[5] COVID: testing for the virus and for antibodies, T-cell immunity and impacts on survivors

Many factors influence the rate of infection and mortality across countries. In addition to social distancing and quarantine (including restrictions on mass gatherings and school closures), scientists have published papers suggesting that COVID-19 incidence and/or mortality can be traced to weather, latitude, pollution, smoking/vaping, obesity, age distributions, intergenerational cohabitation, gender, pre-existing conditions, population density and BCG infant tuberculosis vaccine usage (see section 4). While many studies claim to isolate the impact of individual factors, I doubt that COVID infection or mortality outcomes can be ascribed that neatly to any one determinant.

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.

The progression of the virus. As shown on the left, by day 10, viral culture studies from Germany show that most people that contract SARS-CoV-2 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. 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](image1)

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

![Development of antibodies in COVID-19 patients](image2)

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

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
Testing for the presence of the virus

Based on information gathered from 7 different studies with a total of 1,330 samples, PCR tests may only identify 30% of infected people on Day 4. "Sensitivity" (the probability of infection actually being detected in an infected person) peaks at 80% on Day 8 and falls back to 30% by Day 21 as they clear the virus. In other words, even at peak effectiveness, the PCR test only found 80% of infected people (see chart below).

This error level may be the reason for news stories of people being “reinfected”. A handful of people testing positive again a few weeks after disease onset most likely represents either a prolonged tail to the infection with false negative testing somewhere along the way, or prolonged shedding of virus with false negative testing as well. So far there are less than 100 reports of reinfection, which should be expected based on test sensitivity errors alone.

**Probability PCR test is positive, given individual is infected with COVID-19**

![Graph showing the probability of a PCR test being positive given infection](image)

Source: Lauren Kucirka et al, Johns Hopkins School of Medicine. April 2020.

Testing for antibodies

There are two main concerns about the use of serological tests for policy purposes:

- **COVID-19 virus antibodies may not be as prevalent in all recovered patients.** Fudan University reported that one third of recovered patients in a 175-person cohort did not possess high levels of COVID-19 antibodies normally associated with disease recovery. The low-antibody patients might have recovered since their T-cells, cytokines or other parts of their immune systems defeated the virus instead. In addition, a serology study from Spain found that around 15% of people that tested positive for antibodies then tested negative two months later, raising questions about the durability of immunity. Whether low-antibody patients are still susceptible to the disease remains to be determined.

- **Serology kits may differ on “specificity” (false anti-body positive) and “sensitivity” (false anti-body negative), in which case antibody presence could be misestimated.** 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”. Latest news: Roche has announced that their serology test has 100% sensitivity and 99.8% specificity, other serology test kits may now improve as well.

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1 "Variation in False Negative Rate of RT-PCR Based SARS-CoV-2 Tests by Time Since Exposure”, Lauren Kucirka et al, Johns Hopkins School of Medicine, April 2020.

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.

What are the latest serology test results in actual populations?

Research institutions and hospital systems have released results of random serological tests for COVID-19 antibodies. As shown below, these results indicate much higher levels of COVID-19 exposure than are implied by reported case to population ratios, which are often at least one order of magnitude smaller. In simpler terms, serology results show 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. Since antibodies show up with a lag, current and prior infections may be even higher than serology results indicate. Many studies report very wide confidence bands around their results; mean levels shown below could be substantially different from actual infection levels in broader populations. Some of the study sizes are also very small. Anyway, warts and all, here are some serology test results.

Serology test results to date

<table>
<thead>
<tr>
<th>Location</th>
<th>Date</th>
<th>Time from outbreak to day of serology test</th>
<th>Reported case to population ratio</th>
<th>Est. population with antibodies</th>
<th>Estimated true infections to reported cases</th>
<th>Reported case fatality rate</th>
<th>Infection fatality rate based on serology results</th>
<th>Study size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santa Clara</td>
<td>4/4/2020</td>
<td>64</td>
<td>0.1%</td>
<td>3.3%</td>
<td>54.6x</td>
<td>3.4%</td>
<td>0.06%</td>
<td>3,330</td>
</tr>
<tr>
<td>Gangelt, Ger</td>
<td>4/9/2020</td>
<td>73</td>
<td>2.4%</td>
<td>14.0%</td>
<td>5.8x</td>
<td>2.3%</td>
<td>0.40%</td>
<td>500</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>4/11/2020</td>
<td>76</td>
<td>0.1%</td>
<td>4.2%</td>
<td>49.9x</td>
<td>2.9%</td>
<td>0.06%</td>
<td>863</td>
</tr>
<tr>
<td>Belgium</td>
<td>4/14/2020</td>
<td>70</td>
<td>0.3%</td>
<td>4.3%</td>
<td>16.0x</td>
<td>13.4%</td>
<td>0.83%</td>
<td>1,327</td>
</tr>
<tr>
<td>Wuhan, China</td>
<td>4/15/2020</td>
<td>106</td>
<td>0.5%</td>
<td>9.6%</td>
<td>21.1x</td>
<td>5.2%</td>
<td>0.24%</td>
<td>1,021</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4/16/2020</td>
<td>49</td>
<td>0.2%</td>
<td>3.2%</td>
<td>18.7x</td>
<td>11.3%</td>
<td>0.61%</td>
<td>4,208</td>
</tr>
<tr>
<td>Denmark</td>
<td>4/17/2020</td>
<td>50</td>
<td>0.1%</td>
<td>1.7%</td>
<td>13.5x</td>
<td>4.6%</td>
<td>0.34%</td>
<td>9,496</td>
</tr>
<tr>
<td>Geneva, Swi</td>
<td>4/17/2020</td>
<td>52</td>
<td>0.5%</td>
<td>5.5%</td>
<td>11.3x</td>
<td>8.8%</td>
<td>0.78%</td>
<td>760</td>
</tr>
<tr>
<td>Miami-Dade, FL</td>
<td>4/24/2020</td>
<td>43</td>
<td>0.4%</td>
<td>6.0%</td>
<td>14.9x</td>
<td>2.6%</td>
<td>0.18%</td>
<td>1,400</td>
</tr>
<tr>
<td>NY State</td>
<td>5/1/2020</td>
<td>60</td>
<td>1.6%</td>
<td>12.3%</td>
<td>7.8x</td>
<td>7.8%</td>
<td>1.00%</td>
<td>15,000</td>
</tr>
<tr>
<td>San Miguel, CO</td>
<td>5/4/2020</td>
<td>44</td>
<td>0.3%</td>
<td>0.5%</td>
<td>2.1x</td>
<td>0.0%</td>
<td>0.00%</td>
<td>5,455</td>
</tr>
<tr>
<td>Spain</td>
<td>5/11/2020</td>
<td>100</td>
<td>0.5%</td>
<td>5.0%</td>
<td>10.2x</td>
<td>11.8%</td>
<td>1.15%</td>
<td>61,075</td>
</tr>
<tr>
<td>Brazil</td>
<td>5/21/2020</td>
<td>84</td>
<td>0.1%</td>
<td>1.4%</td>
<td>9.5x</td>
<td>6.5%</td>
<td>0.68%</td>
<td>24,995</td>
</tr>
<tr>
<td>Tokyo, Japan</td>
<td>6/3/2020</td>
<td>131</td>
<td>0.1%</td>
<td>3.8%</td>
<td>67.1x</td>
<td>6.1%</td>
<td>0.09%</td>
<td>1,071</td>
</tr>
</tbody>
</table>

Source: JPMAM, JHU. 2020. Serology sources available on request.

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.
Do falling antibody levels in survivors suggest risk of reinfection?

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 to sufficient to fend off the virus to some extent in vitro, and there is evidence that the body could produce more antibodies if needed.

- 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


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“"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-cell immunity and COVID

Antibodies are not the only weapon that the human body uses to fight off viruses; T-cells play a role as well, often through a process called “lysis” in which invading pathogens are killed directly. This research is still early-stage, but some scientists now believe that a subset of people have pre-existing T-cells that recognize SARS-CoV-2 upon being exposed to it and give the body a head start in fighting it. In some individuals, these T-cells may prevent them from getting sick at all.

- Pre-existing T-cells that react to SARS-CoV-2 appear to result from past exposure to more widely circulating “common cold” coronaviruses, and not from prior exposure to SARS-CoV-1, SARS-CoV-2 or MERS\

- 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)\(^6\). Their results are similar to a May La Jolla Institute study finding T-cell reactivity in 50% of blood donor samples dating from 2015 – 2018\(^7\), and an April study from Berlin University finding T-cell reactivity in 34% of healthy blood donors\(^8\)

- After SARS-CoV-1 in 2003, antibodies faded in some recovered patients. However, their T-cell responses to the SARS were still robust 17 years later. This might explain the paradox of falling antibodies in patients recovering from COVID 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”\(^9\)

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

<table>
<thead>
<tr>
<th></th>
<th>Unexposed</th>
<th>SARS-CoV-2</th>
<th>SARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural proteins only</td>
<td>4 (11%)</td>
<td>24 (67%)</td>
<td>21 (91%)</td>
</tr>
<tr>
<td>Non-structural proteins only</td>
<td>8 (22%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Structural and non-structural proteins</td>
<td>7 (19%)</td>
<td>12 (33%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Negative</td>
<td>18 (49%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>


\(^{5}\) “SARS-CoV-2-Reactive T Cells Found in Patients with Severe COVID-19”, Scientist.com, July 30, 2020

\(^{6}\) “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

\(^{7}\) “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

\(^{8}\) Presence of SARS-CoV-2 reactive T cells in COVID-19 patients and healthy donors”, Braun et al. Berlin University.

\(^{9}\) “New Data on T Cells and the Coronavirus”, Derek Lowe, July 15, 2020
Longer term effects 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. Bottom line: you do not want to get this disease, no matter your age. Some recent after-effect studies shown below; more detailed source information available on request10.

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

10 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
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 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 are 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
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