

Developing a WHO position on COVID-19 reinfection

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The COVID-19 pandemic already exceeding 30 million cases reported worldwide and more than 1,000,000 deaths. With well over 100,000 scientific publications, an increasing wealth of knowledge about the SARS-CoV-2 virus is becoming available. However, only rather limited data on confirmed reinfection with SARS-CoV-2 has been published, and it is not yet well understood what the mechanism of virus reinfection is, what the role immunity plays in allowing or preventing reinfection, how often it takes place and how best reinfection can be studied. Future vaccination efforts may be influenced by the amount of immune protection can be mounted and how long the immunity may last. The epidemiology of the virus may play an important role when long lasting immunity is not mounted and may create public anxiety around vaccination efforts. Of note is that reinfection with common cold coronaviruses are common but episodes separated by at least 6 months¹.

Introduction – Setting the scene

SARS-CoV-2 reinfection can occur when an individual has cleared an initial SARS-CoV-2 infection, and after a novel exposure becomes actively infected again with the virus. In between two consecutive infections the virus is not present in the human host and the virus is actively replicating in the infected host. Clinically, reinfection can display symptoms, potentially milder but it can even be asymptomatic, although more severe outcome has also been reported².

Goal

To provide insights on SARS-CoV-2 reinfection and the role it may play in public health and future vaccination efforts and to provide ideas on supporting research towards better understanding the role and extent of reinfection through a standardized approach to a case definition and surveillance and monitoring.

What do we know so far about SARS-CoV-2 reinfection?

With the pandemic some 6 months underway, the first reports on reinfection started to appear in the scientific literature. The first report came from Hong Kong where a asymptomatic man in a routine screening tested positive 4.5 months after his first episode. These have been confirmed by the significant sequence divergence between the strains from the first and second infection. Additional reports mounted of reinfection cases, often asymptomatic or with mild disease outcome (with exceptions in severity) in various countries, including the US, Ecuador, The Netherlands, Belgium, India, South Africa, Brazil and various other countries. However, preliminary data from Australia indicate that sequence analysis may not always be the holy grail, as prolonged clonal spread could mask reinfection. However, viral relapse could also be misinterpreted as reinfection.

How is reinfection confirmed?

Need for investigation criteria: proposal by US-CDC and NICD-SA to set an artificial cutoff at 90 days between the first detection of antigen or RNA and second one. Sera from both episodes and PCR data including Ct value will make the likelihood of reinfection highest even if no symptoms are present. A period of 45-89 days between episodes may still be called reinfection but should be confirmed with serology, and with a clinical evaluation. A time interval of less than 45 days makes reinfection considerably less likely albeit not unlikely. Persistent infection of up to 100 days has been reported previously but is not considered common (REFs).

Standardized evaluation criteria for reinfection

- Clinical evidence: various clinical outcomes are possible during first and subsequent infection from asymptomatic, mild, and severe during both episodes each combination posing a different degree of complexity to assess a case/infection.
- Epidemiological evidence: contact tracing and other epidemiological tools may have to be deployed to assess the likelihood of reinfection.
- Laboratory evidence:
 - antigen test positivity at both instances,
 - molecular test positivity during first and subsequent episode with negative molecular test results in between,
 - sequence availability with significant divergence providing strongest evidence for reinfection,
 - antibody test with initial negative test and positivity at start of second episode, where titer has risen between episodes.
 - Avidity test on reinfection serum with high index (>60%) indicate maturation of antibodies
 - Virus neutralization titers

Six fundamental questions on reinfection to be answered

1. Why do reinfections with SARS-CoV-2 occur? Is it because failure of the infected patient to develop protective antibodies or does immunity wanes quickly? SARS-CoV-2 genomic evolution rates are relatively slow and changes in viral makeup to help it evade immunity may not occur rapidly.
2. What is the frequency of reinfection?

Currently, various seroprevalence studies have been or are being conducted to determine the epidemiologic impact of COVID-19 in a given population. Seroprevalence rates vary greatly in the different cohorts that have been studied, between just a very few percentage points in remote secluded communities on island nations to very high levels up to 60% in high density populations like in slum areas in Mumbai. Repeat sampling of similar but not necessarily identical cohorts like blood bank donors (recurring donors) may reveal some variation over time in seroprevalence. Results from such studies may have limited value in understanding the role of reinfection.

A more conclusive approach to determine frequency of reinfection would be based on a longitudinal surveillance, prospectively monitoring individual confirmed COVID-19 cases, ideally with a sequence and antibody profile against SARS-CoV-2 from their first infection. The follow up of these

convalescent cases involved regular sampling and testing for antibodies and ideally by PCR or another NAAT to continuously monitor reinfection until the person has cleared the reinfection and has stable antibody levels.

3. What is the clinical relevance?

The limited number of reinfection cases currently reported in the literature show various degrees of clinical outcome varying from asymptomatic, to mild and even severe. A first death of reinfection has also been reported in the Netherlands (Oct 2020). Understanding the severity of COVID-19 reinfection may guide control measures.

However, as there is only limited data available on onward transmission by reinfection cases, such cases should be treated as primo infection cases.

4. What is the role of reinfection in onwards transmission?

A case with reinfection may drive an outbreak in a naive population or potentially in a population with some degree of immunity (see above). Assessing the level of transmission will not be an easy task when reinfections do not lead to clinical outcome and therefore reinfection will be underestimated with a conventional approach to surveillance based on case notification and confirmation. Furthermore, the number of reported cases due to reinfection that are reported at the moment most likely are underestimated as case-based testing is not feasible during the current pandemic and particularly not in asymptotically infected persons. However, evidence on onward transmission of reinfection cases is limited.

5. What is the epidemiological relevance, e.g., how well can SARS-CoV-2 sustain transmission in a previously exposed population?

If virus transmission cannot be interrupted by populations through “herd” immunity, i.e. a high enough proportion of individuals are immune to COVID-19 either through previous exposure or vaccination, what effect would this have on the epidemiology of the virus?

6. What is the relevance of reinfection towards vaccination control programs.

If reinfection is going to play a big role in sustaining virus transmission, this may potentially have an effect on vaccination efforts to control virus circulation. Protective immunity will be an important variable that will determine the level of continued virus circulation in a given population with previous virus exposure. Can vaccination induce protective immunity, for how long and will it prevent infection and sustained transmission in a vaccinated population?

¹ <https://www.nature.com/articles/s41591-020-1083-1>

² [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30764-7/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30764-7/fulltext)