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MAJOR ARTICLE

Assessment of the Risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection in an Intense Reexposure Setting

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Background. Risk of reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown. We assessed the 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 1 polymerase chain reaction–positive swab that was ≥45 days after a first positive swab were individually investigated for evidence of reinfection. Viral genome sequencing of the paired first positive and reinfection viral specimens was conducted to confirm reinfection.

Results. Out of 133 266 laboratory-confirmed SARS-CoV-2 cases, 243 persons (0.18%) had at least 1 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 the first swab 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 1 person was hospitalized at the time of reinfection but was discharged the next day. No deaths were recorded. Viral genome sequencing confirmed 4 reinfections of 12 cases with available genetic evidence. Reinfection risk was estimated at 0.02% (95% confidence interval [CI], .01%–.02%), and reinfection incidence rate was 0.36 (95% CI, .28–.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.

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 reexposure 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 reinfection. This is a poorly understood feature of SARS-CoV-2 epidemiology, and its 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

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stringent criteria for assessing reinfection. We further performed viral genome sequencing to confirm the reinfections.

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 28 February 2020–12 August 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, Germantown, Maryland, USA) and tested with real-time reverse-transcription quantitative PCR (RT-qPCR) using the TaqPath COVID-19 Combo Kit (100% sensitivity and specificity [18]; Thermo Fisher Scientific, Waltham, Massachussets, USA) on ABI 7500 FAST (Thermo Fisher, Waltham, Massachussets, USA), extracted using a custom protocol [19] on Hamilton Microlab STAR (Hamilton, Reno, Nevada, USA) and tested using AccuPower SARS-CoV-2 real-time RT-PCR Kit (100% sensitivity and specificity [20]; Bioneer, Daejeon, Korea) on ABI 7500 FAST or loaded directly to the Roche Cobas 6800 system and assayed with the Cobas SARS-CoV-2 test (95% sensitivity, 100% specificity [21]; Roche Basel, Switzerland). The first assay targets the virus's *S, N,* and *ORF1ab* regions, the second targets the virus's *RdRp* and *E* gene regions, and the third targets the *ORF1ab* and *E* gene regions.

Serological testing was performed using the 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 that represents 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 1 PCR-positive swab that was ≥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 nonviable virus fragments) rather than reinfection and thus should not be included in analysis.

Suspected Reinfection Case Classification

Suspected cases of reinfection, that is, cases that fit the above-indicated inclusion criteria, were classified as showing 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 that supported 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 the time interval between repeated swabs was not short (to exclude cases under clinical management that are indicative of poor control of first infection).

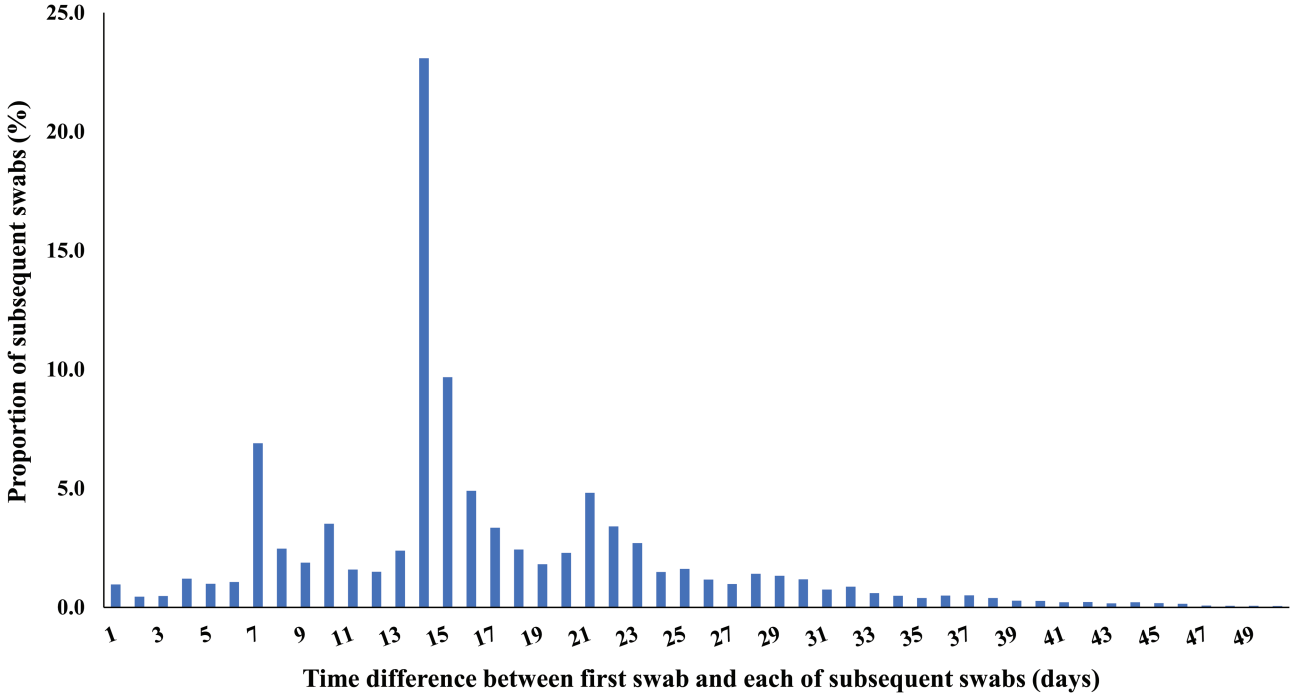

Figure 1. Distribution of the time difference between the first swab and subsequent swabs among all laboratory-confirmed severe acute respiratory syndrome coronavirus 2 cases with more than 1 positive swab. The cutoff of 45 days was at the 99th percentile and thus provides an appropriate mark for defining the end of the prolonged polymerase chain reaction positivity.

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 or 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 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 is that hospitalized COVID-19 cases often had multiple subsequent swabs administered as part of clinical care. Repeated swabbing was standard earlier in the epidemic, as the criteria for discharge from an isolation facility required at least 2 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. The 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 the 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 that is prone to overestimate risk of documented reinfection, several sensitivity analyses were conducted to implement more stringent criteria for assessing reinfection. This included excluding 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-positive cases), changing the ≥45-day cutoff to a ≥60-day cutoff to further exclude potential cases of long-term prolonged PCR positivity, and (most stringent) setting the definition of recent active infection at a 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 the Supplementary Materials.

Box 1. Classification of suspected cases of severe acute respiratory syndrome coronavirus 2 reinfection based on the strength of supporting epidemiological evidence

Suspected cases of severe acute respiratory syndrome coronavirus 2 reinfection: all laboratory-confirmed cases with at least 1 polymerase chain reaction (PCR)–positive swab that was ≥45 days after a first positive swab.

Strong evidence for reinfection: individuals having positive swabs with a 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 (WHO) disease classifications.

Good evidence for reinfection: individuals having positive swabs with a 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 with 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 WHO disease classifications.

Some evidence for reinfection: individuals having positive swabs with a 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 a 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 WHO disease classifications).

Ethical Approval

The HMC and Weill Cornell Medicine–Qatar institutional review boards approved the study.

RESULTS

Epidemiological Analysis

Figure 2 illustrates the selection process of SARS-CoV-2 eligible cases and summarizes the results of their reinfection status evaluation. Of 133 266 laboratory-confirmed cases, 117 458 had only a 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 1 subsequent positive swab that was ≥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.

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 that showed strong or good evidence for reinfection were hospitalized at any time. However, all but 1 occurred following the primary infection; only 1 hospitalization occurred at the 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 1 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, the vast majority of infections in Qatar occurred in young, healthy men and were of low severity [6, 12].

Antibody test results were available for 48 of the 243 assessed individuals (Supplementary Table 1), of whom 30 (62.5%) had detectable antibodies. Of the 13 with strong evidence for reinfection and available antibody results, 7 (53.9%) were seronegative. Both individuals with good evidence for reinfection, 3 of the 4 individuals with some evidence for reinfection, and 19 of the 29 individuals with weak evidence for reinfection were seropositive.

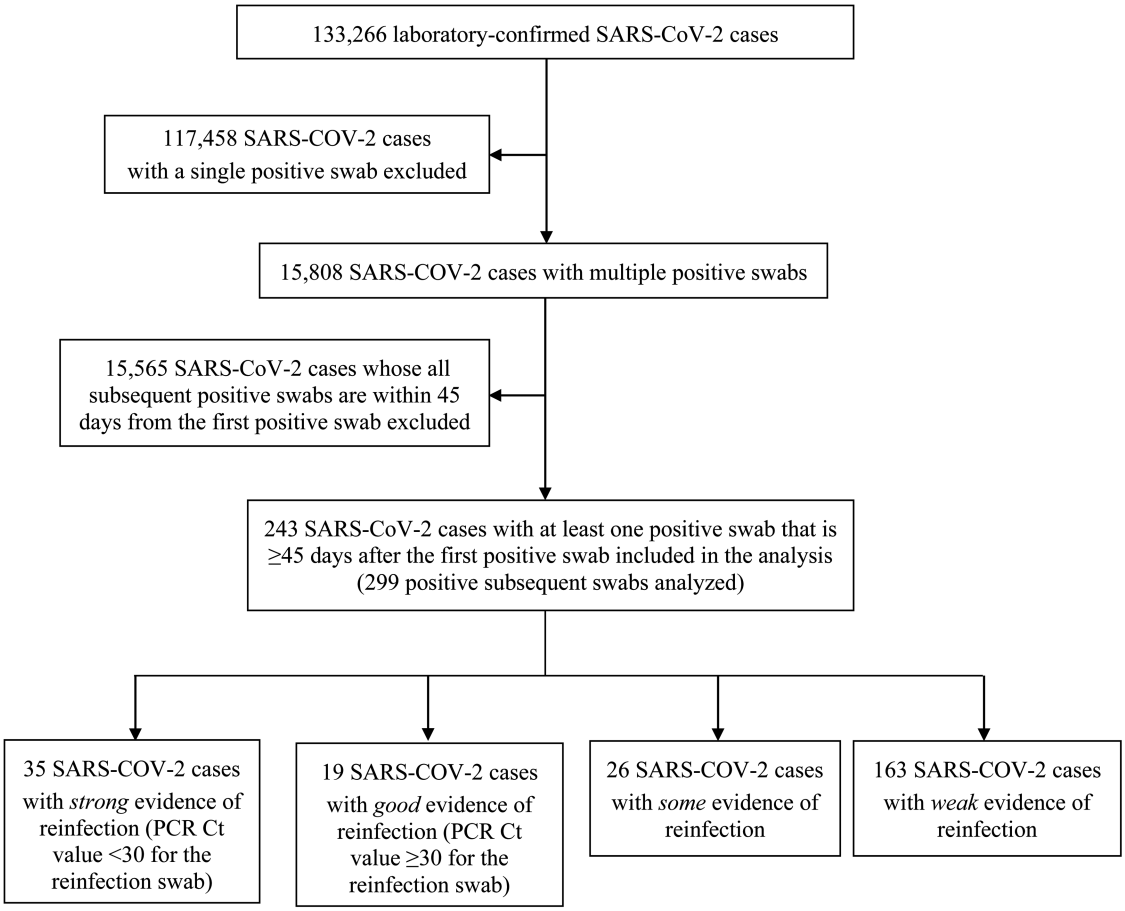

Figure 2. Flow chart describing the selection process of SARS-CoV-2 eligible cases and summarizing the results of their reinfection status evaluation. Abbreviations: Ct, cycle threshold; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Risk of documented reinfection was estimated at 0.05% (95% confidence interval [CI], .04%–.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). The incidence rate of reinfection was estimated at 1.09 (95% CI, .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 2. In these analyses, the estimate for the risk of reinfection was between 0.02% (95% CI, .01–.03) and 0.03% (95% CI, .02–.04), while that for the incidence rate of reinfection was between 0.38 (95% CI, .24–.60) and 1.06 (95% CI, .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 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 1 and 2 show the detailed analysis for each genome pair.

There was insufficient evidence to warrant interpretation for 11 pairs because of low genome quality. For 6 pairs, there were 1 to several changes of allele frequency indicative, at best, of a shifting balance of quasi-species and thus no evidence for reinfection. For 2 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 2 cases were also seropositive (Table 1).

For 2 pairs, there was conclusive evidence for reinfection with multiple changes of allele frequency and presence of the D614G mutation (23403bp A>G), which is a variant that appeared and expanded replacing the original D614 form [27, 28]. Although 1 of the genomes was of inferior quality, for 2 pairs there was sufficient evidence for differences, including the presence of the D614G mutation, thereby rendering evidence for reinfection. Three of these 4 cases

Table 1. Characteristics of Individuals Classified as Showing Strong or Good Evidence for Reinfection

Sociodemographic			PCR Testing				Hospitalization			Ab Testing	
ID	Sex	Age Group (years)	Sample Type	PCR Swab Date	Positive Swab Type	Average Cycle Threshold Value	Case Severity[a]	Hospital Admission[b]	Length of Stay (days)	Ab Test Date	Ab Status
Strong evidence for reinfection											
1	Male	50–54	Survey[c]	14 May	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	50–54	Survey[c]	23 July	Reinfection swab	14	Not assessed[d]	Not hospitalized	0	26 July	Negative
2	Male	30–34	Health facility	16 June	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Health facility	10 August	Reinfection swab	16	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
3	Male	30–34	Contact tracing	2 April	First positive swab	Unknown	Not assessed[d]	7 April	1	Not tested	Unknown
	Male	30–34	Survey[c]	26 June	Reinfection swab	17	Not assessed[d]	Not hospitalized	0	27 June	Negative
4	Male	25–29	Health facility	30 April	First positive swab	33	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Health facility	15 July	Reinfection swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
5	Male	35–39	Contact tracing	31 March	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Health facility	20 April	Subsequent positive swab	24	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Health facility	7 August	Reinfection swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
6	Female	50–54	Contact tracing	4 June	First positive swab	34	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	50–54	Health facility	27 July	Reinfection swab	17	Not assessed[d]	Not hospitalized	0	14 July	Negative
7	Female	20–24	Health facility	26 April	First positive swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	20–24	Health facility	19 July	Reinfection swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
8	Male	30–34	Health facility	5 June	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Contact tracing	4 August	Reinfection swab	18	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
9	Male	20–24	Contact tracing	3 April	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Health facility	9 July	Reinfection swab	18	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
10	Female	20–24	Health facility	24 March	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	20–24	Contact tracing	23 June	Reinfection swab	19	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
11	Male	35–39	Contact tracing	30 March	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Contact tracing	24 June	Reinfection swab	19	Not assessed[d]	Not hospitalized	0	19 July	Positive
12	Female	45–49	Health facility	28 May	First positive swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	45–49	Health facility	10 August	Reinfection swab	20	Not assessed[d]	Not hospitalized	0	4 June	Negative
13	Male	30–34	Contact tracing	3 April	First positive swab	Unknown	Not assessed[d]	6–7 April	1	Not tested	Unknown
	Male	30–34	Survey[c]	15 July	Reinfection swab	20	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
14	Female	40–44	Contact tracing	12 June	First positive swab	24	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	40–44	Health facility	8 August	Reinfection swab	21	Not assessed[d]	Not hospitalized	0	3 July	Positive
15	Male	50–54	Contact tracing	22 April	First positive swab	34	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	50–54	Contact tracing	23 July	Reinfection swab	21	Not assessed[d]	Not hospitalized	0	22 July	Negative
16	Male	25–29	Health facility	9 March	First positive swab	Unknown	Not assessed[d]	9–14 March[b]	5	Not tested	Unknown
	Male	25–29	Contact tracing	21 May	Reinfection swab	21	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
17	Male	20–24	Health facility	15 May	First positive swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Health facility	12 August	Reinfection swab	22	Not assessed[d]	13 August	1	Not tested	Unknown
18	Female	20–24	Health facility	23 May	First positive swab	33	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Female	20–24	Health facility	7 August	Reinfection swab	22	Not assessed[d]	Not hospitalized	0	2 August	Negative
19	Male	40–44	Health facility	3 June	First positive swab	23	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	7 August	Reinfection swab	23	Not assessed[d]	Not hospitalized	0	13 July	Positive
20	Female	45–49	Health facility	2 May	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown

Table 1. Continued

Sociodemographic			PCR Testing				Hospitalization			Ab Testing	
ID	Sex	Age Group (years)	Sample Type	PCR Swab Date	Positive Swab Type	Average Cycle Threshold Value	Case Severity[a]	Hospital Admission[b]	Length of Stay (days)	Ab Test Date	Ab Status
	Female	45–49	Health facility	29 July	Reinfection swab	25	Not assessed[d]	Not hospitalized	0	30 July	Negative
21	Male	30–34	Survey[c]	12 May	First positive swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Survey[c]	27 July	Reinfection swab	25	Not assessed[d]	Not hospitalized	0	28 July	Positive
22	Male	20–24	Health facility	31 May	First positive swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Health facility	5 August	Reinfection swab	26	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
23	Male	20–24	Health facility	16 June	First positive swab	31	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Contact tracing	11 August	Reinfection swab	27	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
24	Male	35–39	Health facility	8 June	First positive swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Health facility	3 August	Reinfection swab	27	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
25	Male	40–44	Health facility	28 May	First positive swab	21	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Contact tracing	30 July	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
26	Male	40–44	Survey[c]	22 April	First positive swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	6 May	Subs positive swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	14 May	Subsequent positive swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Survey[c]	12 June	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
27	Male	25–29	Health facility	25 April	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Health facility	10 June	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
28	Male	40–44	Health facility	11 March	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Contact tracing	8 June	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	10 July	Positive
29	Male	30–34	Survey[c]	12 May	First positive swab	21	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Survey[c]	30 June	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
30	Male	15–19	Health facility	5 June	First positive swab	20	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	15–19	Health facility	8 August	Reinfection swab	28	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
31	Male	35–39	Health facility	25 April	First positive swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Survey[c]	22 June	Reinfection swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
32	Male	35–39	Survey[c]	12 May	First positive swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Survey[c]	30 June	Reinfection swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
33	Male	40–44	Health facility	26 April	First positive swab	17	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	6 July	Reinfection swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
34	Male	40–44	Health facility	11 May	First positive swab	33	Not assessed[d]	14 May	1	Not tested	Unknown
	Male	40–44	Contact tracing	28 July	Reinfection swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
35	Male	35–39	Health facility	17 May	First positive swab	25	Not assessed[d]	31 May-1 June	2	Not tested	Unknown
	Male	35–39	Health facility	20 July	Reinfection swab	29	Not assessed[d]	Not hospitalized	0	26 July	Positive
Good evidence for reinfection											
36	Male	30–34	Health facility	30 April	First positive swab	22	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Contact tracing	26 June	Reinfection swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
37	Male	40–44	Health facility	4 May	First positive swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	11 July	Reinfection swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
38	Male	25–29	Health facility	2 June	First positive swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Contact tracing	4 August	Reinfection swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
39	Male	20–24	Survey[c]	6 May	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown

Table 1. Continued

Sociodemographic			PCR Testing				Hospitalization			Ab Testing	
ID	Sex	Age Group (years)	Sample Type	PCR Swab Date	Positive Swab Type	Average Cycle Threshold Value	Case Severity[a]	Hospital Admission[b]	Length of Stay (days)	Ab Test Date	Ab Status
	Male	20–24	Survey[c]	10 May	Subsequent positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Survey[c]	20 May	Subsequent positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Survey[c]	30 June	Reinfection swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
40	Male	55–59	Health facility	10 March	First positive swab	Unknown	Mild	14–20 March[b]	7	Not tested	Unknown
	Male	55–59	Health facility	3 June	Reinfection swab	31	Not assessed[d]	Not hospitalized	0	22 July	Positive
41	Male	30–34	Survey[c]	23 April	First positive swab	26	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Health facility	7 May	Subsequent positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Survey[c]	12 June	Reinfection swab	31	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
42	Male	15–19	Health facility	10 April	First positive swab	33	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	15–19	Health facility	26 May	Reinfection swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
43	Male	15–19	Health facility	9 March	First positive swab	Unknown	Not assessed[d]	16–23 March[b]	8	Not tested	Unknown
	Male	15–19	Contact tracing	26 May	Reinfection swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
44	Male	25–29	Survey[c]	26 April	First positive swab	30	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Survey[c]	16 May	Subsequent positive swab	34	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Survey[c]	20 June	Reinfection swab	32	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
45	Male	25–29	Contact tracing	26 April	First positive swab	29	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	25–29	Contact tracing	23 June	Reinfection swab	33	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
46	Male	20–24	Health facility	23 April	First positive swab	20	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Contact tracing	20 June	Reinfection swab	34	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
47	Male	20–24	Survey[c]	29 April	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	20–24	Survey[c]	20 June	Reinfection swab	34	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
48	Male	35–39	Health facility	8 April	First positive swab	20	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	35–39	Health facility	16 June	Reinfection swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
49	Male	40–44	Survey[c]	6 April	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	40–44	Health facility	4 June	Reinfection swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
50	Male	50–54	Contact tracing	20 April	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	50–54	Contact tracing	11 June	Reinfection swab	35	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
51	Male	45–49	Health facility	21 April	First positive swab	37	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	45–49	Survey[c]	19 June	Reinfection swab	36	Not assessed[d]	Not hospitalized	0	2 August	Positive
52	Male	30–34	Contact tracing	29 March	First positive swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Survey[c]	15 June	Reinfection swab	37	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
53	Male	30–34	Contact tracing	20 April	First positive swab	36	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
	Male	30–34	Contact tracing	4 June	Reinfection swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown
54	Male	20–24	Health facility	11 April	First positive swab	27	Not assessed[d]	14–30 April[b]	17	Not tested	Unknown
	Male	20–24	Health facility	26 April	Subsequent positive swab	36	Not assessed[d]	Inpatient	--	Not tested	Unknown
	Male	20–24	Survey[c]	24 June	Reinfection swab	Unknown	Not assessed[d]	Not hospitalized	0	Not tested	Unknown

Individuals with ID numbers 20, 27, 33, and 44 were confirmed as reinfection cases by viral genome sequencing.

Abbreviations: Ab, antibody; PCR, polymerase chain reaction.

[a]Severity classification per World Health Organization 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.

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

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

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

Table 2. Results of Reinfection Confirmatory Analysis

Viral Genome Sequencing Evidence for Reinfection	Indication Upon Comparing Each Genome Pair	N
Insufficient evidence to warrant interpretation	One or 2 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

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.

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). The antibody test result was available for 1 case at the time of reinfection, and the individual was seronegative.

In summary, for the 12 cases where viral genome sequencing evidence was available, 4 cases were confirmed as reinfections,

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.

Figure 3. Viral genome sequencing analysis of the paired viral specimens of the first positive and reinfection swabs for the 6 patients with conclusive or supporting evidence for reinfection or no reinfection.

a confirmation rate of 33.3%. Applying this rate to the above-estimated reinfection metrics yielded a risk of documented reinfection of 0.02% (95% CI, .01%–.02%) and incidence rate of reinfection of 0.36 (95% CI, .28–.47) per 10 000 person-weeks.

DISCUSSION

Using several analyses and sensitivity analyses, our results indicate conclusive evidence for the presence of reinfections in the SARS-CoV-2 epidemic in 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 20 May 2020 [6], it is all but certain that a significant proportion of the population has been repeatedly exposed to the infection, but such reexposures did not lead to any documentable reinfections.

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 develop immunity against reinfection that lasts for at least a 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 2559 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 more than 3 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. 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 who were antibody-positive had a prior documented laboratory-confirmed infection [9], suggesting that undocumented infections (or reinfections) could possibly be 10-fold higher than documented infections (or reinfections). This finding indicates that the incidence rate of both documented and undocumented reinfections may add up to approximately 10 per 10 000 person-weeks. 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 approximately 200 per 10 000 person-weeks [8]. Comparison of these incidence rates suggests 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 available for a small number of cases, limiting use and inferences of the link between antibody status and risk of reinfection. It is of note that for 1 of the genetically confirmed reinfections, the antibody test result was available but was seronegative (Table 1), as with 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. L. J. A. conceived and codesigned the study and led the statistical analyses. H. C. codesigned the study, performed the data analyses, and wrote the first draft of the manuscript. J. A. M. led the viral genome sequencing analyses, and A. A. A., Y. A. M., and S. Y. conducted these analyses. All authors contributed to data collection and acquisition, database development, discussion and interpretation of the results, and writing of the manuscript. All authors read and approved the final manuscript.

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