Mounting evidence of COVID-19 reinfection

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Recently released research indicated that surviving COVID-19 may not confer long-lasting immunity, although there is conflicting data. Perhaps most notable are the studies that have showed a drop-off of neutralizing antibodies in circulation after just a couple of months post-COVID infection (which is in line with most seasonal coronaviruses, where immunity doesn't last long at all).

Some newer studies, however, have shown that despite an early drop-off, the decrease then levels out after the initial drop and we still maintain relatively high levels of neutralizing antibodies which would indicate that perhaps immunity would be longer lasting than we were first fearing it may be (perhaps on the order of a couple of years, as long-term antibody studies in SARS-1 have indicated).

It is important to determine whether or not reinfections are occurring and over how short a period of time. Up to the present, we've seen a few cases (primarily in health care workers) of where people have tested positive for COVID using the RT-PCR test, then clear the infection, and after a little while test positive again.

These isolated cases, however, have not been confirmed reinfections, because the RT-PCR test is looking for viral RNA and not live virus in the system. While live virus would lead to viral RNA being present (which is why this test works really well for active infections), sometimes it picks up some viral "junk" after the infection has passed.

Let's think of it this way: our immune system, over the course of its response, totally destroyed all the viral particles in our body, leaving viral debris in its wake. Some of this debris is the RNA from the virus itself, and it's possible for this RNA to be maintained in our system for some time after the virus itself is destroyed. Since the people who tested positive the second time were asymptomatic, it was just assumed that it was in fact simply junk that was being picked up by the test the second time.

Now, however, the story changes. We have several cases that have turned up in the last week where people who have tested positive a second time have had the viral RNA from their first and second positive tests sequenced, and there was enough genetic variation between the two RNA samples to convince the researchers that it was in fact a new infection the second time around.

When viruses travel through a population, they pick up tiny mutations along the way. By sequencing the viral genetic information, we can track these mutations, and therefore find when a specific sample was from, based on how many of the mutations it had.

You can think of it this way (though this is incredibly oversimplified for illustration purposes): for each 10 people a virus infects, it picks up on average one mutation. Then, after 10,000 people have been infected, we will have approximately 1,000 mutations. Therefore, if we take a sample of the viral RNA in someone's system, and find that it had 600 mutations from the original virus, that means that the person had been infected around the time that the 6,000th person had been infected. Of course, it's way more complex than this, but the point is simply that we can look for these mutations to determine whether it's the same virus, or if it came from a different stage in the virus's development.

We now have cases in Hong Kong (set to be published in Clinical Infectious Diseases, as of now only excerpts are available of the study: Belgium and the Netherlands, and La Crosse, Wisconsin, of individuals who had sequencing done on both their first and second positive tests and sufficient differences were found where it is more than likely that these were

cases of reinfections occurring. The cases have been mild, but these reinfections have occurred three to six months after their initial infection.

While these are isolated cases, and a lot more sequencing will have to be done on other individuals who are testing positive more than once, this is certainly not a good sign. While it is certainly possible that the majority of people will maintain antibodies to a level sufficient for protection from subsequent infections after a first infection (or potential vaccination), it now appears that at least some number of people will be susceptible again to infection shortly after their initial infection. This throws into question even more the possibility of generating "herd immunity," producing high levels of the population being immune to SARS-CoV-2, even with a vaccination.

Meanwhile, another new preprint was just released today that, frankly, is even more worrying than the earlier cases discussed. This new paper, released as a preprint from *The Lancet* , looks at a case study of a likely reinfection in Nevada. The individual, a 25-year-old, had originally been infected in April, tested positive for COVID, and presented with a sore throat, cough, headache, nausea, and diarrhea. After nine days, the symptoms had resolved, and two tests, conducted 12 and 29 days after symptom resolution, both came back negative, indicating the infection had been cleared.

However, 31 days after the symptoms had abated initially, the individual began to experience symptoms again, and was hospitalized two days later. Within a week, the symptoms had escalated to hypoxia (low oxygen levels) and atypical pneumonia, requiring emergency supplemental oxygen. When retested, the individual tested positive for COVID.

Importantly, a sample from the initial test in April, and a sample from this later test in June were both sequenced genetically. Once sequencing was completed, mutations between the two samples were mapped, and it was determined that the two samples had enough mutations between them that it was almost certainly two separate infections that took place.

The two main things to note here is that the second infection was significantly MORE severe than the initial infection, which is something that we had not seen in the previous cases of likely reinfection, and that the time between initial infection and reinfection was only 48 days.

We haven't seen direct evidence of antibody-dependent enhancement (ADE) of SARS-CoV-2 yet (which is where a low level of antibodies actually aids viral entry into cells and makes the infection much worse), but we do have some evidence of ADE occurring in SARS-CoV-1, the closest related virus to the causative agent of COVID-19, leading to more severe illness and acute lung injury when low levels of antibodies are present due to vaccination of animal models.

This evidence not only complicates the picture in regards to "herd immunity," but potentially even complicates the vaccine development process. This demonstrates once again that proper public health measures would have been far more rational if they sought to understand the science of the virus rather than looking for biomolecular "silver bullets."