Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting

Laith J. Abu-Raddad,[1,2,3*] Hiam Chemaitelly,[1,2] Joel A. Malek,[4,5] Ayeda A. Ahmed,[4] Yasmin A. Mohamoud,[4] Shameem Younuskunju,[4] Houssein H. Ayoub,[6] Zaina Al Kanaani,[7] Abdullatif Al Khal,[7] Einas Al Kuwari,[7] Adeel A. Butt,[7] Peter Coyle,[7] Andrew Jeremijenko,[7] Anvar Hassan Kaleeckal,[7] Ali Nizar Latif,[7] Riyazuddin Mohammad Shaik,[7] Hanan F. Abdul Rahim,[8] Hadi M. Yassine,[9,10] Mohamed G. Al Kuwari,[11] Hamad Eid Al Romaihi,[12] Mohamed H. Al-Thani,[12] and Roberto Bertollini[12]

[1]*Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar*
[2]*World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine–Qatar, Cornell University, Qatar Foundation – Education City, Doha, Qatar*
[3]*Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, New York, New York, USA*
[4]*Genomics Laboratory, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar*
[5]*Department of Genetic Medicine, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar*
[6]*Department of Mathematics, Statistics, and Physics, Qatar University, Doha, Qatar*
[7]*Hamad Medical Corporation, Doha, Qatar*
[8]*College of Health Sciences, QU Health, Qatar University, Doha, Qatar*
[9]*Biomedical Research Center, Qatar University, Doha, Qatar*
[10]*Department of Biomedical Science, College of Health Sciences, Member of QU Health, Qatar University, Doha, Qatar*
[11]*Primary Health Care Corporation, Doha, Qatar*
[12]*Ministry of Public Health, Doha, Qatar*

[*]Address reprints requests or correspondence to Professor Laith J. Abu-Raddad, Infectious Disease Epidemiology Group, World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine - Qatar, Qatar Foundation - Education City, P.O. Box 24144, Doha, Qatar. Telephone: +(974) 4492-8321. Fax: +(974) 4492-8333. E-mail: lja2002@qatar-med.cornell.edu.

Summary: In a cohort of 133,266 laboratory-confirmed cases, SARS-CoV-2 risk of reinfection was 0.02% and incidence rate of reinfection was 0.36 per 10,000 person-weeks. Reinfection occurs but rarely indicating protective immunity for at least a few months post primary infection.

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ABSTRACT

Background: Risk of reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown. We assessed risk and incidence rate of documented SARS-CoV-2 reinfection in a cohort of laboratory-confirmed cases in Qatar.

Methods: All SARS-CoV-2 laboratory-confirmed cases with at least one PCR positive swab that is ≥45 days after a first-positive swab were individually investigated for evidence of reinfection, and classified as showing *strong*, *good*, *some*, or *weak/no* evidence for reinfection. Viral genome sequencing of the paired first-positive and reinfection viral specimens was conducted to confirm reinfection. Risk and incidence rate of reinfection were estimated.

Results: Out of 133,266 laboratory-confirmed SARS-CoV-2 cases, 243 persons (0.18%) had at least one subsequent positive swab ≥45 days after the first-positive swab. Of these, 54 cases (22.2%) had strong or good evidence for reinfection. Median time between first and reinfection swab was 64.5 days (range: 45-129). Twenty-three of the 54 cases (42.6%) were diagnosed at a health facility suggesting presence of symptoms, while 31 (57.4%) were identified incidentally through random testing campaigns/surveys or contact tracing. Only one person was hospitalized at time of reinfection, but was discharged the next day. No deaths were recorded. Viral genome sequencing confirmed four reinfections out of 12 cases with available genetic evidence. Reinfection risk was estimated at 0.02% (95% CI: 0.01-0.02%) and reinfection incidence rate at 0.36 (95% CI: 0.28-0.47) per 10,000 person-weeks.

Conclusions: SARS-CoV-2 reinfection can occur but is a rare phenomenon suggestive of protective immunity against reinfection that lasts for at least a few months post primary infection.

Keywords: SARS-CoV-2; epidemiology; reinfection; immunity; genetics

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spreading around the globe causing severe disruptions to social and economic activities [1-3]. Qatar, a peninsula in the Arabian Gulf region with a diverse population of 2.8 million [4, 5], has experienced a large epidemic with one of the highest laboratory-confirmed rates of infection at >60,000 infections per million population [6-8]. Antibody testing and mathematical modeling indicated that about half of the population has already been infected [6, 8-12].

The intensity of the epidemic with a high risk of re-exposure to the infection, as well as the availability of a centralized data-capture system of all laboratory-confirmed infections, provided an opportunity to epidemiologically assess the presence and incidence of reinfections; a poorly-understood feature of SARS-CoV-2 epidemiology whose elucidation is critical to inform global response, timing and intensity of future cycles, and impact and durability of potential vaccines [13-16].

Our aim was to assess the risk and incidence rate of documented reinfection in a cohort of 133,266 SARS-CoV-2 laboratory-confirmed infected persons. Since the relevant underlying question is whether risk of reinfection is appreciable or not, we implemented a conservative epidemiological approach for assessing documented reinfections, that is prone to overestimate rather than underestimate risk of reinfection. However, we also conducted sensitivity analyses implementing more stringent criteria for assessing reinfection. We further performed viral genome sequencing to confirm the reinfections.

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METHODS

Sources of data

We analyzed the centralized and standardized national SARS-CoV-2 testing and hospitalization database compiled at Hamad Medical Corporation (HMC), the main public healthcare provider and nationally-designated provider for Coronavirus Disease 2019 (COVID-19) healthcare needs. The database covers all SARS-CoV-2 cases in Qatar and encompasses data on all polymerase chain reaction (PCR) testing conducted from February 28-August 12, 2020, including testing of suspected SARS-CoV-2 cases and traced contacts and infection surveillance testing. The database further includes data on hospital admission of COVID-19 patients and the World Health Organization (WHO) severity classification for each infection [17], which is assessed through individual chart reviews by trained medical personnel. Recently, data on serological testing for antibody on residual blood specimens collected for routine clinical care from attendees at HMC were also incorporated [6, 10].

Laboratory methods

All PCR testing was conducted at HMC Central Laboratory or at Sidra Medicine Laboratory, following standardized protocols. Nasopharyngeal and/or oropharyngeal swabs (Huachenyang Technology, China) were collected and placed in Universal Transport Medium (UTM). Aliquots of UTM were: extracted on the QIAsymphony platform (QIAGEN, USA) and tested with real-time reverse-transcription PCR (RT-qPCR) using TaqPath™ COVID-19 Combo Kit (100% sensitivity and specificity [18]; Thermo Fisher Scientific, USA) on ABI 7500 FAST (Thermo Fisher, USA); extracted using a custom protocol [19] on Hamilton Microlab STAR (Hamilton, USA) and tested using AccuPower SARS-CoV-2 Real-Time RT-PCR Kit (100% sensitivity and specificity [20]; Bioneer, Korea) on ABI 7500 FAST; or loaded directly to Roche cobas® 6800 system and

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assayed with cobas® SARS-CoV-2 Test (95% sensitivity, 100% specificity [21]; Roche, Switzerland). The first assay targets the virus' S, N, and ORF1ab regions; the second targets the virus' RdRp and E-gene regions; and the third targets the ORF1ab and E-gene regions.

Serological testing was performed using Roche Elecsys® Anti-SARS-CoV-2 (99.5% sensitivity [22], 99.8% specificity [22, 23]; Roche, Switzerland), an electrochemiluminescence immunoassay that uses a recombinant protein representing the nucleocapsid (N) antigen for determination of antibodies against SARS-CoV-2. Qualitative anti-SARS-CoV-2 results were generated following the manufacturer's instructions (reactive: cutoff index for optical density ≥1.0 vs. non-reactive: cutoff index <1.0).

Inclusion criteria

All SARS-CoV-2 laboratory-confirmed cases with at least one PCR positive swab that is ≥45 days after a first-positive swab were considered as *suspected cases* of reinfection. The 45-day cutoff was informed by data from observational cohorts of SARS-CoV-2 infected persons [24, 25], and was set to account for the duration of prolonged PCR positivity of several weeks in these patients. Cutoff determination was further informed by the distribution of the time difference between the first-positive swab and subsequent positive swabs among SARS-CoV-2 cases with multiple swabs (Figure 1). The tail of this distribution indicates that a cutoff of 45 days (at the 99th percentile) provides an appropriate mark for defining the end of prolonged PCR positivity: a subsequent positive swab within 45 days of the first-positive swab is likely to reflect prolonged PCR positivity (due to non-viable virus fragments) rather than reinfection, and thus should not be included in analysis.

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Suspected reinfection case classification

Suspected cases of reinfection, that is cases fitting above indicated inclusion criteria, were classified as showing either *strong* evidence, *good* evidence, *some* evidence, or *weak* (or *no*) evidence for reinfection (Box 1). Classification was based on holistic quantitative and qualitative criteria applied to each investigated case. Criteria included the pattern and magnitude of the change in PCR cycle threshold (Ct) value across repeated swabs, time interval between subsequent swabs, PCR testing site (such as outpatients at primary care, hospital emergency, or inpatient hospitalization), purpose of PCR testing (such as appearance of symptoms, contact tracing, or survey/testing campaign), age, history of COVID-19-related hospital admission, and case severity per WHO classification [17].

Overall, swabs with Ct <30 (suggestive of recent active infection) at least 45 days after the first-positive swab were considered as showing *strong evidence for reinfection*. Swabs with Ct ≥30 at least 45 days after the first-positive swab were considered as showing *good evidence for reinfection* if PCR positivity was associated with *contextual evidence* supporting the status of "reinfection" including appearance of symptoms (often as proxied by being diagnosed at a health facility), if the infection was diagnosed through contact tracing (indicating recent exposure to an infected person), if the change in Ct value from the last swab was to a lower Ct value (indicating increasing viral load), and/or if the repeated swabbing did not follow a regular pattern and time interval between repeated swabs was not short (to exclude cases under clinical management that are indicative of poor control of first infection).

Shorter durations bordering the 45-day cutoff with Ct values ≥30 and no contextual evidence supporting the status of "reinfection" were indicative of *some evidence for reinfection*, but not strong nor good evidence for reinfection, as they are more likely to reflect the long tail of the prolonged PCR positivity distribution (Figure 1) [24, 25]. Age ≥70 years, repeated swabs

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on hospitalized patients, and severe or critical WHO disease classifications were considered as contextual factors indicative of poor control of the first infection rather than reinfection. Cases that had such contextual factors (and implicitly did not fit the criteria of strong, good, or some evidence for reinfection) were considered to have *weak (or no) evidence for reinfection*.

Of note that hospitalized COVID-19 cases often had multiple subsequent swabs administered to them as part of clinical care, and repeated swabbing was standard earlier in the epidemic, as the criteria for discharge from an isolation facility required at least two subsequent PCR negative swabs. This was changed later to a time-based criteria per updated WHO recommendation [26].

Reinfection risk and rate

Documented reinfection *risk* was assessed by quantifying the proportion of cases with *strong or good evidence for reinfection* out of all laboratory-confirmed SARS-CoV-2 cases that were diagnosed ≥45 days from end-of-study censoring. *Incidence rate* of documented reinfection was calculated by dividing the number of cases with strong or good evidence by the number of person-weeks contributed by all laboratory-confirmed cases who had their first-positive swab ≥45 days before day of analysis. The follow-up person-time was calculated starting from 45 days after the first-positive swab and up to the reinfection swab, all-cause death, or end-of-study censoring.

Sensitivity analyses

Since we implemented a conservative approach prone to overestimate risk of documented reinfection, several sensitivity analyses were conducted implementing more *stringent criteria* for assessing reinfection: 1) exclusion of cases where the Ct value for the first and/or subsequent positive swab was unknown or with a value ≥35 (to exclude potential PCR false-

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positive cases), 2) changing the ≥45-day cutoff to a ≥60-day cutoff to further exclude potential cases of long-term prolonged PCR positivity, and (*most stringent*) 3) setting definition of recent active infection at Ct cutoff value of <25 (instead of <30) and excluding any suspected reinfection case with Ct >25.

Viral genome sequencing and analysis

Viral genome sequencing was conducted on retrieved paired samples of the first-positive swab and reinfection swab for patients with *strong* or *good evidence for reinfection* as confirmatory analysis. Further details about the viral genome sequencing methods can be found in Supplementary Text S1.

Ethical approval

Study was approved by HMC and Weill Cornell Medicine-Qatar Institutional Review Boards.

RESULTS

Epidemiological analysis

Figure 2 illustrates the selection process of SARS-CoV-2 eligible cases and summarizes the results of their reinfection status' evaluation. Out of 133,266 laboratory-confirmed cases, 117,458 had only one single positive swab and thus were excluded from further analysis. Of the remaining 15,808 cases with multiple swabs, only 243 persons had *at least* one subsequent positive swab that is ≥45 days from the first-positive swab, and thus qualified for inclusion in analysis.

There were 299 positive swabs collected ≥45 days after the first-positive swab for these 243 persons. Individual investigation of each of these swabs yielded 54 cases with *strong* or *good* evidence for reinfection. Of these, 35 had *strong* evidence for reinfection (Ct <30) while the remaining 19 had *good* evidence for reinfection (Ct ≥30). An additional 26 cases showed *some* evidence for reinfection, while evidence was *weak* for the remaining 163 cases.

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Table 1 shows the characteristics of the 54 cases classified as showing strong or good evidence for reinfection. Almost all cases were males, but this reflects the focus of the epidemic in craft and manual workers [6]. Median age was 33 years (range: 16-57) and median time between the *first* swab and the *reinfection* swab was 64.5 days (range: 45-129). Median Ct value was 28 (range: 14-37): it was 22 (range 14-29) for the 35 swabs classified with strong evidence (Ct <30) and 32 (range: 30-37) for the remaining swabs (Ct ≥30). Twenty-three cases (42.6%) were diagnosed at a health facility, suggesting presence of symptoms while 31 (57.4%) were identified incidentally either through random testing campaigns/surveys (n=15; 27.8%) or contact tracing (n=16; 29.6%), suggesting minimal symptoms if any.

Nine of the 54 cases showing strong or good evidence for reinfection were hospitalized at any time. However, all but *one* occurred following the primary infection—only one hospitalization occurred at time of reinfection but the patient was discharged the next day. Most hospitalizations occurred for isolation or initial assessment purposes as cases had no or minimal symptoms. Only one case had sufficient symptoms to warrant an infection severity assessment (during primary infection), but was classified with "mild" severity per WHO classification. No deaths were recorded. Of note that the vast majority of infections in Qatar occurred in young and healthy men and had low severity [6, 12].

Antibody test results were available for 48 out of the 243 assessed individuals (Supplementary Table S1), of whom 30 (62.5%) had detectable antibodies. Of the 13 with strong evidence for reinfection *and* available antibody results, seven (53.9%) were sero-negative. Meanwhile, both individuals with good evidence for reinfection, three of the four individuals with some evidence for reinfection, and 19 of the 29 individuals with weak evidence for reinfection, were sero-positive.

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Risk of documented reinfection was estimated at 0.05% (95% CI: 0.04-0.07%)—that is a total of 54 reinfections among 101,349 persons with laboratory-confirmed infection (the cohort of infected persons after excluding persons who were diagnosed within 45 days from end-of-study censoring). Incidence rate of reinfection was estimated at 1.09 (95% CI: 0.84-1.42) per 10,000 person-weeks—that is a total of 54 reinfection events in a follow-up person-time of 495,208.7 person-weeks.

Results of sensitivity analyses can be found in Supplementary Table S2. In these analyses, the estimate for the risk of reinfection ranged between 0.02% (95% CI: 0.01-0.03) and 0.03% (95% CI: 0.02-0.04), while that for the incidence rate of reinfection ranged between 0.38 (95% CI: 0.24-0.60) and 1.06 (95% CI: 0.75-1.50) per 10,000 person-weeks. Although these sensitivity analyses confirmed our results, they suggested overestimation of the already low risk of reinfection.

Confirmation of reinfection through viral genome sequencing

Paired specimens of the first-positive and reinfection swabs could be retrieved for 23 out of the 54 cases with strong or good evidence for reinfection. Table 2 summarizes the viral genome sequencing results and Figure 3 and Supplementary Figures S1-S2 show the detailed analysis for each genome pair.

There was insufficient evidence to warrant interpretation for 11 pairs because of low genome quality. For six pairs, there were one to several changes of allele frequency indicative at best of a shifting balance of quasi-species, and thus no evidence for reinfection. For two pairs, remarkably, there was conclusive evidence for *no reinfection* as both genomes were of high quality yet no differences were found. For both patients, Ct was <25 for the first-positive and reinfection swabs indicating persistent active infection (Table 1). These two cases were also sero-positive (Table 1).

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Meanwhile, for two pairs, there was conclusive evidence for reinfection with multiple changes of allele frequency and presence of the D614G mutation (23403bp A>G)—a variant that appeared and expanded replacing the original D614 form [27, 28]. Also for two pairs, and although one of the genomes was of inferior quality, there was sufficient evidence for differences including the presence of the D614G mutation, thereby rendering evidence for reinfection. Three out of these four cases with viral genome sequencing confirmation of reinfection were classified above (epidemiological criteria) as having strong evidence for reinfection, with the fourth classified as having good evidence (Table 1). Antibody test result was available for one case at time of reinfection, and the individual was sero-negative.

In sum, for the 12 cases where viral genome sequencing evidence was available, four cases were confirmed as reinfections, a confirmation rate of 33.3%. Applying this rate to the above-estimated reinfection metrics yielded risk of documented reinfection of 0.02% (95% CI: 0.01-0.02%) and incidence rate of reinfection of 0.36 (95% CI: 0.28-0.47) per 10,000 person-weeks.

DISCUSSION

Results indicate, employing several analyses and sensitivity analyses, conclusive evidence for presence of reinfections in the SARS-CoV-2 epidemic of Qatar, but the risk for documented reinfection was very rare at about 2 reinfections per 10,000 infected persons. This finding is striking as the epidemic in Qatar has been intense with half of the population estimated to have been infected [6, 8-12]. Considering the strength of the force of infection, estimated at a *daily* probability of infection exceeding 1% at the epidemic peak around May 20 [6], it is all but certain that a significant proportion of the population has been repeatedly exposed to the infection, but such re-exposures hardly led to any documentable reinfections.

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Indeed, of all epidemiologically-identified reinfections, nearly two-thirds (57%) were discovered accidentally, either through random testing campaigns/surveys or through contact tracing. None were severe, critical, or fatal; all reinfections were asymptomatic or with minimal or mild symptoms. These findings may suggest that most infected persons appear to develop immunity against reinfection that lasts for at least few months, and that reinfections (if they occur) are well tolerated and no more symptomatic than primary infections. Further follow up of this cohort of infected persons over time may allow elucidation of potential effects of waning of immunity.

Other lines of evidence for this cohort also support this conclusion. Among 2,559 PCR positive persons where an antibody test outcome was available [6], and where the first-positive PCR test was conducted >3 weeks before the serology test to accommodate for the delay in development of detectable antibodies following onset of infection [24, 25], 91.7% were antibody positive [6]. The high antibody positivity was also stable for over three months [6], as described elsewhere [14, 25]. The epidemic curve in Qatar was further characterized by rapid growth followed by rapid decline [6, 8, 12], at a time when levels of social and physical distancing restrictions were fairly stable. This points to susceptibles-infected-recovered "SIR" epidemic dynamics with most infections eliciting immunity against reinfection.

This assessment has limitations. We assessed risk of only *documented* reinfections, but other reinfections could have occurred but went undocumented, perhaps because of minimal/mild or no symptoms. It is also possible that with the primed immune system following primary infection, reinfections could be milder and shorter [15]. A recent nationwide population-based survey in Qatar estimated that only 9.3% (95% CI: 7.9-11.0%) of those antibody positive had a prior documented laboratory-confirmed infection [9], suggesting that undocumented infections (or reinfections) could possibly be ten-fold higher than documented

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infections (or reinfections). This finding indicates that incidence rate of both *documented and undocumented* reinfections may add up to perhaps ~10 per 10,000 person-weeks. Meanwhile, a recent mathematical modeling study estimated the incidence rate of *infection* in Qatar at the time of the present study, including both documented and undocumented infections, at ~200 per 10,000 person-weeks [8]. Comparing these incidence rates suggest that the "efficacy" of natural infection against reinfection is around $1-10/200 \approx 95\%$.

Viral genome sequencing analysis was possible for only a subset of reinfections. Antibody testing outcomes were also available for only a number of cases, limiting use and inferences of the link between antibody status and risk of reinfection. Of note that for one of the genetically-confirmed reinfections the antibody test result was available but was sero-negative (Table 1), just as the Hong Kong reinfected patient [29].

In conclusion, SARS-CoV-2 reinfection appears to be a rare phenomenon. This may suggest that immunity develops after the primary infection and lasts for at least few months, and that immunity may protect against reinfection.

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Author contributions

LJA conceived and co-designed the study and led the statistical analyses. HC co-designed the study, performed the data analyses, and wrote the first draft of the article. JAM led the viral genome sequencing analyses and AAA, YAM, and SY conducted these analyses. All authors contributed to data collection and acquisition, database development, discussion and

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interpretation of the results, and to the writing of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

We declare no competing interests.

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Box 1. Classification of suspected cases of SARS-CoV-2 reinfection based on strength of supporting epidemiological evidence.

Suspected cases of SARS-CoV-2 reinfection: all laboratory-confirmed cases with at least one polymerase chain reaction (PCR) positive swab that is ≥45 days after a first-positive swab.

Strong evidence for reinfection: individuals having positive swabs with PCR cycle threshold (Ct) value <30 at least 45 days after the first-positive swab. No contextual evidence supporting poor control of first infection such as age ≥70 years, repeated swabs on hospitalized patients, and severe or critical World Health Organization disease classifications.

Good evidence for reinfection: individuals having positive swabs with PCR Ct value ≥30 at least 45 days after the first-positive swab, but where PCR positivity was associated with contextual evidence supporting the status of reinfection:

- Appearance of symptoms (often as proxied by being diagnosed at a health facility)
- Infection diagnosis through contact tracing (indicating recent exposure to an infected person)
- Lower Ct value compared to last positive swab (indicating increasing viral load)
- Irregular and spaced-out pattern for repeated swabbing (to exclude cases under clinical management that are indicative of poor control of first infection).

No contextual evidence supporting poor control of first infection such as age ≥70 years, repeated swabs on hospitalized patients, and severe or critical World Health Organization disease classifications.

Some evidence for reinfection: individuals having positive swabs with PCR Ct value ≥30 at least 45 days after the first-positive swab, but typically bordering the cutoff of 45 days. PCR positivity was **not** associated with evidence supporting the status of reinfection (listed above).

Weak evidence for reinfection: individuals having swabs with PCR Ct value ≥30 at least 45 days after the first-positive swab, but typically bordering the cutoff of 45 days. PCR positivity was associated with contextual evidence indicative of poor infection control of the first infection rather than reinfection (such as age ≥70 years, repeated swabs on hospitalized patients, and severe or critical World Health Organization disease classifications).

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FIGURE LEGENDS

Figure 1. Distribution of the time difference between the first swab and subsequent swabs among all laboratory-confirmed SARS-CoV-2 cases with more than one positive swab. The cutoff of 45 days was at the 99th percentile, and thus provides an appropriate mark for defining the end of the prolonged polymerase chain reaction (PCR) positivity.

Figure 2. Flow chart describing the selection process of SARS-CoV-2 eligible cases and summarizing the results of their reinfection status' evaluation.

Figure 3. Viral genome sequencing analysis of the paired viral specimens of the first-positive and reinfection swabs for the six patients with conclusive or supporting evidence for reinfection or no reinfection.

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Table 1. Characteristics of individuals classified as showing strong or good evidence for reinfection.

	Socio-demographic		PCR testing				Hospitalization			Ab testing	
ID#	**Sex**	**Age group**	**Sample type**	**PCR swab date**	**Positive swab type**	**Average Ct value**	**Case severity** *	**Hospital admission**†	**LOS (days)**	**Ab test date**	**Ab status**
Strong evidence for reinfection											
1	Male	50-54	Survey‡	14 May	First pos swab	Unk	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	50-54	Survey‡	23 July	Reinf swab	14	Not assessed§	Not hospitalized	0	26 July	Negative
2	Male	30-34	Health facility	16 June	First pos swab	36	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	30-34	Health facility	10 August	Reinf swab	16	Not assessed§	Not hospitalized	0	Not tested	Unk
3	Male	30-34	Contact tracing	02 April	First pos swab	Unk	Not assessed§	07 April	1	Not tested	Unk
	Male	30-34	Survey‡	26 June	Reinf swab	17	Not assessed§	Not hospitalized	0	27 June	Negative
4	Male	25-29	Health facility	30 April	First pos swab	33	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	25-29	Health facility	15 July	Reinf swab	17	Not assessed§	Not hospitalized	0	Not tested	Unk
5	Male	35-39	Contact tracing	31 March	First pos swab	Unk	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	35-39	Health facility	20 April	Subs pos swab	24	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	35-39	Health facility	07 August	Reinf swab	17	Not assessed§	Not hospitalized	0	Not tested	Unk
6	Female	50-54	Contact tracing	04 June	First pos swab	34	Not assessed§	Not hospitalized	0	Not tested	Unk
	Female	50-54	Health facility	27 July	Reinf swab	17	Not assessed§	Not hospitalized	0	14 July	Negative
7	Female	20-24	Health facility	26 April	First pos swab	35	Not assessed§	Not hospitalized	0	Not tested	Unk
	Female	20-24	Health facility	19 July	Reinf swab	17	Not assessed§	Not hospitalized	0	Not tested	Unk
8	Male	30-34	Health facility	05 June	First pos swab	36	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	30-34	Contact tracing	04 August	Reinf swab	18	Not assessed§	Not hospitalized	0	Not tested	Unk
9	Male	20-24	Contact tracing	03 April	First pos swab	Unk	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	20-24	Health facility	09 July	Reinf swab	18	Not assessed§	Not hospitalized	0	Not tested	Unk
10	Female	20-24	Health facility	24 March	First pos swab	Unk	Not assessed§	Not hospitalized	0	Not tested	Unk
	Female	20-24	Contact tracing	23 June	Reinf swab	19	Not assessed§	Not hospitalized	0	Not tested	Unk
11	Male	35-39	Contact tracing	30 March	First pos swab	Unk	Not assessed§	Not hospitalized	0	Not tested	Unk
	Male	35-39	Contact tracing	24 June	Reinf swab	19	Not assessed§	Not hospitalized	0	19 July	Positive
12	Female	45-49	Health facility	28 May	First pos swab	30	Not assessed§	Not hospitalized	0	Not tested	Unk
	Female	45-49	Health facility	10 August	Reinf swab	20	Not assessed§	Not hospitalized	0	04 June	Negative
13	Male	30-34	Contact tracing	03 April	First pos swab	Unk	Not assessed§	06-07 April	1	Not tested	Unk
	Male	30-34	Survey‡	15 July	Reinf swab	20	Not assessed§	Not hospitalized	0	Not tested	Unk
14	Female	40-44	Contact tracing	12 June	First pos swab	24	Not assessed§	Not hospitalized	0	Not tested	Unk

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	Female	40-44	Health facility	08 August	Reinf swab	21	Not assessed[§]	Not hospitalized	0	03 July	Positive
15	Male	50-54	Contact tracing	22 April	First pos swab	34	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	50-54	Contact tracing	23 July	Reinf swab	21	Not assessed[§]	Not hospitalized	0	22 July	Negative
16	Male	25-29	Health facility	09 March	First pos swab	Unk	Not assessed[§]	09-14 March[†]	5	Not tested	Unk
	Male	25-29	Contact tracing	21 May	Reinf swab	21	Not assessed[§]	Not hospitalized	0	Not tested	Unk
17	Male	20-24	Health facility	15 May	First pos swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Health facility	12 August	Reinf swab	22	Not assessed[§]	13 August	1	Not tested	Unk
18	Female	20-24	Health facility	23 May	First pos swab	33	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Female	20-24	Health facility	07 August	Reinf swab	22	Not assessed[§]	Not hospitalized	0	02 August	Negative
19	Male	40-44	Health facility	03 June	First pos swab	23	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	07 August	Reinf swab	23	Not assessed[§]	Not hospitalized	0	13 July	Positive
20	Female	45-49	Health facility	02 May	First pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Female	45-49	Health facility	29 July	Reinf swab	25	Not assessed[§]	Not hospitalized	0	30 July	Negative
21	Male	30-34	Survey[‡]	12 May	First pos swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Survey[‡]	27 July	Reinf swab	25	Not assessed[§]	Not hospitalized	0	28 July	Positive
22	Male	20-24	Health facility	31 May	First pos swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Health facility	05 August	Reinf swab	26	Not assessed[§]	Not hospitalized	0	Not tested	Unk
23	Male	20-24	Health facility	16 June	First pos swab	31	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Contact tracing	11 August	Reinf swab	27	Not assessed[§]	Not hospitalized	0	Not tested	Unk
24	Male	35-39	Health facility	08 June	First pos swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	35-39	Health facility	03 August	Reinf swab	27	Not assessed[§]	Not hospitalized	0	Not tested	Unk
25	Male	40-44	Health facility	28 May	First pos swab	21	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Contact tracing	30 July	Reinf swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
26	Male	40-44	Survey[‡]	22 April	First pos swab	17	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	06 May	Subs pos swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	14 May	Subs pos swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Survey[‡]	12 June	Reinf swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
27	Male	25-29	Health facility	25 April	First pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	25-29	Health facility	10 June	Reinf swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
28	Male	40-44	Health facility	11 March	First pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Contact tracing	08 June	Reinf swab	28	Not assessed[§]	Not hospitalized	0	10 July	Positive
29	Male	30-34	Survey[‡]	12 May	First pos swab	21	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Survey[‡]	30 June	Reinf swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
30	Male	15-19	Health facility	05 June	First pos swab	20	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	15-19	Health facility	08 August	Reinf swab	28	Not assessed[§]	Not hospitalized	0	Not tested	Unk
31	Male	35-39	Health facility	25 April	First pos swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	35-39	Survey[‡]	22 June	Reinf swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
32	Male	35-39	Survey[‡]	12 May	First pos swab	17	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	35-39	Survey[‡]	30 June	Reinf swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
33	Male	40-44	Health facility	26 April	First pos swab	17	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	06 July	Reinf swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
34	Male	40-44	Health facility	11 May	First pos swab	33	Not assessed[§]	14 May	1	Not tested	Unk

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	Male	40-44	Contact tracing	28 July	Reinf swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
35	Male	35-39	Health facility	17 May	First pos swab	25	Not assessed[§]	31 May-01 June	2	Not tested	Unk
	Male	35-39	Health facility	20 July	Reinf swab	29	Not assessed[§]	Not hospitalized	0	26 July	Positive
Good evidence for reinfection											
36	Male	30-34	Health facility	30 April	First pos swab	22	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Contact tracing	26 June	Reinf swab	30	Not assessed[§]	Not hospitalized	0	Not tested	Unk
37	Male	40-44	Health facility	04 May	First pos swab	35	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	11 July	Reinf swab	30	Not assessed[§]	Not hospitalized	0	Not tested	Unk
38	Male	25-29	Health facility	02 June	First pos swab	35	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	25-29	Contact tracing	04 August	Reinf swab	30	Not assessed[§]	Not hospitalized	0	Not tested	Unk
39	Male	20-24	Survey[‡]	06 May	First pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Survey[‡]	10 May	Subs pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Survey[‡]	20 May	Subs pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Survey[‡]	30 June	Reinf swab	30	Not assessed[§]	Not hospitalized	0	Not tested	Unk
40	Male	55-59	Health facility	10 March	First pos swab	Unk	Mild	14-20 March[†]	7	Not tested	Unk
	Male	55-59	Health facility	03 June	Reinf swab	31	Not assessed[§]	Not hospitalized	0	22 July	Positive
41	Male	30-34	Survey[‡]	23 April	First pos swab	26	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Health facility	07 May	Subs pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Survey[‡]	12 June	Reinf swab	31	Not assessed[§]	Not hospitalized	0	Not tested	Unk
42	Male	15-19	Health facility	10 April	First pos swab	33	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	15-19	Health facility	26 May	Reinf swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
43	Male	15-19	Health facility	09 March	First pos swab	Unk	Not assessed[§]	16-23 March[†]	8	Not tested	Unk
	Male	15-19	Contact tracing	26 May	Reinf swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
44	Male	25-29	Survey[‡]	26 April	First pos swab	30	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	25-29	Survey[‡]	16 May	Subs pos swab	34	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	25-29	Survey[‡]	20 June	Reinf swab	32	Not assessed[§]	Not hospitalized	0	Not tested	Unk
45	Male	25-29	Contact tracing	26 April	First pos swab	29	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	25-29	Contact tracing	23 June	Reinf swab	33	Not assessed[§]	Not hospitalized	0	Not tested	Unk
46	Male	20-24	Health facility	23 April	First pos swab	20	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Contact tracing	20 June	Reinf swab	34	Not assessed[§]	Not hospitalized	0	Not tested	Unk
47	Male	20-24	Survey[‡]	29 April	First pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	20-24	Survey[‡]	20 June	Reinf swab	34	Not assessed[§]	Not hospitalized	0	Not tested	Unk
48	Male	35-39	Health facility	08 April	First pos swab	20	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	35-39	Health facility	16 June	Reinf swab	35	Not assessed[§]	Not hospitalized	0	Not tested	Unk
49	Male	40-44	Survey[‡]	06 April	First pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	40-44	Health facility	04 June	Reinf swab	35	Not assessed[§]	Not hospitalized	0	Not tested	Unk
50	Male	50-54	Contact tracing	20 April	First pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	50-54	Contact tracing	11 June	Reinf swab	35	Not assessed[§]	Not hospitalized	0	Not tested	Unk
51	Male	45-49	Health facility	21 April	First pos swab	37	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	45-49	Survey[‡]	19 June	Reinf swab	36	Not assessed[§]	Not hospitalized	0	02 August	Positive
52	Male	30-34	Contact tracing	29 March	First pos swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Survey[‡]	15 June	Reinf swab	37	Not assessed[§]	Not hospitalized	0	Not tested	Unk

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53	Male	30-34	Contact tracing	20 April	First pos swab	36	Not assessed[§]	Not hospitalized	0	Not tested	Unk
	Male	30-34	Contact tracing	04 June	Reinf swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk
54	Male	20-24	Health facility	11 April	First pos swab	27	Not assessed[§]	14-30 April[†]	17	Not tested	Unk
	Male	20-24	Health facility	26 April	Subs pos swab	36	Not assessed[§]	Inpatient	--	Not tested	Unk
	Male	20-24	Survey[‡]	24 June	Reinf swab	Unk	Not assessed[§]	Not hospitalized	0	Not tested	Unk

Ab, antibody; LOS, length of stay; Reinf, reinfection; PCR, polymerase chain reaction; Pos, positive; Subs, subsequent; Unk, unknown.

[*]Severity classification per WHO guidelines was conducted only on a subset of all cases where it was deemed relevant. Asymptomatic cases or cases with minimal symptoms were not formally assessed for severity.

[†]It has been common to use hospitalization as a form of isolation especially early in the epidemic.

[‡]The category "survey" refers to surveillance testing campaigns conducted in workplaces and residential areas.

[§]Not assessed because of no or minimal symptoms to warrant clinical assessment.

The light blue color highlights reinfection cases that were confirmed by viral genome sequencing.

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Table 2. Results of reinfection confirmatory analysis based on viral genome sequencing of the paired viral specimens of the first-positive and reinfection swabs for 23 patients with strong or good epidemiological evidence for reinfection.

Viral genome sequencing evidence for reinfection	**Indication upon comparing each genome pair**	**N**
Insufficient evidence to warrant interpretation	One or two genomes of low quality	11
No evidence for reinfection	One change of allele frequency	3
Shifting balance of quasi-species with no evidence for reinfection	Several changes of allele frequency	3
Conclusive evidence for no reinfection	Both genomes of high quality yet no differences found	2
Supporting evidence for reinfection	One genome of inferior quality but with D614G mutation	2
Conclusive evidence for reinfection	Multiple changes of allele frequency and D614G mutation	2
Total		**23**

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Figure 1

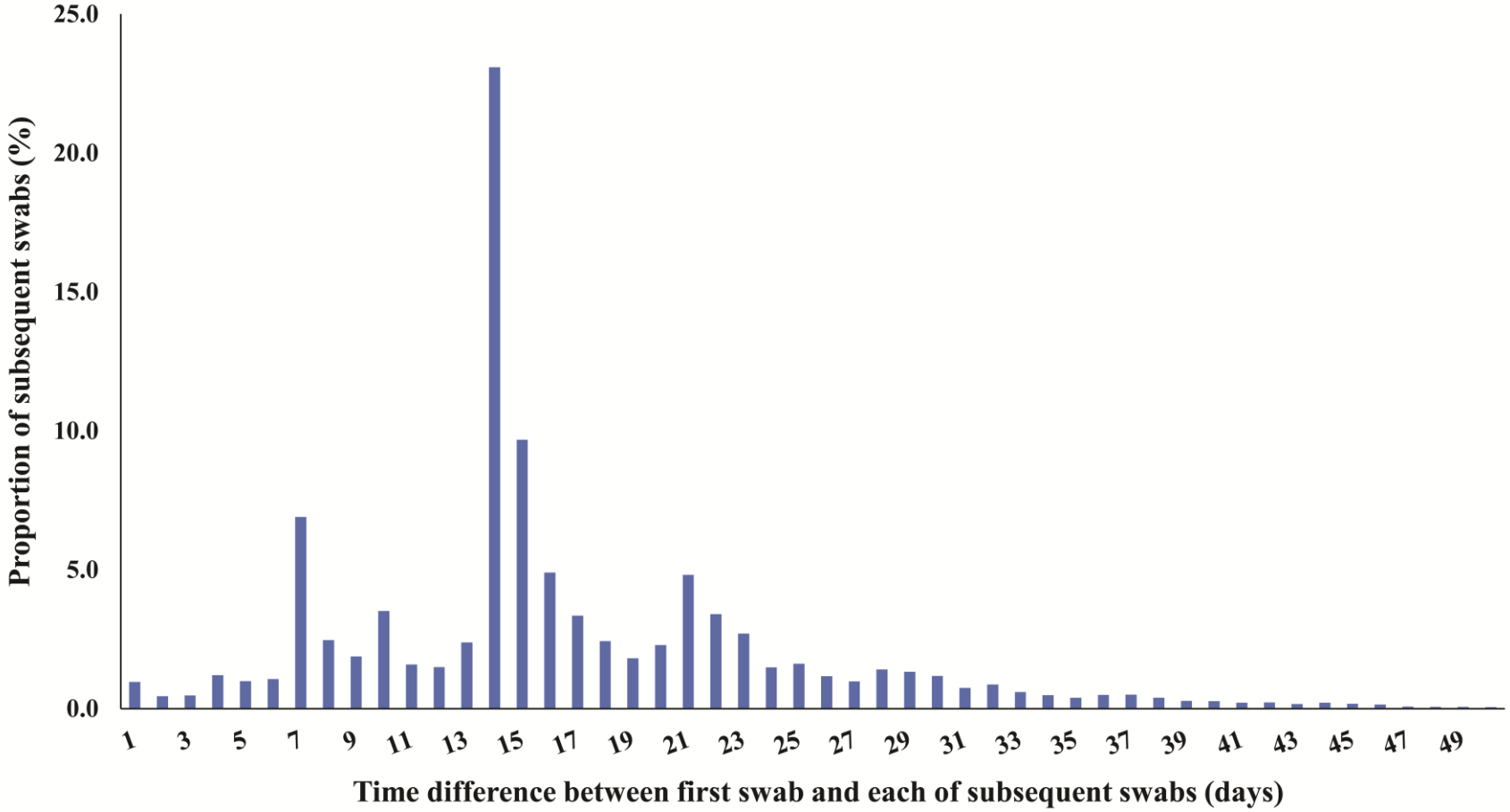
Proportion of subsequent swabs (%)
25.0
20.0
15.0
10.0
5.0
0.0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49
Time difference between first swab and each of subsequent swabs (days)

Figure 2

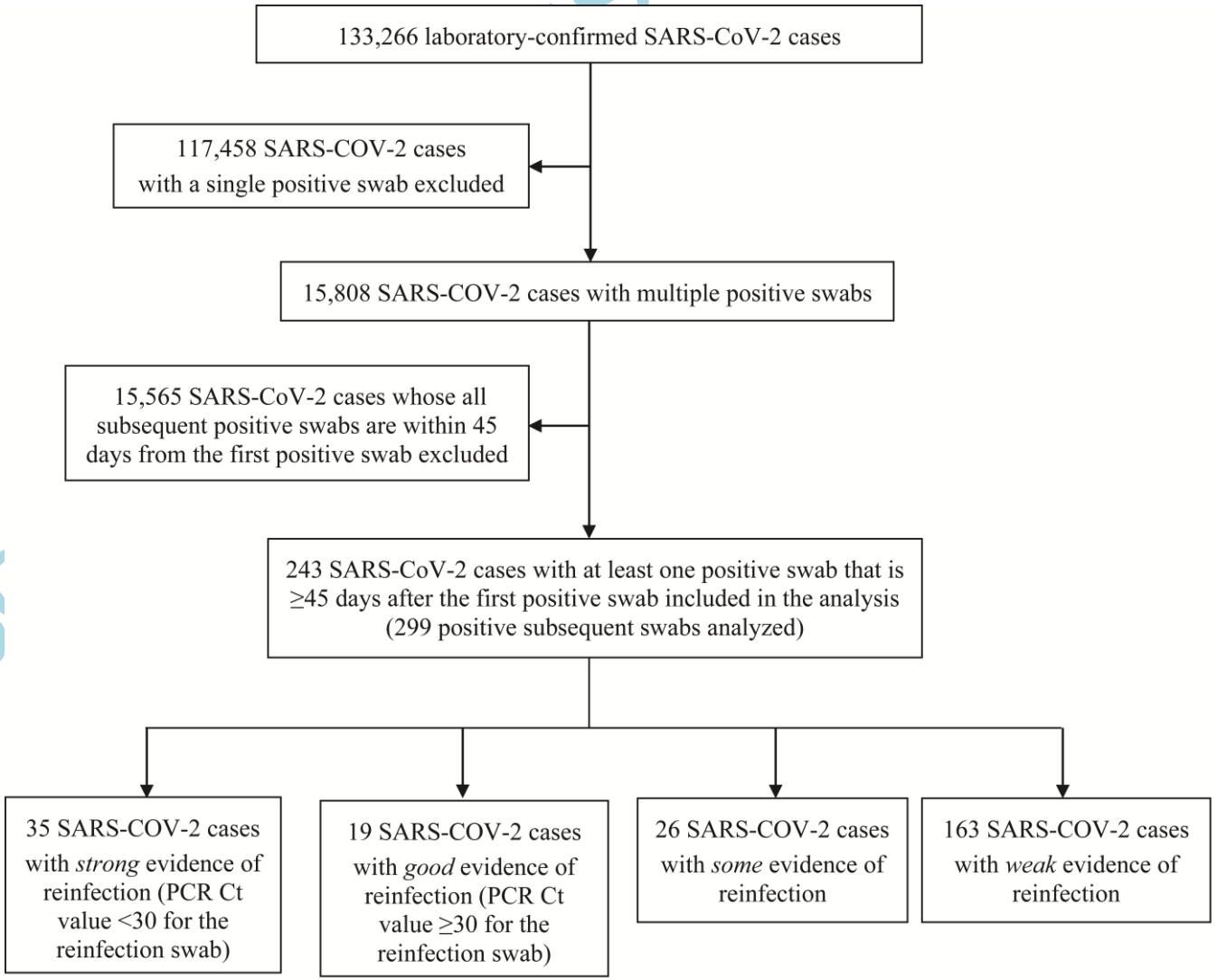
133,266 laboratory-confirmed SARS-CoV-2 cases
117,458 SARS-COV-2 cases with a single positive swab excluded
15,808 SARS-COV-2 cases with multiple positive swabs
15,565 SARS-CoV-2 cases whose all subsequent positive swabs are within 45 days from the first positive swab excluded
243 SARS-CoV-2 cases with at least one positive swab that is ≥45 days after the first positive swab included in the analysis (299 positive subsequent swabs analyzed)
35 SARS-COV-2 cases with *strong* evidence of reinfection (PCR Ct value <30 for the reinfection swab)
19 SARS-COV-2 cases with *good* evidence of reinfection (PCR Ct value ≥30 for the reinfection swab)
26 SARS-COV-2 cases with *some* evidence of reinfection
163 SARS-COV-2 cases with *weak* evidence of reinfection

Figure 3

Patient ID		Patient 14		Patient 19		Patient 27		Patient 33		Patient 20		Patient 44	
Positive swab type		First positive swab	Reinfection swab	First positive swab	Reinfection swab	First positive swab	Reinfection swab	First positive swab	Reinfection swab	First positive swab	Reinfection swab	First positive swab	Reinfection swab
Swab date		12-Jun	8-Aug	3-Jun	7-Aug	25-Apr	10-Jun	26-Apr	6-Jul	2-May	29-Jul	26-Apr	20-Jun
241	C	T	T	T	T	C	T	C	T	N	T	T	N
373	G	G	G	G	G	G	G	G	G	N	G	G	N
1302	C	T	T	T	T	C	T	C	T	N	T	T	N
2644	C	C	C	C	C	C	C	C	C	N	C	N	N
2788	C	C	C	C	C	C	C	C	C	N	C	C	C
2878	C	C	C	C	C	C	C	C	C	N	C	C	N
3037	C	T	T	T	T	C	T	C	T	N	T	T	N
3373	C	C	C	C	C	C	C	C	C	N	C	C	N
3695	C	C	C	C	C	C	C	C	C	N	C	C	N
6181	T	T	T	T	T	T	T	T	T	N	T	T	N
6817	A	A	A	A	A	A	19\7	A	A	N	A	A	A
7733	A	A	A	A	A	A	A	A	A	N	A	A	A
9841	G	G	G	G	G	G	G	G	G	N	G	G	N
10595	T	T	T	T	T	T	T	T	T	N	T	T	N
12695	C	C	C	C	C	C	C	C	C	N	C	C	N
14408	C	T	T	T	T	C	T	C	T	N	T	T	N
14805	C	C	C	C	C	T	C	T	C	Evid of T	C	C	C
15315	C	C	C	C	C	C	C	C	C	N	C	C	N
15486	A	A	A	A	A	A	A	A	A	N	A	A	N
15672	G	G	G	G	G	G	G	G	G	N	G	G	N
16537	G	G	G	G	G	A	G	A	G	Evid of A	G	G	N
16989	C	C	C	C	C	C	C	C	T	N	C	C	N
17193	G	G	G	G	G	G	G	G	G	N	G	G	N
17550	C	N	C	N	N	N	C	N	C	N	N	N	N
17907	T	T	T	T	T	T	T	T	T	N	T	T	N
20870	G	G	G	G	G	G	G	G	G	N	G	G	N
21712	A	A	A	A	A	A	A	A	A	N	A	A	N
21737	T	T	T	T	T	T	T	T	T	N	T	T	N
21846	C	C	C	C	C	C	C	C	C	N	C	C	N
22015	T	T	T	T	T	T	T	T	T	N	T	T	N
23403	A	N	G	G	G	A	G	A	G	1 read A	G	G	A
24675	A	A	A	A	A	A	A	A	A	N	A	A	N
24926	G	G	G	G	G	G	G	G	G	N	G	G	N
25207	C	C	C	C	C	C	C	C	C	N	C	C	N
25460	C	C	C	C	C	C	C	C	C	N	C	C	C
25552	G	G	G	G	G	G	G	G	G	N	G	G	N
25563	G	T	T	T	T	G	T	G	T	N	T	T	N
25704	T	T	T	T	T	T	T	T	T	N	T	T	N
26144	G	G	G	G	G	T	G	T	G	N	G	G	N
26801	C	N	N	N	N	N	C	N	C	N	N	C	C
26963	A	A	A	A	A	A	A	A	A	N	A	A	A
27341	A	A	A	A	A	A	A	A	A	A	A	A	A
27476	C	C	C	C	C	C	C	C	C	N	C	C	N
27769	C	C	C	C	C	C	C	C	C	N	C	41\45	N
28054	C	C	C	C	C	C	C	C	C	N	N	18\28	N
28087	C	C	C	C	C	C	C	C	C	N	C	C	C
29144	C	C	C	C	C	C	C	C	C	N	C	C	N
29370	C	T	T	C	C	C	C	C	C	N	T	C	N
29554	G	G	G	T	T	G	G	G	T	N	G	G	N
29642	C	C	C	C	C	C	C	C	C	N	C	C	N
Description		Both genomes of high quality yet no difference found		Both genomes of high quality yet no difference found		Multiple changes of allele frequency and D614G mutation		Multiple changes of allele frequency and D614G mutation		One of the genomes of inferior quality, but with differences including the D614G mutation		One of the genomes of inferior quality, but with differences including the D614G mutation	
Interpretation		Conclusive evidence for no reinfection		Conclusive evidence for no reinfection		Conclusive evidence for reinfection		Conclusive evidence for reinfection		Supporting evidence for reinfection		Supporting evidence for reinfection	

Letter N denotes unknown.
Numbers in cells represent the balance of reads for the reference and alternate alleles in that order.
Manual calls are represented by white cells with the nucleotide call.
Yellow-color-highligted positions are likely homoplasic.
Green-color-highlighted positions denote a D614G mutation.
Light blue color highlights reinfection cases that were confirmed by viral genome sequencing.
Light grey color highlights no reinfection cases that were confirmed by viral genome sequencing.