COVID-19 (SARS Co-V-2) UPDATE: REINFECTION

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REPORTS OF SARS-CoV-2 REINFECTION: TIME FROM 1\textsuperscript{ST} TO 2\textsuperscript{ND} COVID-19 EPISODES

- 48 days (by RT-PCR, less by symptom onset), healthy (Tillett RL. Lancet ID 2020)
- 51 days, healthy (Larson D, et al. CID)
- 59 days, Waldenstrom’s macroglobulinemia (Mulder M, et al CID)
- 72 days, (Prado-Vivar B, et al. Preprint)
- 93 days, (van Elslande J, et al. CID)
- 109 days, HCP (Gupta V, et al. CID)
- 111 days, HCP (Gupta V, et al. CID)
- 140 days, (Goldman, preprint)
- 142 days, immunocompetent (To KK, et al. CID)

Dates may vary between papers based on whether they represented times of SARS-CoV-2 test positivity or date of symptom onset.
Figure: Immunity after re-challenge; re-infections may have variable incidence and outcomes

- **Primary immune response**
- **Secondary immune response**

Response may be influenced by factors such as viral strain, host immune status, time elapsed first infection.

- Humoral and cell-mediated immunity
- 1st infection or vaccination
- Re-exposure
- Boosted memory response

<table>
<thead>
<tr>
<th>Memory Response</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>sterilizing immunity</td>
<td>no infection</td>
</tr>
<tr>
<td>protective immunity</td>
<td>reduced severity and/or contagion</td>
</tr>
<tr>
<td>enhanced immunity</td>
<td>increased disease severity</td>
</tr>
</tbody>
</table>

Kim AY, Gandhi RT. Clin Infect Dis 2020
EARLY REINFECTION WITH SARS-CoV-2: 2ND EPISODE MORE SEVERE THAN 1ST EPISODE

- **Demographics:** 25 year old male, healthy, US
- **First episode:** Initial symptoms included sore throat, cough, headache, nausea and vomiting; symptoms completely resolved
- **Second episode:** Outpatient visit for subjective fever, headache, dizziness, cough, nausea, and diarrhea; 5 days later admitted with SOB and hypoxia; CxR = pneumonia; developed myalgias, cough and SOB
- **Viral genomic sequencing suggested re-infection**

EARLY REINFECTION WITH SARS-CoV-2:
2ND EPISODE MORE SEVERE THAN 1ST EPISODE

- Demographics: 42 year old male, healthy HCP, US
- First episode: Presented with cough, subjective fever, and myalgias following workplace exposure; symptoms resolved by day 10
- Second episode: Presented with fever, cough, SOB, GI symptoms after household exposure; abn CxR with O2 sat of 92-94%
- Partial genome sequencing suggested new SARS-CoV-2 infection

Demographics: 89 year old woman with Waldenström’s macroglobulemia treated with B-cell depleting therapy, Holland

First episode: Presented with fever and severe cough; hospitalized for 5 days, discharged asymptomatic

Second episode: 2 days after new chemotherapy therapy and 59 days after onset of first COVID-19 episode, patient developed fever, cough and dyspnea; O₂ sat was 90%; at days 4 and 6, serum tested positive for COVID-19 antibodies; deteriorated on day 8 and died 2 weeks later

Reinfection demonstrated by SARS-CoV-2-specific multiplex qPCR and nonopore sequencing

ASYMPTOMATIC REINFECTION IN TWO HCP

- Demographics: 25 year old male and 28 year old female, HCP, India
- First episodes: Both were asymptomatic (but hospitalized per institutional policy); tested negative (8 and 10 days) after initial tests
- Second episodes: Both were asymptomatic; both had a higher viral load on the second episode (Pt 1, Ct values of 36 and 16.6; Pt 2, Ct values of 28.16 and 16.92)
- Reinfection demonstrated by WGS

**REINFECTION WITH SARS-CoV-2**

- **Goal:** Assess SARS-CoV-2 RNA duration
- **Results**
  - 11,622 patients tested; 643 positive test (5.5%); 176 had at least 2 positive samples – shedding duration=12.1 days (6.4, 24.7) (1A)
  - Shedding <59 days in 95% and >75 days in only two patients
  - Re-positivity in 43 patients (1B)
  - Pt 139, 60-69 year old, nursing home, not immuno-compromised
    - 1st episode: Pneumonia, hospitalized
    - 2nd episode: 2 weeks of cough and weakness, hospitalized, treated with Remdesivir plus steroids
    - Sequencing suggested reinfection

Goldman JD, et al. Preprint
SARS-CoV-2 REINFECTION

- Demographics: 33-year old male residing in Hong Kong

- Initial episode: Presented with cough, sputum, sore throat, headache and fever for 3 days – diagnosis confirmed by RT-PCR
  - At discharge, symptom free
  - Subsequently had 2 negative COVID tests
  - Antibodies 10 days after sx onset were negative

- Second episode: Tested positive at airport after returning from Spain
  - Hospitalized but remained asymptomatic
  - Initial antibodies negative

- WGS sequencing confirmed re-infection

## SUMMARY OF SELECTED CASES OF COVID-19 REINFECTION

<table>
<thead>
<tr>
<th>Country</th>
<th>Sex</th>
<th>Age (years)</th>
<th>First infection (Ct)</th>
<th>Second infection (Ct)</th>
<th>Intervening period (days)</th>
<th>Antibody after first infection</th>
<th>Antibody after reinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>Male</td>
<td>33</td>
<td>Mild (N/A)</td>
<td>Asymptomatic (27)</td>
<td>142</td>
<td>Negative</td>
<td>IgG+</td>
</tr>
<tr>
<td>Nevada, USA</td>
<td>Male</td>
<td>25</td>
<td>Mild (35)</td>
<td>Hospitalised (35)</td>
<td>48</td>
<td>N/A</td>
<td>IgM+ and IgG+</td>
</tr>
<tr>
<td>Belgium</td>
<td>Female</td>
<td>51</td>
<td>Mild (26–27)</td>
<td>Milder (33)</td>
<td>93</td>
<td>N/A</td>
<td>IgG+</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Male</td>
<td>46</td>
<td>Mild (37)</td>
<td>Worse (N/A)</td>
<td>63</td>
<td>IgM– and IgG–</td>
<td>IgM+ and IgG+</td>
</tr>
</tbody>
</table>

Data were obtained Sept 14, 2020, for reinfection cases confirmed by viral genome sequences. Ct=cycle threshold. N/A=not available. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

**Table:** Characteristics associated with reinfection with SARS-CoV-2

Iwasaki A. Lancet ID 2020
**Definition of reinfection:** 1) Initial SARS-CoV-2 PCR confirmed COVID-19 illness; 2) Followed by clinical recovery with at least 1 negative SARS-CoV-2 result; 3) Followed by confirmed SARS-CoV-2 positive result (with or without symptoms) at least 28 days after previous SARS-CoV-2 PCR result

- 6 patients met study criteria;
- 2\(^{nd}\) episode 38-84 days later (median, 56 days)
- Three symptomatic and three asymptomatic
- **Comment:** This is one of many reports of reinfection in based on repeat positive SARS-CoV-2 tests without genome analysis of strains

CONCLUSIONS

- Possible reasons for re-positive SARS-CoV-2 tests
  - Inadequate sampling technique
  - Assay limitations with the Ct result hovering at the limit of detection
  - Prolonged shedding, potentially combined with either of the former
  - Reinfection

- Demonstration of re-infection based on sequencing initial and subsequent viral isolates

- Illness severity of 2nd episode have ranged from none (asymptomatic) to more severe than 1st episode

- Current reports likely only the tip of the iceberg – likely many more will appear shortly
  - Difficult to detect asymptomatic reinfection (would only be detected via routine community testing or at an airport)

- However, given the millions of COVID-19 cases, re-infection appear to be rare
Kim AY, Gandhi RT. Clin Infect Dis 2020


