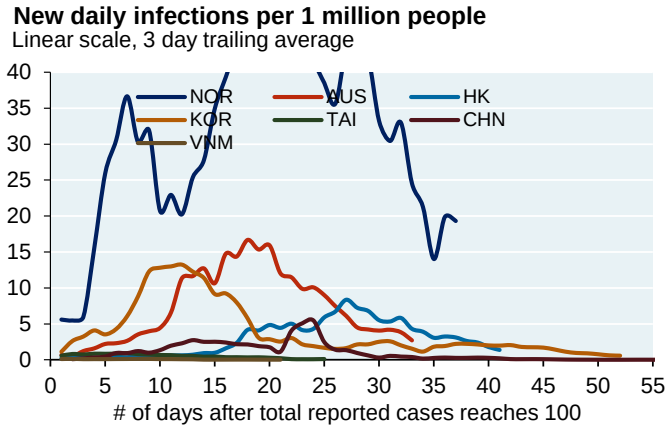
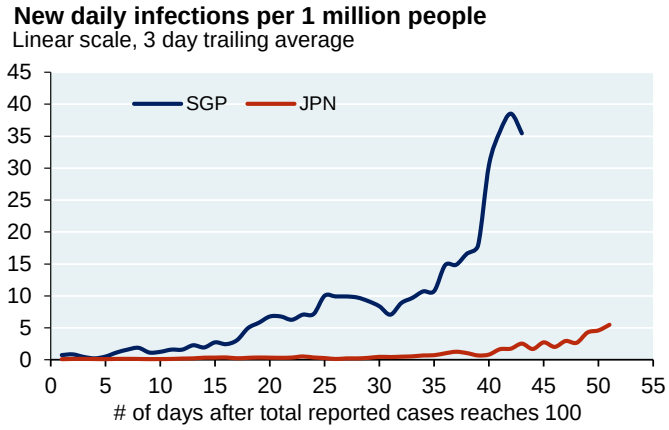
[4] After the first wave: getting back to "normal", and the importance of virus/antibody testing

How will countries try and get back to normal after the first COVID infection wave has subsided? This is an issue that several countries in Asia are already facing (although infections appear to have re-ignited in both Singapore and Japan, perhaps as social distancing measured eased).



Source: Johns Hopkins University, IMF, JPMAM. April 12, 2020



Source: Johns Hopkins University, IMF, JPMAM. April 12, 2020

At the risk of over-simplification, there are three main approaches a country could take after the first COVID-19 wave subsides (and in each case, restrictions on international travel will be required to prevent importation of new cases):

- **Keep flattening the curve and gradually let people go back to work as infection levels drop**. The problem with this approach: it only takes a small number of infectious people wandering around to ignite a second infection wave without a healthcare system that can track down and isolate new clusters[1]. It is still unclear if seasonal changes (sunlight/heat/humidity) will materially change the virus dynamics, and even if they did, a new wave could appear in the fall
- **Relax lockdowns, and use a swat-team approach to identify any new clusters**. Immediately isolate and quarantine new clusters as well as their contacts via contact tracing[2]. Life gets back to normal faster, but this approach works best when combined with an **extremely well organized healthcare system**, a compliant population that obeys social distancing rules, a legal system that allows the government to use a wide variety of tracking approaches (credit card receipts, cell phones, close circuit television, GPS, etc) to monitor the population and enforce rules; and **when the run rate of new daily infections is low enough to handle the influx of new cases.** I consider this scenario to be the most likely in many countries
- **Through serological testing, identify people who have been exposed to the disease, possess the antibodies to prevent them from infecting others or getting sick again, and let them get back to work**. Biggest challenge: requires herd immunity for maximum impact, which we discuss on the next 3 pages

[1] Best illustrated via a visualization from Grant Sanderson at 3 Blue 1 Brown

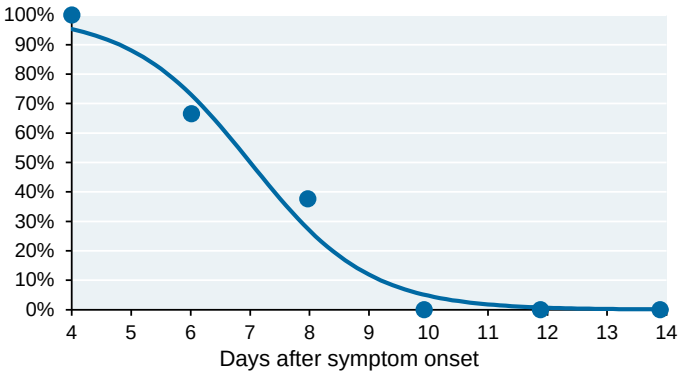
[2] This approach can be thought of as a real-life version of "**Code 2319**" in the movie *Monsters Inc*, when a swat team descends on anyone infected by a human article of clothing, and then quarantines and decontaminates them.

Serology testing for COVID-19 antibodies

Antibody testing could determine who has been exposed to the virus so they could go back to work once they recover. Once people have had COVID-19, they usually develop anti-bodies that virologists believe will prevent them from getting sick again. 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.

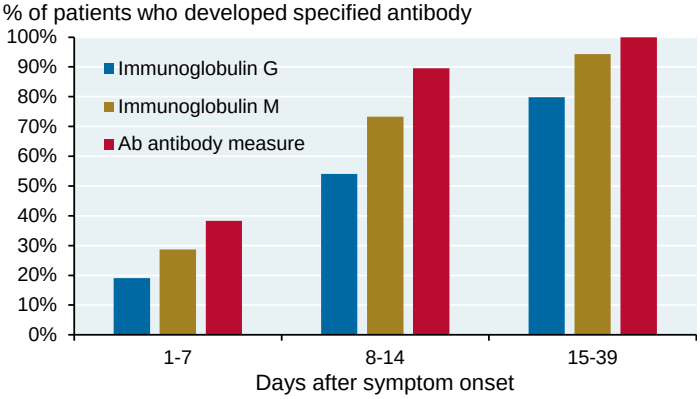
How might an antibody-based "return to work" process occur? First, a period of days is needed for people to recover from the virus. As shown on the left, by day 10, viral culture studies from Germany show that most people are no longer infectious. The viral decline is the result of the body's immune response, part of which involves the appearance of virus **antibodies** in many patients which can be measured as well. 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.

One issue that policymakers will have to consider: COVID-19 virus antibodies may not be as prevalent in all recovered patients. A recent paper from Fudan University reported that as many as one third of recovered patients in a 175-person cohort did not possess high levels of COVID-19 antibodies normally associated with disease recovery. They concluded that the low-antibody patients might have recovered since their T-cells, cytokines or other parts of their immune systems defeated the virus instead. Whether low-antibody patients are still susceptible to the disease remains to be determined.

The bigger issue when thinking about serology testing as a "back to work" mechanism: you need higher levels of infection first. To mitigate the burden on healthcare systems, many countries have used lockdown and other measures to "flatten the infection curve". While this mitigates the healthcare burden, it also delays the onset of "herd immunity", which is a general marker for when a disease is no longer a considered a pandemic. Once herd immunity is reached, while the virus still spreads, it does so at a manageable rate involving smaller clusters that are dealt with independently.

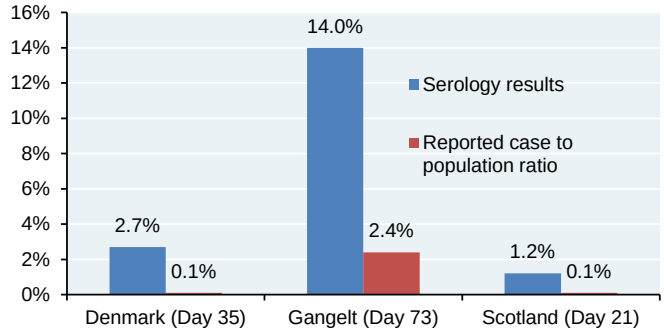
What are the latest serology test results in actual populations?

Over the last 3-4 days, a small number of research institutions and hospital systems in Europe have released the results of random serological tests for COVID-19 antibodies. There are only a few so far:

- Denmark[3], where 2.7% of 1,500 people tested antibody-positive 34 days after its outbreak
- Gangelt, Germany where 14% of 509 people tested antibody-positive 73 days after its outbreak
- Scotland, where1.2% of 500 people tested antibody-positive 21 days after its outbreak

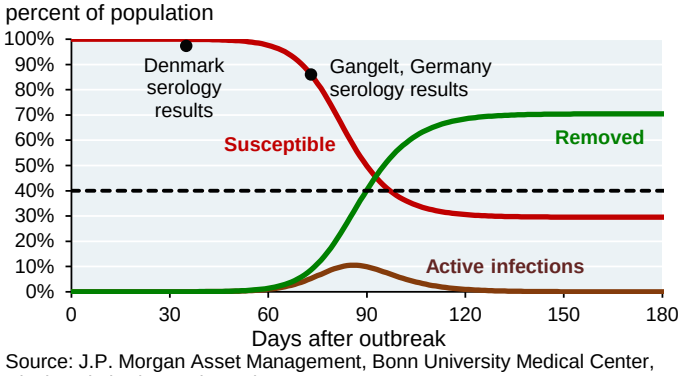
These results indicate *much* higher levels of COVID-19 exposure than by simply looking at reported case to population ratios for each region (chart below, left), which are at least one order of magnitude smaller. In simpler terms, serology results indicate that there's **a large number of unreported infections** due to people who couldn't get tested, only had mild symptoms, were asymptomatic, etc. And since antibodies show up with a lag, current infection levels are likely to be even higher than serology results indicate[4].

How widespread is COVID-19? Serology test results vs reported cases as a % of population



Source:Bonn University Medical Center, Rigshospitalet (Copenhagen), Evolutionary Ecology of Infectious Disease (UK), JHU, JPMAM. April 2020.

When might herd immunity occur, after which serology tests could have a greater "return to work" impact?



Source: J.P. Morgan Asset Management, Bonn University Medical Center, Rigshospitalet (Copenhagen). 2020.

Now let's get to the next question: how long until herd immunity might arrive simply through passage of time? Antibody presence of 2.7% and 14% might seem small, and *would* be if viruses evolved linearly. But viruses only attack susceptible hosts, and as they progress, susceptible populations shrink. An epidemiologist contact of mine was pleased to see the Denmark and Gangelt results, and suggested we look at them through the lens of our "SIR" model[5] to see why, using serology results as a proxy for "true" infection. Here's what we found: **herd immunity, estimated as 60% population exposure[6], might be closer than you think**. Following each serological observation along the red curve to the dotted line, greater levels of immunity could be one month away in Gangelt, and two months away in Denmark.

[3] The best studies, like the Danish one, will conduct "ELISA" tests and then cross check them with a more specific test called a viral neutralization assay to make sure the tests are right.

[4] **I do not believe it is advisable to estimate true infection levels using PCR tests that look for the presence of the virus;** they underestimate infections by ignoring people who are late in the course of infection and those who are very early in infection. Based on information from individuals in China with known COVID-19 infection, it can be estimated that PCR tests only identify 40% of infected people on Day 3. "Sensitivity" (probability of infection being detected in an infected person) peaks at 75% on Day 7 and falls back to 40% by Day 21 as they clear the virus.

[5] "**SIR" models** are used to track the distribution of a population exposed to a virus over time into three categories: "susceptible", "infected" and "removed" (recovered or deceased). The susceptible population declines rapidly once the pool of potential hosts migrates into the removed category. However, the susceptible population does not decline to zero since immune individuals act as "fire-breaks" who buffer susceptible individuals from infection.

[6] **Herd immunity requires at least 60% exposure since** the effective reproductive number must fall below 1.0x. Assuming an initial reproductive number of 2.5, that would require a 60% decline in the susceptible population.

To be clear, there are a lot of uncertainties: these models are highly sensitive to input parameters (particularly the timing of outbreak and serology test results); serology tests for COVID-19 may involve false positives (unclear how large an issue this might be), as well as people who test positive with "insufficient" antibodies; sample populations might not be representative of the whole; and they may not be applicable across countries. **Furthermore,** even if herd immunity were reached, the virus would still spread, but at a more manageable rate involving smaller clusters that are dealt with independently.

Even with all these caveats, the projections on the prior page are helpful in illustrating the evolution of the virus and its antibody aftermath, and **provide a rationale for serological testing as part of a "back to work" plan in the summer or fall (under the presumption that a society can organize itself to do it)**. We will update the chart above as new serological observations emerge.

Serology tests: who's using them, who's making them and what the CDC has to say about it

The CDC and private companies are scrambling to produce serology tests; the UK has ordered 3.5 million, Germany may use them to issue immunity certificates to survivors, and China and Singapore are using them to measure more accurate infection rates. On top of that, the US FDA is allowing doctors to use serology tests to identify recovered patients whose antibodies could treat emergency cases of the disease. There are now over 50 companies that have informed the FDA of their intention to sell serology testing kits in the US, many of which are already available. However, to be clear, these 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.

What about the risk of a second wave?

If lockdowns are relaxed quickly, a second wave is considered likely by many virologists. However, if instead at some point over the summer there are no 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.

Sources used in this section include:

"*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

"*Preliminary results and conclusions of the COVID-19 case cluster study*", Bonn University Hospital, March 2020

"*Blood banks will test whether donors have had coronavirus*", SN.DK, April 4, 2020

"*Serological analysis of 1000 Scottish blood donor samples for anti-SARS-COV-2 antibodies collected in March 2020*", Oxford Immunology Consortium, Scottish National Blood Transfusion Service and University of Kent

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