



The Importance and Challenges of Identifying SARS-CoV-2 Reinfections

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ABSTRACT Reports of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection have raised important questions about the strength and durability of the immune response to primary infection, which are key factors in predicting the course of the pandemic. Identifying reinfection requires detecting the virus at two different time points and using viral genomic data to distinguish reinfection from persistent viral carriage. This process is hindered by challenges of logistics and capacity, such as banking samples from primary infection and performing viral genome sequencing. These challenges may help to explain why very few cases have been described to date. In addition, reinfection may be a rare phenomenon, but detailed prospective studies are needed to rigorously assess its frequency. To provide context for future investigations of SARS-CoV-2 reinfection, we review 16 cases that have been published to date or are available in preprint. Reinfection occurred across demographic spectra and in patients whose initial infections were both asymptomatic/mild and moderate/severe. For cases in which severity could be compared between episodes, half of reinfections were less severe, raising the possibility of partial immune protection. Although many patients had a positive total immunoglobulin or IgG result at the time of reinfection, very little examination of their immune response was performed. Further work is needed to elucidate the frequency, determinants, and consequences of SARS-CoV-2 reinfection. Establishing the necessary frameworks for surveillance and investigation will rely heavily on clinical laboratories and clinical investigators, and we propose several considerations to guide the medical community in identifying and characterizing SARS-CoV-2 reinfections.

KEYWORDS reinfection, COVID-19, SARS-CoV-2, viral immunity

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has had profound effects not only on human health but also on the collective mental well-being, social fabric, and economy of communities across the globe. There have been more than 64 million cases and 1.4 million deaths globally as of 2 December 2020 (1). While a highly susceptible population is assumed to be a key factor responsible for the explosiveness of the pandemic, one of the main questions in predicting its course is how well and for how long the immune response to an initial SARS-CoV-2 infection protects from reinfection.

On 25 August, the first case of reinfection by a phylogenetically distinct variant of SARS-CoV-2 was reported in the medical literature (2) and was rapidly followed by additional cases across the globe (3–8). These cases have garnered considerable media and academic attention (9) because they indicate that infection by SARS-CoV-2 does not uniformly confer protective immunity to all individuals. They raise several critical questions. Is SARS-CoV-2 reinfection a widespread phenomenon or is it limited to a small number of individuals who may have immune deficits? Does reinfection indicate that the natural immune response to SARS-CoV-2 is too weak, too short, or too narrow to protect against subsequent exposure? What are the clinical consequences for

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patients who experience reinfection, and to what extent might reinfection contribute to forward transmission? Understanding the frequency, determinants, and consequences of SARS-CoV-2 reinfection is essential to predicting the course of the COVID-19 pandemic, gaining important insight into the pathophysiology of this new disease, and guiding ongoing vaccine development efforts. However, there are considerable logistic challenges to identifying reinfection cases. Here, we review emerging data and concepts regarding SARS-CoV-2 reinfection, highlight important knowledge gaps, and offer suggestions for future surveillance and investigation.

CHALLENGES IN DETECTING SARS-CoV-2 REINFECTION

Identification of SARS-CoV-2 reinfection currently relies upon molecular detection of the virus at two different time points, often with intervening negative tests, as well as viral genetic sequencing data to support reinfection rather than persistent viral carriage. Because of the limited availability of routine sequencing capabilities at hospital and public health laboratories, clinical and laboratory criteria must be used to prioritize suspected reinfection cases for detailed investigation. Recently, the Centers for Disease Control and Prevention (CDC) released a guidance protocol designed to support public health laboratory investigation into suspected SARS-CoV-2 reinfections (10). This guidance defines epidemiological criteria for suspected reinfections, as well as cycle threshold (C_T) value cutoffs and sequencing parameters (Fig. 1). Specifically, investigative criteria include a positive real-time reverse transcription-PCR (RT-PCR) test more than 90 days after the initial test (with C_T of <33) or a positive RT-PCR test more than 45 days after the initial test (with C_T of <33) that is accompanied by compatible symptoms or epidemiological exposure.

These guidelines help address one of the most important challenges in identifying reinfections, which is accounting for the fact that RT-PCR test positivity can persist for weeks following the resolution of clinical symptoms (11–13). A meta-analysis of 43 studies and 3,229 individuals (excluding case reports and case series with fewer than 5 patients) found the mean duration between first and last positive RT-PCR test to be 17 days, with a maximum duration of 83 days (14). Our experience in the Emory Healthcare system between 15 March 2020 and November 2020 is consistent with this. Of 22,443 unique patients who had at least two tests each (for a total of 51,134 tests), 456 patients had at least 2 positive tests. The median (interquartile range [IQR]) duration between first and last positive test was 19 days (12, 15), and durations of 45 and 90 days represented the 88th and 97th percentiles, respectively. Applying the CDC investigative criteria would thus identify 58 cases of potential reinfection in our system, a tractable number to study, assuming that all initial samples and clinical data are available for investigation. An important caveat to the investigative criteria is that they likely do not apply to immunocompromised individuals, who can have prolonged virus replication (16). In addition, imposing a cutoff C_T of <33 may miss cases in which partial immune protection leads to lower viral loads during reinfection, though this cutoff is sensible in selecting cases for which viral genome sequencing is likely to be successful.

The second challenge addressed by CDC guidance is how to use viral genome sequencing to distinguish reinfection from within-patient virus evolution. Compared to many RNA viruses, SARS-CoV-2 has a relatively stable genome due to inherent proof-reading activity by a 3'-to-5' exoribonuclease (17). Because there is limited viral diversity, reinfection is considered confirmed when the viruses from the first and second infections are different enough to belong to different clades (18) or lineages (19) or when they differ by more than 2 substitutions per month, which is the general population-level viral substitution rate as assessed by multiple studies (10). This comparison is dependent on the availability of isolates from both the first and second infections, which can only be achieved through extensive biobanking during primary infection. Of note, these criteria may miss cases of reinfection by closely related viruses, which would have important implications for understanding natural immunity to SARS-CoV-2.

CDC Protocol for Investigating Suspected SARS-CoV-2 Reinfection

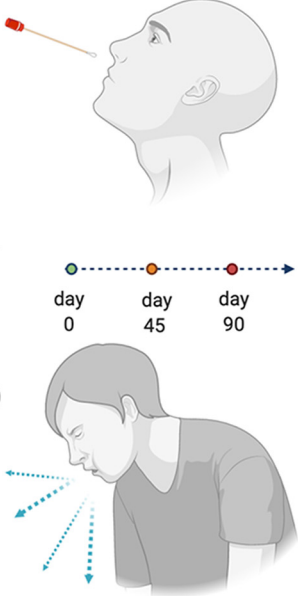
Investigative Criteria:

1- Duration since previous positive test **>90 days** & cycle threshold value **<33 (tier one)**

OR

2- Duration since previous positive test **45-89 days** & cycle threshold value **<33 (tier two)** **AND**

Symptoms typical of COVID-19 or close contact with a confirmed case



Laboratory Evidence *

Observation of different clades between the first and second infection

AND/OR

Detection of **>2 nucleotide differences** for every month separating the first and second samples.

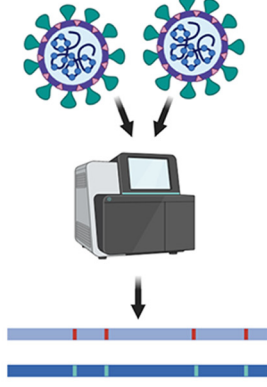


FIG 1 Centers for Diseases Control and Prevention investigation protocol for investigating suspected SARS-CoV-2 reinfection (10). Figure created using BioRender. * CDC also defined poor evidence but possible category as ≤ 2 nucleotide differences per month in consensus between sequences that meet quality metrics or > 2 nucleotide differences per month in consensus between sequences that do not meet the quality metrics, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for subgenomic mRNA [sgmRNA] and culture). COVID-19, coronavirus disease 2019.

PUBLISHED CASES OF SARS-CoV-2 REINFECTION

To synthesize lessons from the cases of SARS-CoV-2 reinfection that have been described to date, we searched MEDLINE, EMBASE, and preprint servers (MedRxiv, BioRxiv, and SSRN) on 15 November 2020 for reports of SARS-CoV-2 reinfection, using

keywords “reinfection,” “re-infection,” “SARS-CoV-2,” and “secondary infection.” We restricted our search to publications in English and limited our review to those confirmed by viral genome sequencing and analysis (Table 1). At the time of the search, there were 16 reported cases of reinfection confirmed by sequencing, 10 of which were in preprint (3, 4, 6–8, 20–24).

Demographic and clinical features of reinfection cases. Reinfection occurred across demographic spectra; half of the patients (50% [8/16]) were between 20 and 30 years old. Gender was reported in 15 cases, among which 11 patients (73%) were male and four (27%) were female. Eight cases (50%) occurred among high-risk groups, including 7 health care workers (HCWs) (4, 7, 22) and 1 nursing home resident (8). While a publication and detection bias may exist for high-risk groups due to increased scrutiny and access to testing, these groups also have a higher burden of exposure for potential reinfection.

Notably, reinfection occurred among patients whose initial infections were both asymptomatic/mild (75% [9/12]) and moderate/severe (25% [3/12]) (25). The demonstration that moderate/severe initial infections do not necessarily provide enhanced protection against reinfection is important because patients with more severe infection have been found to have higher neutralizing antibody titers (26), which may be expected to confer protection.

Also of note, the severity of the reinfection episode itself was asymptomatic/mild in 12 cases (75%) and moderate/severe in 4 cases (25%). Among cases in which severity could be compared across episodes ($n = 12$), half of the patients had less-severe disease during the second infection. The observation that many reinfection cases were less severe than initial cases is interesting because it may suggest partial protection from disease and argues against antibody-dependent immune enhancement, which can be seen with other viral pathogens (27). In the absence of routine surveillance, we would have expected a bias toward detection of symptomatic reinfection, underscoring the importance of prospective screening. Ultimately, increased efforts toward detection and clinical characterization of reinfection will allow a better understanding of its clinical consequences, including the potential impact of repeat infection on long-term outcomes such as “long COVID” (28).

SARS-CoV-2 viral loads in reinfection cases. The SARS-CoV-2 RT-PCR C_T value is a metric that may not only help identify reinfection cases, but also provide information about their clinical and public health implications. C_T value is dependent on sample type (29), severity of infection (30), date of collection relative to symptom onset (15), and assay and platform used (31) and hence may not always be comparable across episodes (32). However, a low or lower C_T value, obtained in the same laboratory with the same method, may provide supporting evidence for reinfection versus persistent viral carriage. Among the 16 published reinfection cases, 14 reported SARS-CoV-2 RT-PCR C_T values at the time of second infection. The median (range) C_T value was 27.3 (16.0 to 39.6), which was similar to the median (range) C_T value at initial infection, 32.5 (17.0 to 38.0).

Beyond a single C_T measurement, serial testing during the initial phase of a suspected reinfection to assess the C_T value trajectory may be informative. This approach was evaluated in a recent study of patients with primary infection, among whom a decreasing C_T over 2 days was found to provide strong evidence of acute infection (33); a similar evaluation may distinguish reinfection from prolonged viral carriage. Another potentially useful test is the detection of subgenomic RNAs, which are transcripts generated during the viral life cycle as the templates for protein synthesis but which are not carried in the viral particle along with genomic RNA. In several studies, detection of subgenomic RNA has been adopted as a surrogate for active replication (34, 35); however, subgenomic RNA has also been detected late in the clinical course and correlated poorly with viral culture, perhaps due to persistence in cellular vesicles (36). If serial C_T testing and/or subgenomic RNA detection prove to be useful markers of reinfection, they may allow detection of reinfections even when isolates from the primary infection are not available for comparative genome sequencing.

TABLE 1 Features of reported SARS-CoV-2 reinfections^a

Authors (reference)	Country	Duration between infections (days or mo)	Initial infection severity (C _T value)	Negative intermittent RT-PCR testing (day[s])	Genomic feature(s)		Reinfection severity (C _T value)	Reinfection (C _T value)	Serology results ^b
					Infection	Reinfection ^c			
Tillett et al. (3)	US (NV)	48	Mild (35.2)	Yes (38)	Clade 20C	Clade 20C	Severe (35.3)	Clade 20C; 7 SNVs compared to reference not seen in initial infection strain	Roche Elecsys anti-SARS-CoV-2 IgM/IgG positive on day 8 of reinfection
To et al. (2)	China (Hong Kong)	142	Mild (NA)	Yes (20)	Clade 19A	Clade 20A	Asymptomatic (26.7)	Clade 20A	Abbott SARS-CoV-2 negative on day 1 of reinfection then positive on day 5
Goldman et al. (8) ^d	US (WA)	140	Severe (26.5)	Yes (39, 40)	Clade 19B	Clade 20A	Severe (39.6)	Clade 20A	Abbott SARS-CoV-2 negative on day 1 of reinfection then positive on day 5 RBD, spike and NC IgG, spike IgM, spike and NC IgA positive on day 14 of reinfection; nAbs detected on days 14 and 42 of reinfection
Gupta et al. (4) Case 1 Case 2	India India	108 111	Asymptomatic (36) Asymptomatic (28.2)	Yes (8) Yes (10)	NA NA	NA NA	Asymptomatic (16.6) Asymptomatic (16.9)	9 SNVs compared to initial infection 10 SNVs compared to initial infection	NA NA
Larson et al. (7)	US (VA)	64	Moderate (NA)	NA	Partial genome obtained ^e	Lineage B.1.26; several potential variations and one high-confidence infection, including D614G	Severe (NA)	Lineage B.1.26; several potential variations and one high-confidence infection, including D614G	Spike IgG positive on day 8 of reinfection
Van Elslande et al. (24)	Belgium	3 mo	Moderate (25.6)	NA	Lineage B.1.1	Lineage B.1.1	Mild (32.6)	Lineage B.1.1	Roche nucleocapsid IgG positive on day 7 of reinfection
Prado-Vivar et al. (21) ^d	Ecuador	63	Mild (36.9)	Yes (21)	Clade 20A	Clade 20A	Moderate (NA)	Clade 19 B	IgM positive, IgG negative on day 7 of initial infection; IgM and IgG positive on day 28 of reinfection
Shastri et al. (22) ^d Case 1	India	66	Mild (32)	Yes (4)	Lineage B.1	Lineage B.1	Mild (25)	Lineage B	Abbott anti-NC IgG negative on day 5 of reinfection
Case 2	India	65	Asymptomatic (33)	Yes (3)	Lineage B.1.1	Lineage B.1.1	Mild (36)	Lineage B.1.1; 7 SNVs in initial strain compared to reference not present in reinfection strain, including D614G	Abbott NC IgG negative on day 7 of reinfection
Case 3	India	19	Asymptomatic (36)	Yes (2)	Lineage B.1.1	Lineage B.1.1	Mild (21)	Lineage B.1.1; 5 SNVs compared to reference not present in initial infection strain, including D614G	NA
Case 4	India	55	Mild (32)	NA	Lineage B.1.1	Lineage B.1.1	Mild (17)	Lineage B.1.1; 8 SNVs compared to reference not present in initial infection strain, including D614G	Roche NC total antibody negative on day 20 of reinfection
Abu-Raddad et al. (23) ^d Case 1	Qatar	46	Asymptomatic/ mild (36)	NA	NA	NA	Asymptomatic/ mild (28)	9 SNVs compared to initial infection strain, including D614G	NA
Case 2	Qatar	71	Asymptomatic/ mild (17)	NA	NA	NA	Asymptomatic/ mild (29)	11 SNVs compared to initial infection strain, including D614G	NA
Case 3	Qatar	88	Asymptomatic/ mild (36)	NA	NA	NA	Asymptomatic/ mild (25)	Partial genome obtained; 3 SNVs compared to initial strain, including D614G ^e	Roche Elecsys anti-SARS-CoV-2 negative at time of reinfection
Case 4	Qatar	55	Asymptomatic/ mild (30)	NA	Partial genome obtained ^e	Partial genome obtained ^e	Asymptomatic/ mild (32)	1 SNV compared to initial infection strain, including D614G	NA

^aC_T, cycle threshold; NA, not available; nAbs, neutralizing antibodies; NC, nucleocapsid; RBD, receptor binding domain; RT-PCR, reverse transcription-PCR; SNV, single nucleotide variant.

^bSerology results reported relative to the day of symptom onset if reported; if not reported or patient asymptomatic, then serology results relative to day of RT-PCR testing.

^cSNVs reported if infection and reinfection strain from same clade (18)/lineage (19).

^dPreprint study.

^eOne of the genomes reported was of low quality.

Assessing the C_T value during reinfection may also provide information regarding the public health implications of infection. The ability to culture virus (which is itself an imperfect marker of infectiousness) has been linked to C_T value, and most culture-positive samples have C_T values in the mid-20s (37, 38). Among the 16 described reinfection cases, 8 had C_T values of less than 28 and 6 had C_T values of less than or equal to 25, suggesting they may have been infectious and a potential source of transmission (37). While viral culture was only attempted in one of the cases (7) to assess potential infectiousness, some information may be derived from a population level assessment of previously infected residents of Wuhan, China, in May 2020. Among 34,424 patients with a prior documented positive RT-PCR test, 107 tested positive again (after an unclear time interval). Although most of these samples likely reflected persistent test positivity, some may have been reinfections, and notably, virus culture was negative in all cases (39).

In the future, enhanced screening for reinfection will be facilitated by ongoing efforts to increase testing and diagnostic capacity and the availability of different platforms (40). A multitude of rapid antigen and real-time loop-mediated isothermal amplification (LAMP) tests are becoming increasingly available and should be integrated into reinfection surveillance algorithms given their anticipated widespread availability and their ability to capture those with the highest viral loads.

Genomic features of reinfection cases. The current gold standard for identifying reinfection is detection of a distinct virus by genome sequencing. Detection of reinfection is most straightforward when viruses belong to a different clade (18) or lineage (19), as this provides clear evidence of infection by a different virus. Among 16 published reinfection cases, 5 (31%) had a different clade or lineage detected between initial infection and reinfection. Eight (50%) were infected with the same clade but had differences of >2 substitutions/month between them, compatible with CDC criteria. Three cases (19%) had low-quality genome sequences but were found to harbor different D614G alleles between the initial and reinfection strains and, therefore, were considered to represent reinfection.

Given the challenge of detecting reinfection by closely related viruses, it is important to conduct further studies characterizing the within-host evolution of SARS-CoV-2 to better understand the diversity expected over time (41, 42). In addition, although reinfection is most apparent when viruses are different enough to distinguish by genome sequencing, it remains unclear whether these viral genomic differences play a causative role in reinfection. That is, does reinfection occur when viral genomic differences permit escape from an existing, but narrow, immune response to the initial infection? Answering this question will require detailed mapping of the relationship between virus substitutions and immune escape (43).

Immune features of reinfection cases. One of the most important questions about SARS-CoV-2 reinfections is whether they occur in the face of existing immune responses. Among the 16 described cases, the median (range) duration between the first and second infection was 66 (19 to 142) days, suggesting ample time for the development of neutralizing antibodies (44) and cellular immune responses (45). Ten cases reported results of serology testing at the time of the second infection, 6 of which had a positive total immunoglobulin (Ig) or IgG result. None of the patients had a known immunodeficient state. Beyond assessing IgG levels, very little examination of these patients' immune responses has been performed. In one case, neutralizing antibody levels were measured at the time of the second infection and were comparable to those observed after boosted vaccination (8). Further investigation of immune parameters in patients who experience reinfection is critical to understanding its implications for the future of the pandemic (46).

SARS-CoV-2 IMMUNITY AND ITS ROLE IN REINFECTION

The relatively small amount of data currently available from reinfection cases must be considered in the context of what is known about SARS-CoV-2 immunity more broadly. Protection against reinfection by viral pathogens is largely mediated by

adaptive immune memory, which has the long-term potential to maintain and reinforce pathogen-specific antibodies and effector cells (47). Adaptive immune responses to secondary antigen or pathogen exposures are more rapid and potent than primary responses and may substantially mitigate disease or prevent reinfection altogether, particularly via neutralizing or opsonizing antibodies (47, 48). Why this phenomenon is so highly effective and endures for decades for some pathogens (e.g., smallpox and measles) and is shorter lived for others (respiratory syncytial virus [RSV] and rotavirus) remains a fundamental question for immunologists and vaccinologists.

A growing body of literature describes features of the human immune response during asymptomatic, acute, and early convalescent SARS-CoV-2 infection. The vast majority of humans infected by SARS-CoV-2 generate virus-specific antibody responses, including neutralizing antibodies targeting the spike protein (in addition to other viral antigens). There is less population-level information on T cell responses, but several studies indicate SARS-CoV-2 infection consistently elicits CD8⁺ and CD4⁺ T cell responses (49, 50). Interestingly, up to 50% of people harbor preexisting SARS-CoV-2-reactive memory T cells (mostly CD4⁺ T cells) that have been primed via exposure to endemic CoVs (51). T cell immunity rarely if ever provides sterilizing immunity against infection or reinfection *per se*, but it can have beneficial effects, including more rapid viral clearance resulting in decreased disease severity or duration of infectiousness. Importantly, robust CD4⁺ T cells help may favor generation and maintenance of affinity-matured antibodies and memory B cell responses that mediate long-term protection. Finally, recent data indicate that SARS-CoV-2 infection may stimulate some innate immune signaling pathways differently or less strongly than other viral infections (52). It remains unclear what effect these early innate immune events will have on the quality and longevity of ensuing memory responses.

The immunologic determinants of protection against SARS-CoV-2 infection remain under investigation, but neutralizing antibodies are clearly the leading contender. Strong data from animal models indicate that the presence of neutralizing antibodies prevents infection and disease (such as lung pathology) and attenuates virus replication in airway epithelia (53, 54). Anecdotal evidence for protection from neutralizing antibodies was derived from an interesting natural experiment on a fishing vessel that suffered an outbreak with a very high attack rate (55). Three passengers known to have neutralizing antibodies to SARS-CoV-2 due to prior infection were spared, suggesting that neutralizing antibodies are very likely a key mediator of protective immunity to SARS-CoV-2. Samples for study of cellular immune responses were not available. Phase III vaccine studies will give a clearer picture of how neutralizing antibody levels correlate with protection in humans.

Despite evidence for protection from neutralizing antibodies, a major concern during the COVID-19 pandemic has been that protective immunity may be transient. This concern is largely driven by inconsistent findings regarding the duration of seropositivity. Some studies have emphasized “rapid (antibody) decay” (56), with large portions of a study population seroreverting within a few months. Others have found that antibody levels plateau (57) or are maintained at steady-state levels that are lower than initial peak responses (45). It is not clear to what extent these antibody trajectories will affect susceptibility to reinfection. Drawing inferences outside SARS-CoV-2 itself, the duration of protective immunity against seasonal CoVs ranges from a few months to a few years, with reinfections known to occur in that time frame. Detection of antibody responses to SARS and Middle East respiratory syndrome (MERS) also dissipates over approximately 3 to 5 years (58). Of note, animal CoVs are also known to cause reinfection, including in hosts with measurable antibodies (59). Collectively, this information suggests that it would not be surprising to find waning immunity and reversion to a SARS-CoV-2-susceptible state over months to years. To address this, it is critical to establish prospective studies that allow real-time capture of reinfection cases and intensive study of immunologic parameters before, during, and after the reinfection event. In addition, new tools measuring both humoral and cell-mediated immune responses

TABLE 2 Actionable suggestions for SARS-CoV-2 reinfection response

Category	Recommendation
Case definition implementation	Implementation of screening for reinfection based on readily available data points (i.e., laboratory and epidemiological variables) according to CDC guidance. Case definition should be periodically reviewed and updated based on emerging data.
Establishment of surveillance frameworks	Based on case definitions, surveillance systems should be constructed for the identification of reinfections and for prospective follow-up. Extensive biobanking from primary infections is necessary to confirm reinfections (through viral genome sequencing) and fully characterize immune parameters.
Prospective follow-up reinfection cases	To determine the individual clinical burden and public health implications, reinfection cases should be followed prospectively. Predefined clinical endpoints should be measured as well as contact tracing of reinfection patients.
Evaluation of the immunologic and virologic determinants of reinfection	Understanding immune kinetics immediately prior to and following natural reexposure will expand our understanding of correlates of protection and provide guidance for vaccine development and administration.

are needed to support the detailed widespread testing necessary for defining the future susceptibility of individuals to SARS-CoV-2 reinfection (60).

CONCLUSION

Identifying and studying SARS-CoV-2 reinfections will provide critical clinical and public health information for addressing the COVID-19 pandemic. Current data from published reinfection cases and studies of the immune response after initial SARS-CoV-2 infection raise the possibility that reinfection may be common. Prospective studies, including extensive biobanking of samples from primary infection, are necessary to elucidate the full determinants and consequences of reinfection. Establishing these frameworks will rely heavily on clinical laboratories and clinical investigators. We propose several actionable steps for the medical community to consider in the effort to identify, characterize, and contain the impact of SARS-CoV-2 reinfections (Table 2).

With positive results recently released from interim analyses of multiple phase III trials, continued study of reinfection cases as they relate to vaccine efficacy is of critical importance. For example, monitoring of patients for reinfection or postvaccination infection is necessary to assess whether viral escape mutations arise, requiring vaccine modification. This may be relatively simple to achieve given current vaccine constructs, such as mRNA vaccines, and proceed in a manner similar to the annual review and update of influenza vaccines. Ideally, studies of SARS-CoV-2 reinfection should be integrated into efforts to characterize vaccine-elicited immunity compared to that of natural infection, with the goal of developing safe vaccines and efficacious administration schedules that elicit robust and durable immune responses to curb the COVID-19 pandemic.

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