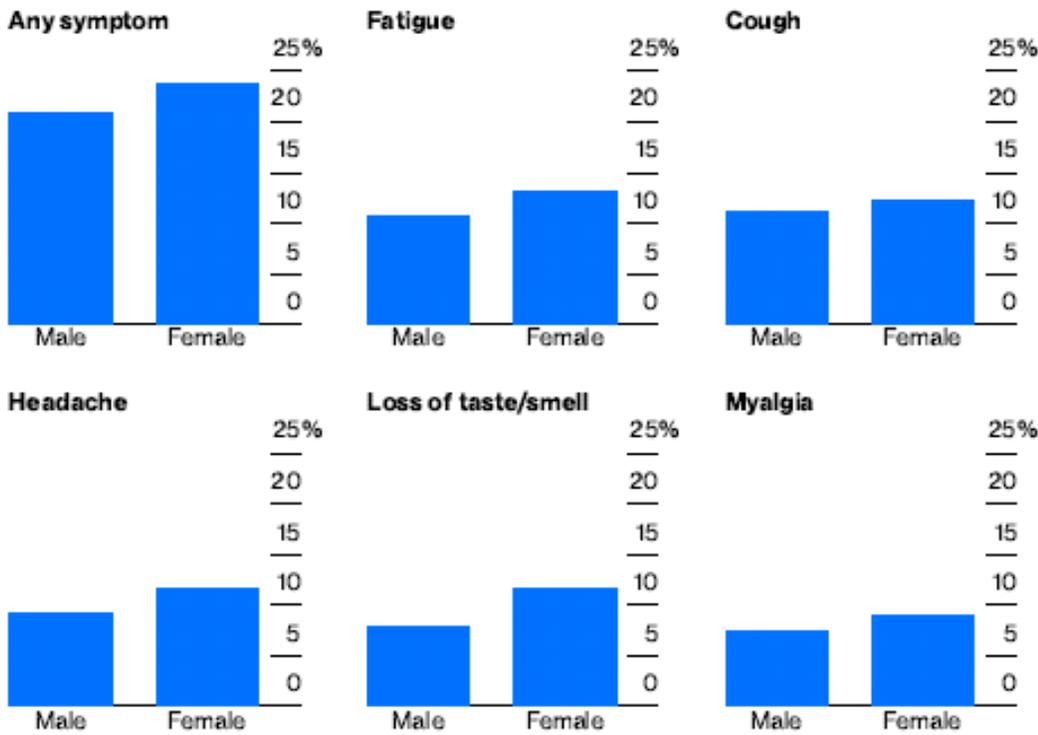
¹ American Heart Association, University of Texas Health Science Center, Columbia University Dep't of Neurology and Epidemiology, Tongji Medical College, Peking University People's Hospital, United Arab Emirates College of Medicine and Health Sciences, USC Keck School of Medicine, Johns Hopkins Medicine, Centre Hospitalier Universitaire de Besancon, Renmin Hospital of Wuhan University, North Bristol NHS Trust (UK), Lancet Psychiatry Journal



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

One recent assessment from the UK covers a variety of mild and more severe long term effects in people infected from April to December 2020, all measured 5 weeks after testing positive. The “any symptom” category results fell to 10% after 12 weeks. The results appear below.



Source: U.K. Office for National Statistics

Note: April 22 to Dec. 14, 2020 survey; estimates based on unweighted data and assumes continuous symptoms among 9,063 respondents who ever tested positive for Covid-19 and were symptomatic at five weeks.



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 misestimated². 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”³. Roche announced that their serology test has 100% sensitivity and 99.8% specificity.

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

² 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.

³ “*Test performance evaluation of SARS-CoV-2 serological assays*”, UCSF/UC Berkeley, April 2020.



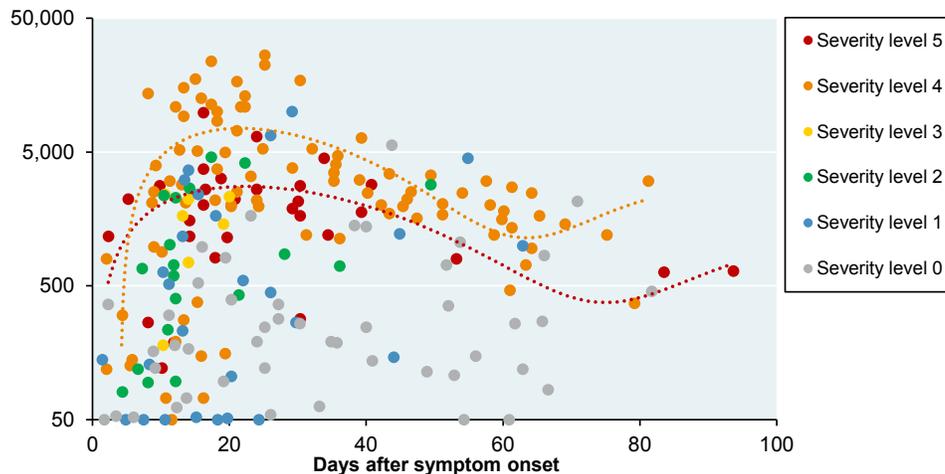
Tracking antibodies in COVID survivors

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 needed⁴
- 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.

⁴ "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.

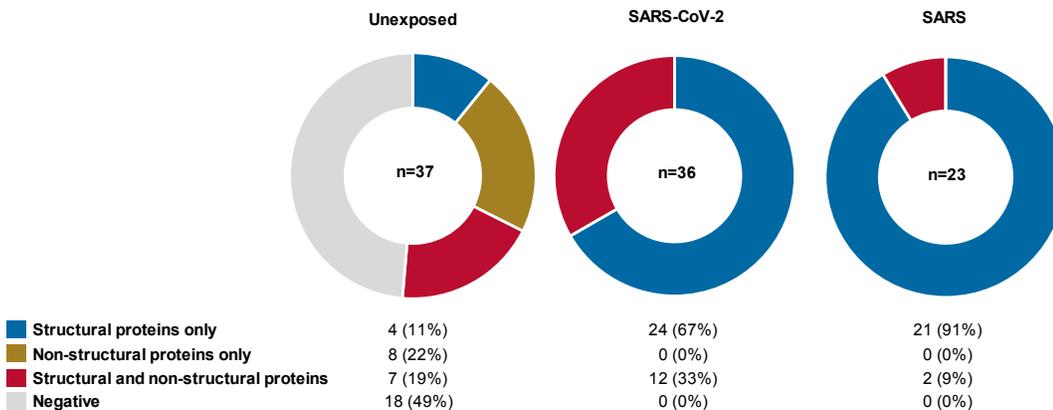


T-cells and COVID

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”⁵
- 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 MERS⁶.
- 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)⁷. Their results are similar to a May La Jolla Institute study finding T-cell reactivity in 50% of blood donor samples dating from 2015 – 2018⁸, and an April study from Berlin University finding T-cell reactivity in 34% of healthy blood donors⁹
- 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”¹⁰

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.

⁵ Shane Crotty, Vaccine Discovery Division at La Jolla Institute for Immunology, August 11, 2020

⁶ “SARS-CoV-2-Reactive T Cells Found in Patients with Severe COVID-19”, Scientist.com, July 30, 2020

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

⁸ “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

⁹ Presence of SARS-CoV-2 reactive T cells in COVID-19 patients and healthy donors”, Braun et al. Berlin University.

¹⁰ “New Data on T Cells and the Coronavirus”, Derek Lowe, July 15, 2020

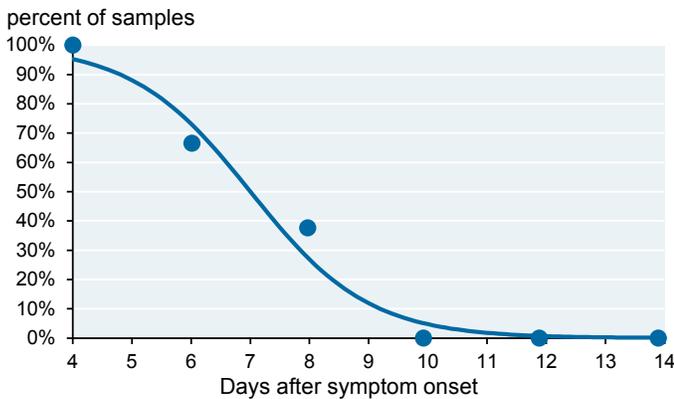


Progression of the virus

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.

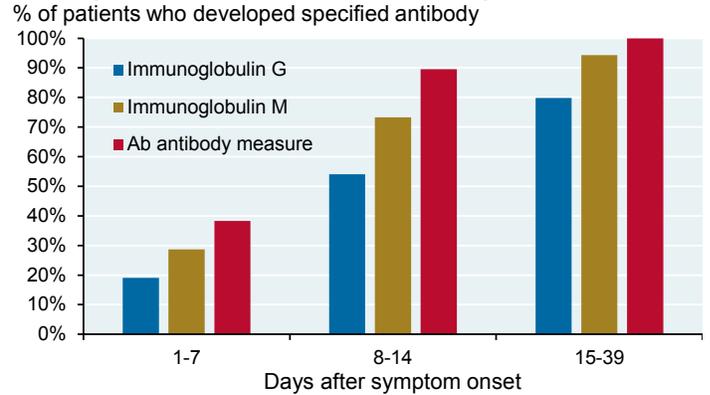
As shown on the left, by day 10, viral culture studies show that most people are no longer infectious. The viral decline is the direct result of the body’s immune response, part of which involves the appearance of virus-specific **antibodies (“seroconversion”)**. A March study from Shenzhen provides 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 them¹¹. As a result, reported infections could fall substantially if all equipment were calibrated similarly¹². 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 spread¹³, 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 3) 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

¹¹ **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.

¹² “*Your coronavirus test is positive. Maybe it shouldn’t be*”, NYT, August 29, 2020

¹³ 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.



Update on anti-viral, immunomodulator and corticosteroid trials

Dexamethasone (corticosteroid). Dexamethasone is a steroid which reduces inflammation (typically used to treat asthma and arthritis), and has now been shown to minimize effects of cytokine storms¹⁴ of severely infected patients. Compared to monoclonal antibodies and immune-modulators, they are **generally much cheaper and also readily available**. Results from the UK “Recovery” trial:

- Randomized, controlled trial of 2,104 patients in treatment group vs 4,321 in control group
- Reduced deaths from 40% to 28% in ventilated patients, and reduced the risk of death from 25% to 20% in patients receiving oxygen only; no benefit for patients not requiring respiratory support

Remdesivir (anti-viral). Modest benefits but only for patients in the earlier stages of disease.

- The New England Journal of Medicine published the final results of a 1000-patient randomized, double-blind controlled trial conducted by the NIH.¹⁵ The study showed Remdesivir reduced time to recovery from 13-18 days in the control group to 9-11 days in the group receiving Remdesivir, and reduced mortality from 15.2% to 11.4%. The benefit of Remdesivir was more pronounced when given to patients earlier in the illness, for example to those receiving oxygen but not yet on a ventilator. While not a “miracle drug”, the NEJM study showed that Remdesivir may provide modest benefits for higher-risk patients when administered in early stages
- However, interim results from the WHO’s “Solidarity” trial concluded that Remdesivir has no benefit in reducing mortality, recovery time or ventilation based on a study of 2,700 hospitalized patients receiving it. In the WHO trials, both treatment and control groups had mortality rates of around 11%. Our sources point out that the NIH/NEJM study had fewer patients on oxygen and ventilation in its treatment group than the WHO study, suggesting the NIH results could be more similar to the WHO study if both treatment groups had the same characteristics (i.e., the NIH/NEJM study concentrated on less sick patients).
- Remdesivir is given intravenously rather than orally, so it would only be used in hospital settings, which implies a narrower healthcare impact than drugs that can be delivered on an outpatient basis. Gilead is currently working on an inhalable Remdesivir treatment and subcutaneous injections as well, which would broaden the scope of potential uses

Tocilizumab (immunomodulator). This FDA-approved drug treats rheumatoid arthritis and cytokine release syndrome. A French study showed that Tocilizumab reduced deaths and the need for ventilators, and in China, Tocilizumab is included in COVID treatment guidelines. In June 2020, a U. Michigan Tocilizumab trial found a 45% lower likelihood of death compared to control group, a higher % of discharged patients and hospitalized patients not requiring ventilation; and appears to dampen “cytokine storm” severity. The study also noted that Tocilizumab suppresses the immune system, which increases risk of infection. The treatment group was twice as likely to develop a further lung infection (generally bacterial pneumonia).

The latest results come from the REMAP-CAP study in Europe which involves more than 3,900 COVID patients. Patients receiving tocilizumab and a second immunomodulator called sarilumab experienced a reduced risk of death by 24% when administered within 24 hours of entering intensive care.

¹⁴ Some COVID-19 fatalities experienced **sudden multiple organ failure**. Doctors don’t know yet if that’s because of the viral infection itself, or because of immune system damage caused by a “cytokine storm”, which is a large, rapid release of cytokines into the blood as a result of viral infections or immunotherapy. From oncology doctors at Washington University in St. Louis: “we believe that there is increasing evidence that cytokine storm syndrome is occurring co-incident with the progressive pneumonia and in severe cases may be driving the pathology and increasing the risk of death above and beyond what would be expected by the viral infection by itself”.

¹⁵ “Remdesivir for the Treatment of COVID-19 – Final Report”, Beigel et al. National Institutes of Health, New England Journal of Medicine. October 8, 2020



Interferon beta (anti-viral). In double-blind placebo controlled trials with 50 patients, nebulized interferon reduced ventilation by 80%. Patients were 2-3x more likely to resume everyday activities, and average time in hospitals was reduced by a third.

Favipiravir (anti-viral). Fujifilm's Phase III trials of 156 COVID patients in Japan demonstrated reduced recovery times for COVID-19 patients with non-severe symptoms. More trials are underway in the US, UK and India. This drug is an existing flu treatment first approved in Japan in 2014.

Ravulizumab-cwbz (immunomodulator). Phase III trials are ongoing in COVID patients with severe pneumonia or acute respiratory distress syndrome. Preclinical data demonstrated reduced lung inflammation in animals with pneumonia.

Apilimod (immunomodulator). The drug showed promise inhibiting COVID in vitro as per a recent *Nature* paper that analyzed 12,000 possible compounds. AI Therapeutics and Yale University announced a randomized, double-blind placebo-controlled Phase II trial with 142 patients. Like other immunomodulators, Apilimod may impair immune functions even as it protects against the virus, so that will be an important outcome to monitor from future trials.

Chloroquine/hydroxychloroquine (anti-viral): In April 2020, an NIH panel recommended against the use of HCQ and azithromycin to treat COVID patients. In June, the US Food and Drug Administration revoked its emergency use authorization for hydroxychloroquine and chloroquine for treatment of Covid-19. A **case study** in bad science, bad medicine, bad reporting and according to some accounts, bad behavior as well¹⁶.

¹⁶ <https://blogs.sciencemag.org/pipeline/archives/2020/03/29/more-on-cloroquine-azithromycin-and-on-dr-raoult>



Convalescent plasma and monoclonal antibody therapy

Convalescent plasma refers to virus-neutralizing antibodies harvested from recovered patients to treat infected patients and vulnerable populations. It was used during the Victorian era before antibiotics to treat meningitis & pneumonia by injecting bacteria into horses and harvesting horse serum. Convalescent plasma is currently used to treat immuno-deficient individuals against measles and mumps, and was successfully used to treat patients during both SARS in 2002 and the 2009-2010 H1N1 influenza pandemic. **Like antivirals and vaccines, convalescent plasma applied to COVID-19 will require clinical trials to demonstrate both safety and efficacy.**

UPDATES:

- **January 16, 2021:** The “Recovery” trial suspended its convalescent plasma study after it showed no benefits for hospitalized patients. Analysis of 1,873 deaths in a study of 10,400 UK patients showed the treatment made “no significant difference”. In the group treated with convalescent plasma, 18% of patients died within 28 days - the same figure for the group given standard treatment.
- **January 29, 2021:** A randomized trial of convalescent plasma for 940 hospitalized adults (CONCOR-1) stopped enrollment after the independent data safety monitoring committee determined the study is unlikely to demonstrate a benefit of convalescent plasma even if more patients were enrolled.
- **February 25, 2021:** An interim analysis of the National Heart, Lung and Blood Institute convalescent plasma trial concluded that, while its treatment of 500 mild to moderate COVID patients caused no harm, it was unlikely to benefit the patients enrolled.

The details: An August 2020 Mayo Clinic study reported that mortality rates were lower for patients given convalescent plasma within 3 days of COVID diagnosis compared to patients receiving it after 3 days (7-day mortality rates 8.7% vs 11.9%, 30-day mortality rates 21.6% vs 26.7%). However, in February 2021, researchers in Argentina published the results of their randomized controlled trial of convalescent plasma. 228 hospitalized patients received convalescent plasma treatment and 105 patients were assigned to a placebo. The study found that there was no significant difference in clinical outcomes between the treatment group and the placebo group.

Rockefeller University released a study on the dynamics of convalescent plasma antibodies. They found that most donors do not have high levels of antibodies, and that for one third of donors, neutralizing antibodies were undetectable, rendering their plasma contributions worthless. Furthermore, only 1% of donors showed “elite” high-level neutralizing antibodies. **However, elite donor antibodies are sufficiently powerful** so that even when diluted 1000-fold, the plasma can still neutralize the virus and last for several months. As a result, Rockefeller scientists initiated clinical trials in January 2021 of a new monoclonal antibody drug created by cloning these elite antibodies



Like convalescent plasma, **monoclonal antibody therapy** (mAb) involves infusion of antibodies with the goal of preventing infected people becoming ill, and preventing the ill from dying. How do mAb work? They are engineered with the goal of being more precise than convalescent plasma: neutralize the infectivity of SARS-CoV-2 by binding specifically to the spike protein that enables it to enter human cells. A likely treatment regimen could contain 2 or 3 different mAbs. While convalescent plasma relies on antibodies harvested from recovered individuals, mAb can be harvested from recovered humans, from mice genetically modified to have the immune system of a human being, via genetic engineering or from advanced cell cultures. While mAb are used to treat cancer and autoimmune diseases, few have been developed for infectious diseases. However, mAb worked against Ebola, several companies are entering human clinical mAb trials:

- **Regeneron (REGN-COV2).** Phase II/III results from Regeneron’s trial of 800 non-hospitalized participants found that the treatment reduced the viral load by 10-fold in the treatment group compared to the placebo, and reduced COVID-related medical visits by 57% through day 29. Final Phase III data indicated that the drug reduced risk of hospitalization or death by 70%. Phase III data also show that, among infected asymptomatic individuals, the treatment reduced the risk of progressing to symptomatic COVID by 76% three days after treatment. Regeneron received Emergency Use Authorization in November 2020 to be used in outpatient settings for people with mild to moderate COVID who are at high risk for hospitalization or developing a severe case. It is not authorized for patients who are already hospitalized or require oxygen. A small study of 1,500 participants also tested Regeneron as a preventative treatment among people living in the same household as COVID-infected individuals. The study found that the treatment, which is administered by injection, was 81% effective at preventing symptomatic infection. Recent preprints from Columbia and NYU showed the mAb cocktail retained efficacy against the B.1.351 variant, though with a 9-fold reduction in neutralizing activity.
- **Eli Lilly/AbCellera (LY-COV55).** Phase II/III trials in 450 recently diagnosed individuals showed that mAb treatment reduced hospitalization rates to 1.7% compared to 6% in the placebo group. Final Phase III results showed the treatment demonstrated 87% efficacy in preventing hospitalizations and deaths among high-risk patients with mild to moderate infections. Eli Lilly received Emergency Use Authorization from the FDA in November 2020 for use of the treatment in high-risk patients in outpatient settings, to be administered in newly infected people within 10 days of developing symptoms. However, in March 2021, the FDA announced that the monoclonal antibody would no longer be distributed due to concerns about efficacy against new variants of concern in the U.S. A recent study from Columbia University showed that, while the mAb retained potency against the B.1.1.7 variant, neutralization of B.1.351 was “completely or markedly abolished.”
- **GSK/Vir (VIR-7831).** In March 2021, GSK/Vir’s Phase III trial of its monoclonal antibody demonstrated 85% efficacy in reducing hospitalization and death among 583 high-risk participants with mild or moderate COVID. A forthcoming in vitro study from GSK/Vir found that the treatment demonstrates efficacy against the UK, South Africa and Brazil variants. Like other monoclonal antibodies, the treatment must be administered intravenously to patients early in the disease, though the company is initiating Phase III trials to test efficacy both as an intramuscular injection and as a preventative measure against COVID in high-risk adults. Based on these results, the companies are seeking Emergency Use Authorization from the FDA and global regulatory authorities.

The advantages of mAb: can be used both as acute therapy for COVID patients and as a prophylactic for front-line health care workers. **The disadvantages:** higher cost than vaccines; harder to produce at scale since a large dose of recombinant proteins might be needed since your body isn’t making them for you; and temporary.



Possible benefits of anticoagulants, statins and ACE inhibitors for infected patients

Healthcare professionals have noticed a range of unconnected vascular phenomena that aren't seen with SARS-CoV-1 or H1N1. Medical directors at Brigham and Women's Hospital Heart and Vascular Center in Boston believe that COVID is a "vasculotropic" disease, and that SARS-CoV-2 can infect endothelial cells that line the inside of blood vessels (these cells protect the cardiovascular system and release proteins that influence everything from blood clotting to the immune response)¹⁷:

- Damage to endothelial cells causes inflammation in blood vessels, which can cause accumulated plaque to rupture, causing a heart attack. Blood vessel damage could also explain why people with pre-existing conditions like high blood pressure, high cholesterol, diabetes, and heart disease are at a higher risk for severe complications from a virus that's supposed to just infect the lungs. All of those diseases cause endothelial cell damage, and additional damage in blood vessels caused by the infection could result in more severe complications and death
- This could explain why ventilation often isn't enough to help patients breathe better. Moving air into the lungs via ventilation can help, but exchange of oxygen and carbon dioxide in the blood is just as important to provide the rest of the body with oxygen; that requires healthy blood vessels in and around the lungs
- **If COVID is a vascular disease, ACE inhibitors and statins might help protect against endothelial cell damage. However, so far, most studies we have seen assess the outcomes for COVID patients that were *already* taking statins and ACE inhibitors (not studies on such treatments being applied for the first time to infected COVID patients)**
 - A UCSD study found that prior statin use was associated with a lower risk of developing severe COVID disease, and a faster time to recovery with patients with severe disease. Similar results were found in studies from Oxford, the Universitat Rovira i Virgili/Pere Virgili Institut (Spain) and the Policlinico di Modena Hospital (Italy)
- **Blood thinners have been shown to help as well.** A May report in the Journal of the American College of Cardiology analyzed medical records of 2,773 COVID-19 patients in NYC hospitals. The study was initiated after doctors realized that COVID can result in life-threatening blood clots. Notable findings: survival rates for 395 intubated patients treated with anticoagulants were 62% compared to 29% for those who were not¹⁸
 - **However, anticoagulation is controversial and a very delicate balance.** COVID physicians we spoke with cite negative side effects such as bleeding (oftentimes brain bleeds that were not recognized until the patients were being considered for extubation), and benefits given the large number of strokes in patients hospitalized with COVID that anticoagulants can prevent. The protocols and research on anticoagulants for COVID patients is still a work in progress

¹⁷ "Endothelial cell infection and endotheliitis in COVID-19", Z. Varga et al. Department of Pathology and Molecular Pathology, University Hospital Zurich. April 20, 2020

¹⁸ "Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19", I. Paranjpe et al. Journal of the American College of Cardiology. May 2020



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