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COVID-19 Update: Thinking About the Implications of SARS-CoV2 Reinfection

Modest rates, mutated strains and a milder course the second time around are telling us something.

While the U.S. appears to be getting the COVID-19 pandemic under control ahead of flu season and back-to-school risks that are likely to create outbreak clusters, three reports of potential "reinfection" of SARS-CoV2 (the virus that causes the COVID-19 disease) have us thinking about the future and how this virus may turn into another nuisance coronavirus like 229E and NL63, evolving so as to potentially linger throughout the year(s) but causing a less severe version of COVID-19 (and hopefully just a bad cold).

The reinfection data does not change our views regarding the odds of success for vaccines and data supports that the second cases were all mild which is suggestive of some sort of initial immune response and mounting evidence for why T-cell responses could be a key in fighting COVID-19.

A few statistics to frame where we are in the pandemic: *Total U.S. cases are at ~5.7M, or 1.7% of the total population, and stabilizing, while Europe is witnessing a sustained upward trend some are calling its "second wave."*

- New U.S. cases continue to drop each day, with ~35,000 added Tuesday vs. ~36,000 on Monday and a seven-day moving average that is heading in the right direction (lower).
- Doubling time for new cases is now 95 days, inching closer to the ~150-day bogey, though this will likely take some time and continued vigilance on the part of all U.S. population, especially as fall approaches in the Northern Hemisphere.
- Currently 14 states have a daily positivity rate of >10%, down by one state vs. five days ago, but this is still too high in our view and needs close monitoring with the U.S. average daily positivity rate sitting around 5% and the Northeast rate at closer to 2%.
- Spain is spiking, while Germany and France are also in an upward trend; Japan, Hong Kong and Australia are in decline after a spike.
- South Korea is adding ~300 new cases per day as per the latest reports—mostly new cases linked to a church event—evidence contributed to contact tracing capabilities and how authorities were able to quickly ring-fence any outbreaks.

Three reported cases of SARS-CoV2 reinfection have some concerned although information is limited:

- In the past 24 hours (through Tuesday afternoon), three cases of SARS-CoV2 reinfection have been reported in Hong Kong, Belgium and the Netherlands, suggesting limited activation and/or duration of immune responses, mutated strains and importantly associated with milder cases.

- As the data in the chart below supports, little information is available on the latter two cases but the Hong Kong case provides us with a window into potential immune scenarios.

Statistics	Hong Kong case	Belgium case	Netherlands case
Age	33	?	elderly
Gender	male	female	?
1st infection & strain	mid March-mild, GISAID clade V	March-mild	?
2nd infection & strain	mid August, clade G L412p mutation asymptomatic	June-mild	?
PCR tests	negative in April	PCR negative	?
Ab tests	IgG (-) followed by positive post 2nd infection	?	?

Source: MedPage Today, Reuters World News August 25th, 2020

- The Hong Kong case is suggestive of a healthier individual who contracted SARS-CoV2 early on and was infected with the predominant strain circulating in the U.S. or England; so, data suggests it is likely a derivative of the Italian strain vs. Chinese strain and the person experienced a mild case that resolved in three days, followed by two negative PCR tests for the virus in April.

- The second "positive PCR test" was via screening at the Hong Kong airport upon reentry, with a genetic variant more akin to that in Switzerland/England; the case was asymptomatic, although the individual generated antibodies against the virus post-second infection, with no data on T-cells.

What could we infer from the Hong Kong case?

Our questions/observations:

- Firstly, the patient may not have had enough exposure to the virus during the first infection given that the case resolved within three days and was characterized as mild, or generated antibodies rapidly and/or at low levels but duration was fleeting and unable to be captured by the serology test performed.

- We would need to know the viral titer from this patient as well as T-cell response information and if the negative antibody test was a false negative, the latter of which is highly probable given the plethora of lackluster antibody tests available early in the pandemic.

- Post-initial infection, the patient's second case was asymptomatic, yet the subject generated detectable antibodies, suggesting a memory T-cell and antibody response that blocked infection into the lower respiratory tract (i.e., lungs) as well as mild if any symptoms in the upper respiratory tract, indicative of IgA responses in the mucosal lining of the nose. It would be helpful to know the subtypes of the second positive antibody response.

- Lastly, it appears that the genetic mutation either does not alter the course of COVID-19 or could represent a less virulent strain of SARS-CoV2 given the asymptomatic case. We would value knowing the transmission rate of this genetic version (clade G) and with contract tracing of this individual this may be possible to evaluate outside of the laboratory.

- This case was accepted by the *Clinical Infectious Diseases* journal, though we have yet to be able to find the publication and read it for ourselves.

Framing the best and worst outcomes on limited data: While three cases out of ~24M globally is anecdotal, and with all the caveats of whether or not the second positive PCR tests yielded infectious viral particles (we assume they did), if the first serology tests were done at the appropriate time and with high sensitivity tests and the status of the three patients' immune systems, we offer the following;

- *The best outcome would be* that the virus has mutated into a less virulent strain, the mutations did not impair the patient's memory T-cell responses to recognize this altered version and the initial negative antibody test was a false negative.

- *The worst outcome would be* that the patient did not mount an immune response to the initial infection (was the 33-year-old male immunocompromised?) which likely had to be of low viral titer given the mild case (three-day duration), suggesting that not all infections generate immunity or if any immunity is generated it is of limited duration and not protective, hence no memory T-cell responses.

- The data suggests that the worst outcome is unlikely, as why would the patient mount an immune response to the second infection only, especially since it was an asymptomatic case and we know both clade G & V are immunogenic? Also, T-cells may not prevent infection but they could certainly contribute to milder cases of COVID-19, which, outside of eradication of SARS-CoV2, is the next-best outcome in our view for a virus we think may linger for some time to come.

So what does this mean for vaccines and potential recombinant antibody treatments? Not very much, as generally, vaccines generate stronger immune responses than naturally occurring responses, data to date across four vaccine platforms (two mRNA vaccines, one non-replicating viral vector and one traditional protein subunit vaccine) demonstrated robust antibody responses and T-cell responses (CD4+ subtype), the latter of which are key should antibody responses fade in the short term. Regarding recombinant antibody therapies, we view this as a bridge to a vaccine as well as a short-term protection strategy for severe cases should several prevention and treatment trials prove safe and efficacious. Data from Regeneron and Eli Lilly are expected in the September/October timeframe, with several other platforms expected in November including GlaxoSmithKline, Biogen & Vir Biotech, Amgen and partner Adaptive Biotech, to name a few.

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For more information on COVID-19, please refer to the Center for Disease Control and Prevention at cdc.gov.

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