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

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Disclosures: Consultant-PDI, Gernitec, Pfizer; Merck, UV Innovators

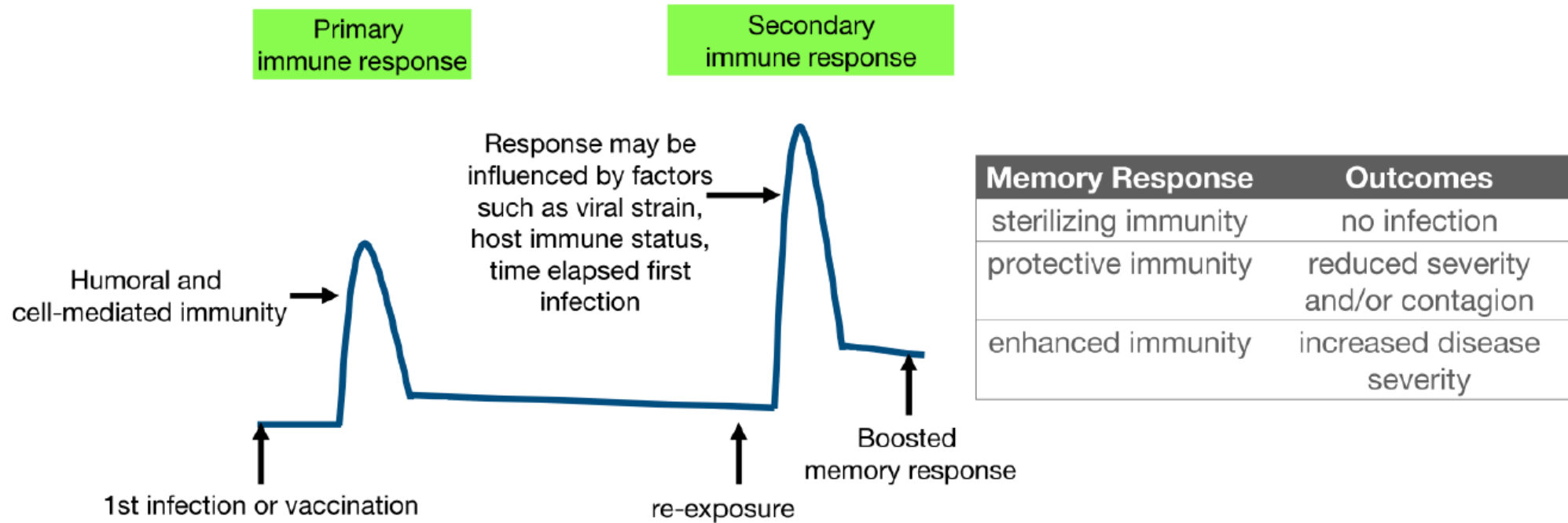
REPORTS OF SARS-CoV-2 REINFECTION: TIME FROM 1ST TO 2ND COVID-19 EPISODES

- 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

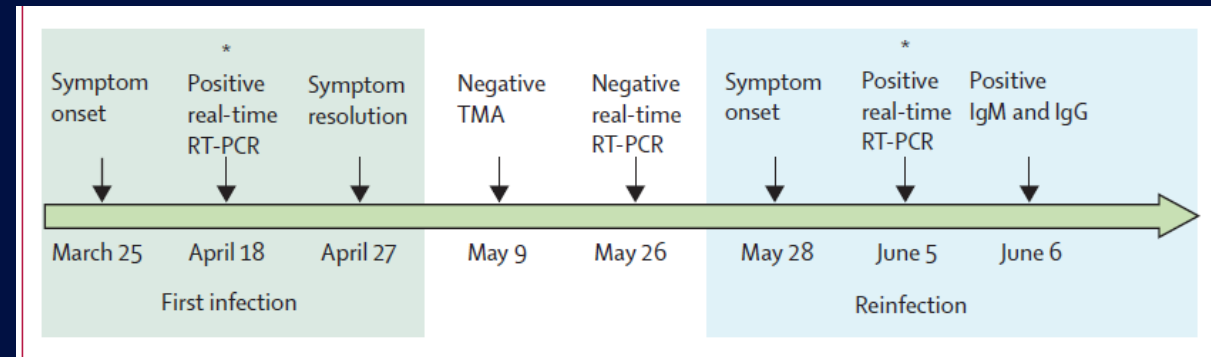
IMMUNOLOGIC RESPONSE AFTER VIRAL RECHALLENGE

Figure: Immunity after re-challenge; re-infections may have variable incidence and outcomes



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



	Specimen A			Specimen B	
	April 18, 2020	May 9, 2020	May 26, 2020	June 5, 2020	June 6, 2020
Test methodology	Real-time RT-PCR	TMA	Real-time RT-PCR	Real-time RT-PCR	Immunoassay (IgG and IgM antibody detection)
Test result	Positive	Negative	Negative	Positive	Positive
Quantitative result	Ct 35.24	RLU 299	..	Ct 35.31	..

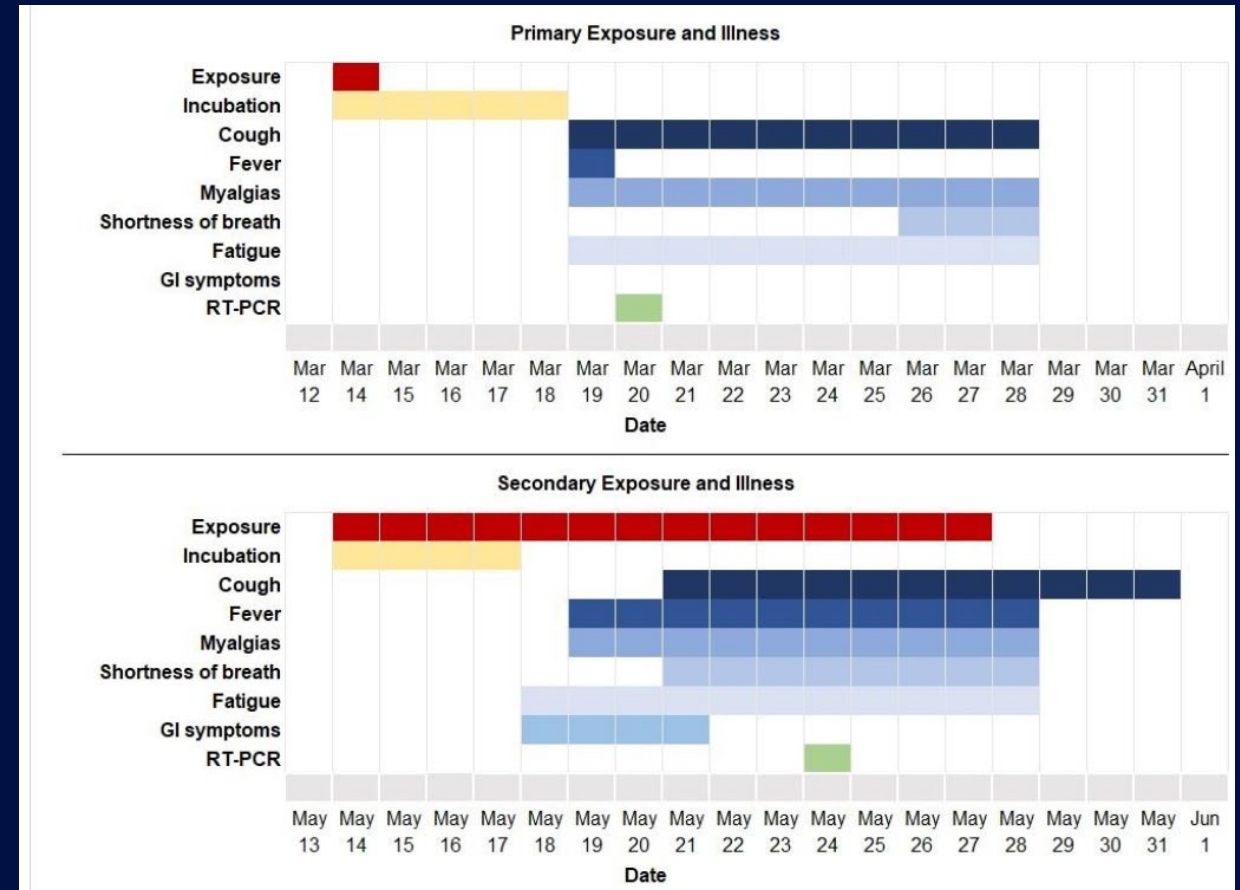
TMA=transcription-mediated amplification. Ct=cycle threshold. RLU=relative light units.

Table 1: Summary of laboratory results

Tillet R, et al. Lancet ID 2020;12 Oct.

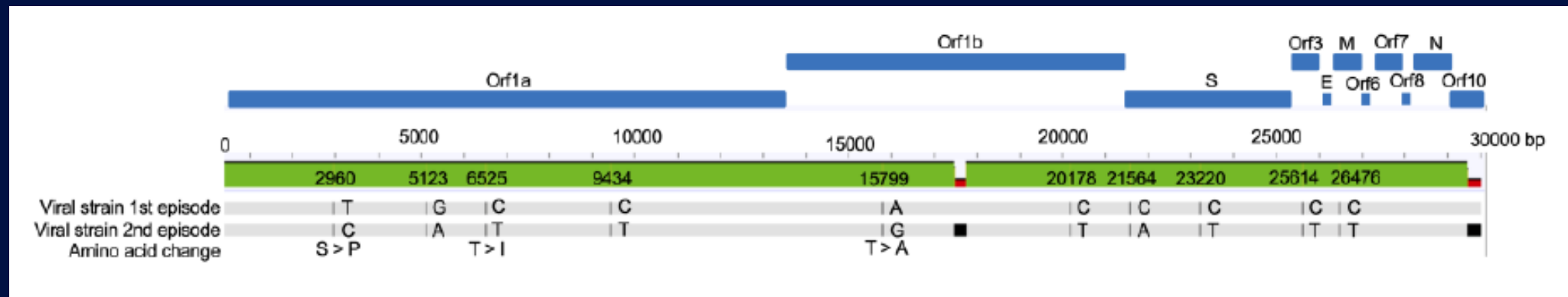
EARLY REINFECTION WITH SARS-CoV-2: 2ND EPISODE MORE SEVERE THAN 1ST EPISODE

- 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



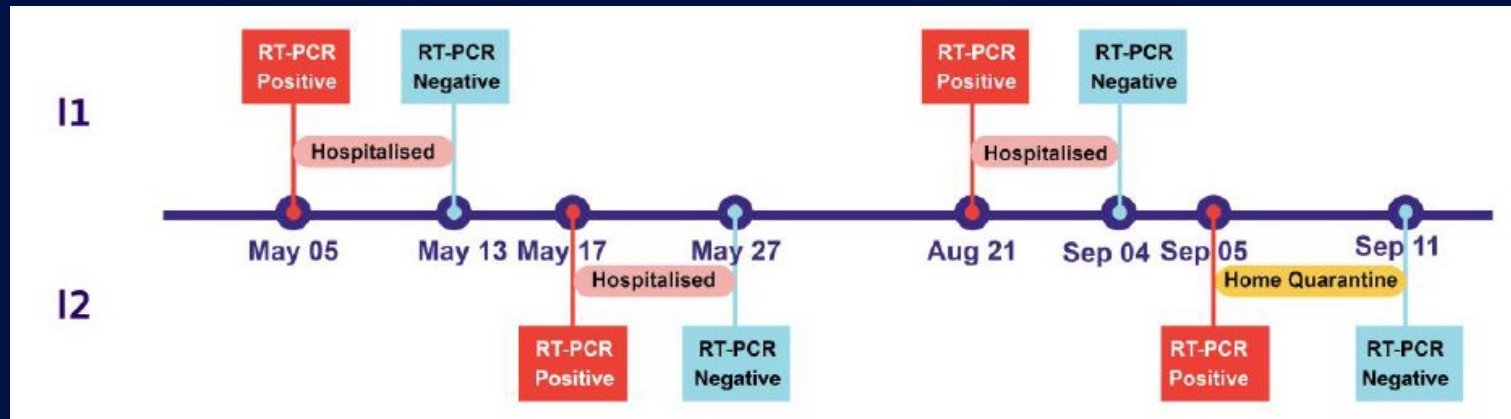
SARS-CoV-2 REINFECTION IN AN IMMUNOCOMPROMISED PERSON

- Demographics: 89 year old women with Waldenstrom'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



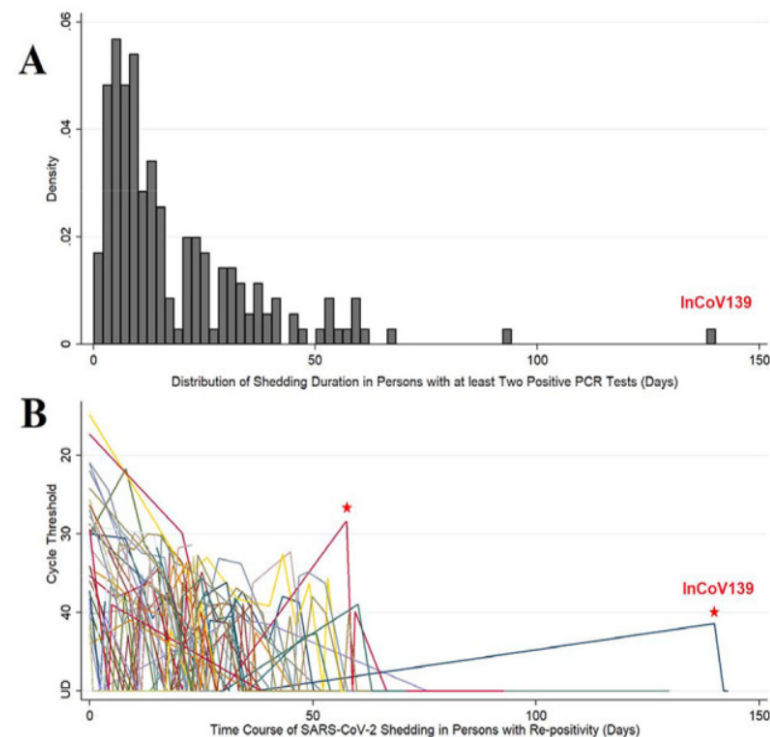
ASYMPTOMATIC REINFECTION IN TWO HCP

- 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



Population viral RNA shedding from patients with COVID-19.

Panel A: Distribution of shedding duration in patients who had at least 2 positive SARS-CoV-2 PCR tests. The shedding duration was calculated as the time from first positive sample to last positive sample. In the histogram (n=176), the proportion of patients is plotted as density on the y-axis and shedding duration (in days) is on the x-axis. Panel B: Time course of SARS-CoV-2 shedding in patients (n=43) who had “re-positive” pattern (repeat SARS-CoV-2 PCR positive after negative testing in patients with initially PCR-confirmed COVID-19, i.e. a positive-negative-positive pattern). In the spaghetti plot, semi-quantitative real-time PCR expressed in cycle thresholds (Ct) is plotted on the y-axis and time course in days from first positive to last positive is on the x-axis. Ct is the average result of E & N2 genes except where one target was undetectable and then Ct was set to value of single positive target. Ct range: 14.9 – 44.0. Negative (undetectable) results are set to Ct = 50 for purposes of display. UD = undetectable. Red stars mark possible reinfections due to low CT value at re-positive, or long duration since last positive PCR, respectively.

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

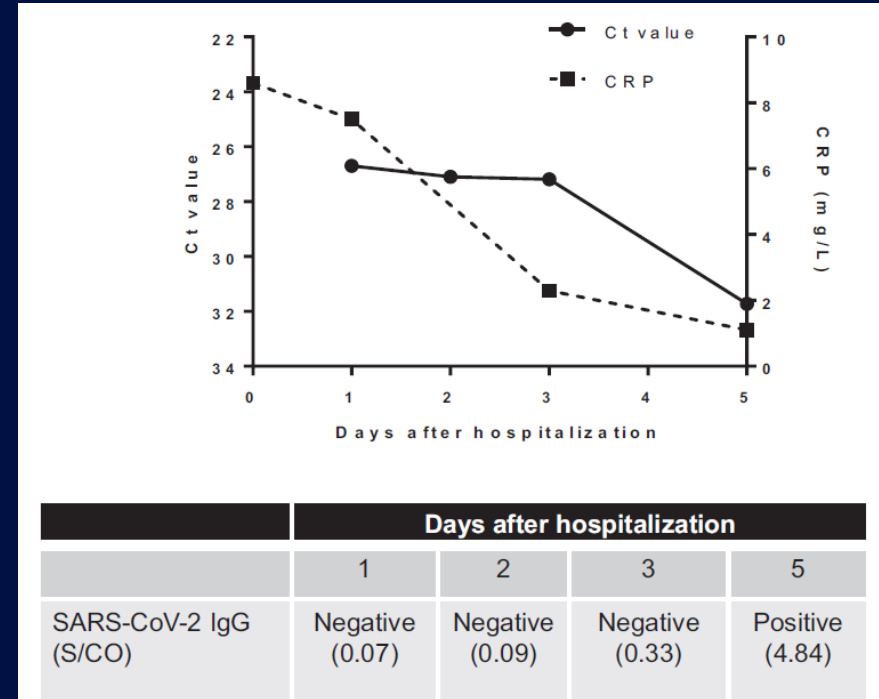


Figure 1. Serial C-reactive protein level, viral load (Ct value), and SARS-CoV-2 IgG result during the second episode. Anti-SARS-CoV-2 IgG was performed with Abbott SARS-CoV-2 antibody assay. Abbreviations: CRP, C-reactive protein; Ct, cycle threshold; IgG, immunoglobulin G; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

SUMMARY OF SELECTED CASES OF COVID-19 REINFECTION

	Sex	Age (years)	First infection (Ct)	Second infection (Ct)	Intervening period (days)	Antibody after first infection	Antibody after reinfection
Hong Kong ³	Male	33	Mild (N/A)	Asymptomatic (27)	142	Negative	IgG+
Nevada, USA ²	Male	25	Mild (35)	Hospitalised (35)	48	N/A	IgM+ and IgG+
Belgium ⁴	Female	51	Mild (26–27)	Milder (33)	93	N/A	IgG+
Ecuador ⁵	Male	46	Mild (37)	Worse (N/A)	63	IgM– and IgG–	IgM+ and IgG+

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

REINFECTION BASED ON RECURRENT SARS-CoV-2 POSITIVE TEST: EXAMPLE OF PUBLISHED REPORTS

- 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;
- 2nd 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

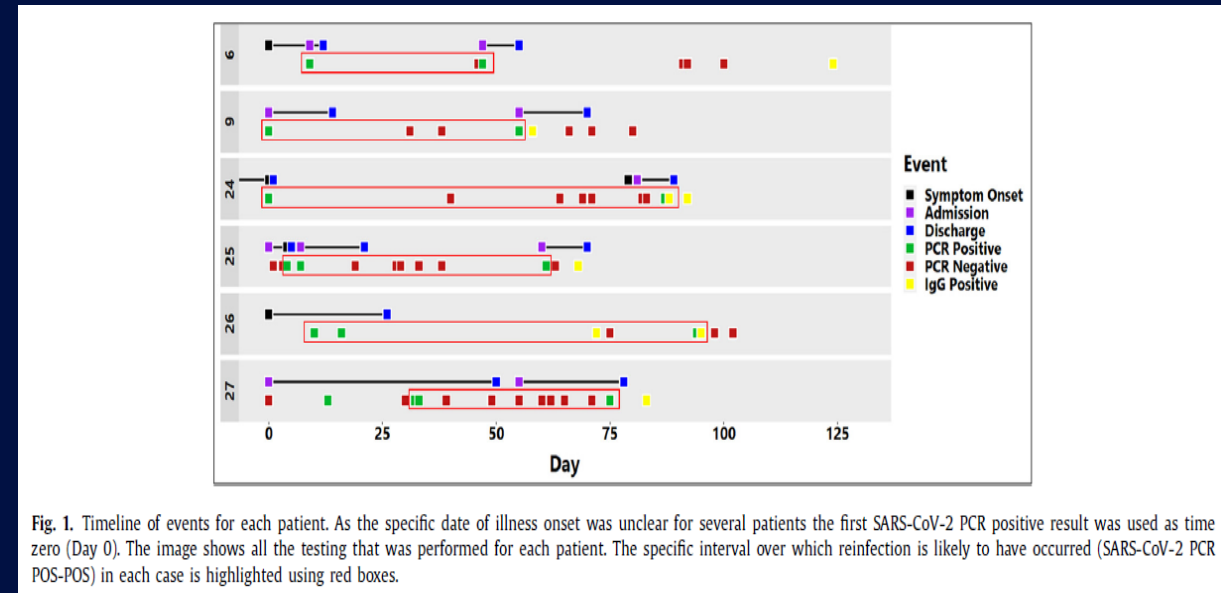


Fig. 1. Timeline of events for each patient. As the specific date of illness onset was unclear for several patients the first SARS-CoV-2 PCR positive result was used as time zero (Day 0). The image shows all the testing that was performed for each patient. The specific interval over which reinfection is likely to have occurred (SARS-CoV-2 PCR POS-POS) in each case is highlighted using red boxes.

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

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