SARS-CoV-2 Reinfection Is a New Challenge for the Effectiveness of Global Vaccination Campaign: A Systematic Review of Cases Reported in Literature

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Abstract: Reinfection with SARS-CoV-2 seems to be a rare phenomenon. The objective of this study is to carry out a systematic search of literature on the SARS-CoV-2 reinfection in order to understand the success of the global vaccine campaigns. A systematic search was performed. Inclusion criteria included a positive RT-PCR test of more than 90 days after the initial test and the confirmed recovery or a positive RT-PCR test of more than 45 days after the initial test that is accompanied by compatible symptoms or epidemiological exposure, naturally after the confirmed recovery. Only 117 articles were included in the final review with 260 confirmed cases. The severity of the reinfection episode was more severe in 92/260 (35.3%) with death only in 14 cases. The observation that many reinfection cases were less severe than initial cases is interesting because it may suggest partial protection from disease. Another interesting line of data is the detection of different clades or lineages by genome sequencing between initial infection and reinfection in 52/260 cases (20%). The findings are useful and contribute towards the role of vaccination in response to the COVID-19 infections. Due to the reinfection cases with SARS-CoV-2, it is evident that the level of immunity is not 100% for all individuals. These data highlight how it is necessary to continue to observe all the prescriptions recently indicated in the literature in order to avoid new contagion for all people after healing from COVID-19 or becoming asymptomatic positive.

Keywords: coronavirus; reinfection; COVID-19; SARS-CoV-2; systematic review

1. Introduction

The novel coronavirus (SARS-CoV-2) outbreak since December 2019 has continued to exhibit devastating consequences, and was declared as a pandemic by the World Health Organization in early 2020 [1–3]. To date, as of 17 October 2021, 240,421,359 infections have been confirmed, with 4,895,034 deaths [4]. In many countries, the vaccination campaign has started with the use of various vaccines recently put on the market and the total number of vaccine doses administered is 6,609,632,994. However, a new problem is emerging with regard to the evolution of the behavior of SARS-CoV-2: the possibility of reinfection of healed subjects after the first infection. On 25 August 2020, the first case of reinfection of SARS-CoV-2 was reported in international literature [5]. This event pointed out that infection by this virus does not uniformly confer protective immunity to all infected individuals [6]. Therefore, several critical questions are intriguing the researchers. Is SARS-CoV-2 reinfection a widespread phenomenon or is it limited to few subjects with immune deficits or specific comorbidities [6]? Can this phenomenon be due to a too weak, too short, or too narrow natural immune response to SARS-CoV-2, that is unable to protect...
from subsequent exposure [6]? What is the clinical behavior, in regard to the evolution of the reinfections? Can these reinfected patients transmit the viruses? This important problem needs to be addressed, because the possibility of reinfection could drastically reduce the effectiveness of the vaccination campaigns in progress. Protective, sustainable and long-lasting immunity following COVID-19 infection is uncertain, but it is essential for the efficacy of vaccine strategy.

For some viruses, the first infection can provide lifelong immunity, for seasonal coronaviruses protective immunity is short-lived [7]. Over the years, other viruses responsible for various infectious respiratory diseases have been able to present reinfection in the originally cured subjects, such as the coronavirus HCoV-NL63 (NL63) [8] and the human respiratory syncytial virus (hRSV) [9].

The SARS-CoV-2 pandemic poses a challenge regarding the follow-up of recovered patients and the question of the reinfection risk. Several reports confirmed that most patients with SARS-CoV-2 produce antibodies against spike and N-proteins of the virus within 30 days after the infection [10,11]. In fact, an outbreak of the virus on a fishery vessel showed that fishers with prior neutralizing antibodies against SARS-CoV-2 were not reinfected [12]. The potential mechanisms that mediate immunity post-COVID-19 are not yet fully understood. COVID-19 typically follows a course similar to other respiratory viral illnesses, and it is self-limiting in more than 80% of cases [13]. An innate immune response involving T cells and B cells is activated, leading to the production of neutralizing antiviral antibodies [13]. The specific IgM antibody response starts to peak within the first 7 days [13]. Specific IgG and IgA antibodies develop a few days after IgM and are hypothesized to persist at low levels, conferring lifelong protective antibodies [14]. While this hypothesis may hold true for symptomatic patients, emerging data have revealed negative IgM and IgG during the early convalescent phase in asymptomatic patients [15] and 40% of asymptomatic patients became seronegative for IgG 8 weeks after discharging compared with 12.9% who were seronegative for the symptomatic group [15]. A seronegative status could leave open the possibility of reinfection. Immunosuppression and comorbid diseases can be other risk factors for a reinfection [16].

However, a distinction must be made between prolonged shedding/reactivation and true reinfection [17], in fact one of the features of SARS-CoV-2 infection is prolonged virus shedding. Several studies reported persistent or recurrent elimination of viral RNA in nasopharyngeal samples starting from first contact with a positive subject [18–20]. For this reason, recently the Center for Disease Control and Prevention (CDC) released a guidance protocol designed to identify cases of real SARS-CoV-2 reinfection [21]. This guidance defines some criteria about sequencing parameters, epidemiological data and laboratory diagnostic data (Table 1). Specifically, investigative criteria include a positive RT-PCR test more than 90 days after the initial test in healed patients or a positive RT-PCR test more than 45 days after the initial test that is accompanied by compatible symptoms or epidemiological exposure, after confirmed healing.

Another emerging problem that can influence the possibility of reinfection and the vaccination efficacy is the new variants of SARS-CoV-2, such us alpha, beta, gamma and delta. A recent study on 9119 patients with SARS-CoV-2 infection identified reinfection in 63 cases (0.7%, 95% confidence interval 0.5–0.9%) [22]. The mean period between two positive tests was 116 ± 21 days [22]. There were no significant differences based on age or sex, while nicotine dependence/tobacco use, asthma were higher in patients with reinfection [22]. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury during reinfection compared with primary infection [22]. There were two deaths (3.2%) associated with reinfection [22].
Another study conducted in Switzerland reported five cases of reinfection (1%) in 498 seropositive individuals followed for 35 weeks [23]. Breathnach et al. examined data of 10,727 patients with COVID-19 in the first wave and individuated eight reinfection cases (0.07%), all in female patients, and only one was admitted in hospital [24]. Bongiovanni et al. examined 677 subjects with at least a positive nasopharyngeal swab, 328 during the first wave and 349 during the second individuating 13 (1.9%) cases of reinfection [25]. Vitale et al. examined a cohort of 1579 patients and reported five reinfections (0.31%, 95% CI, 0.03-0.58%), of whom only one was hospitalized and the mean (SD) interval between primary infection and reinfection was longer than 230 (90) days [26].

The understanding of COVID-19 reinfection will be key in guiding government and public health policy decisions in the coming months.

A systematic review of literature was performed in order to individuate cases of reinfection for SARS-CoV-2. To date there are more than 300 reported cases of COVID-19 reinfection from different countries such as United States [27], Ecuador [28], Hong Kong [5], and Belgium [29]. It is necessary to understand if all these cases are really reinfection.

2. Materials and Methods

This systematic review of literature on reinfections of SARS-CoV-2 was conducted in August 2021. Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to ensure the reliability and validity of this study and results.

### Table 1. Protocol of Center for Disease Control and Prevention for investigating suspected SARS-CoV-2 reinfection.

| Investigative Criteria | Laboratory Evidence |
|------------------------|----------------------|
| 1. People with detected SARS-CoV-2 RNA (if detected by RT-PCR, only include if Ct value < 33 or if Ct value unavailable) ≥90 days after the first detection of SARS-CoV-2 RNA, whether or not symptoms were present | Best evidence 
Differing clades as defined in Nextstrain and GISAID of SARS-CoV-2 between the first and second infection, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for subgenomic mRNA, and culture) |
| 2. People with detection of SARS-CoV-2 RNA (if detected by RT-PCR, only include if Ct value < 33 or if Ct value unavailable) ≥45 days after the first detection of SARS-CoV-2 RNA AND with a symptomatic second episode and no obvious alternate etiology for COVID-19-like symptoms or close contact with a person known to have laboratory-confirmed COVID-19 | Moderate evidence
>2 nucleotide differences per month * in consensus between sequences that meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for subgenomic mRNA, and culture) |
| Poor evidence but possible ≤2 nucleotide differences per month * in consensus between sequences that meet quality metrics above or >2 nucleotide differences per month * in consensus between sequences that do not meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for subgenomic mRNA, and culture) |

* The mutation rate of SARS-CoV-2 is estimated at 2 nucleotide differences per month, therefore if suspected reinfection occurs 90 days after initial infection, moderate evidence would require >6 nucleotide differences.
2.1. Data Sources

By application of a systematic search and using the keywords in the online databases including PubMed, Scopus, Web of Science, Science Direct, EMBASE, and preprint servers (MedRxiv, BioRxiv, and SSRN) on 31 July 2021, we extracted all the papers published in English from December 2019 to July 2021. We included several combinations of keywords in the following orders to conduct the search strategy: (1) “CoVID-19” or “SARS-CoV-2” or “2019-nCoV” [all field]; (2) “Reinfection” or “Re-infection” [all field].

2.2. Study Selection

Three independent investigators retrieved the studies that were the most relevant by titles and abstracts (ELM, LLM, MA). Subsequently, the full text of the retrieved papers was reviewed, and the most relevant papers were chosen according to the eligibility criteria. Then, we extracted the relevant data and organized them in tables. The original papers that were peer-reviewed and published in English and fulfilled the eligibility criteria were included in the final report, together with two works not reviewed at the time of preparation of this report [30,31].

The following inclusion criteria was used: a positive RT-PCR test carried out more than 90 days after the initial test in healed patients or a positive RT-PCR test carried out more than 45 days after the initial test that is accompanied by compatible symptoms or epidemiological exposure, after confirmed healing. This criteria corresponds to the CDC protocol designed to identify cases of real SARS-CoV-2 reinfection (Table 1) [32].

We considered the exclusion criteria for this study as follows: (1) papers conveying non-human studies including in vitro observations or articles focusing on animal experiments; (2) papers in which their full text were out of access; (3) any suspicious and duplicated results in the databases.

2.3. Data Extraction

After summarizing, we transferred the information of the authors, type of article (e.g., case reports), publication date, country of origin, age, gender, and clinical symptoms to a data extraction sheet. Three independent investigators collected this information and subsequently organized them in the tables. Finally, to ensure no duplications or overlap existed in the content, all the selected articles were cross-checked by other authors.

2.4. Quality and Risk of Bias Assessment

As aforementioned, we applied the PRISMA checklist to ensure the quality and reliability of selected articles. Two independent researchers evaluated the consistency and quality of the articles and the risk of bias. In either case of discrepancy in viewpoints, a third independent researcher resolved the issue. The full text of selected articles was read, and the key findings were extracted.

Included studies underwent quality check and risk of bias assessment. This qualitative analysis was performed according Murad’s quality checklist of case series and case report [33]. As reported, the scale consists of four parameters, to evaluate the (a) patient selection; (b) exposure ascertainment; (c) causality; (d) reporting. Each section contains one to four question to be addressed. As it is suggested we performed an overall judgement about methodological quality since questions 4, 5 and 6 are mostly relevant to cases of adverse drug events. Each requested field will be considered as adequate, inadequate or not evaluable. The table showing this tool for evaluating the methodological quality of case reports and case series, is reported in the original manuscript [33].

3. Results

In this study, 117 documents were identified using the systematic search strategy. After a primary review of 2201 retrieved articles, 379 duplicates were removed, and the title and abstract of the remaining 1822 resources were reviewed. After applying the selection
criteria, only 117 articles met the inclusion criteria and were included in the final review (Figure 1). Therefore, the cases confirmed according to these parameters were 260 (Table 2).

![Flow diagram for the selection process of identified articles.](image-url)

**Figure 1.** Flow diagram for the selection process of identified articles.
Table 2. Cases of SARS-CoV2 reinfection in the international literature (all cases were again positive for SARS-CoV-2 after complete symptomatic recovery in addition to negative RT-PCR test for SARS-CoV-2, according to WHO recommendations [34]).

| Authors                                      | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms | Antibody after First Infection or Reinfection |
|----------------------------------------------|------|-----------------|---------|---------------------------------------------------|-----------------------|----------|----------|-----------------------------------------------|
| 1. Abu-Raddad LJ et al. [35]—case 27        | 2021 | Qatar           | 25–29-year-old man | 46 | 9 SNVs compared to initial infection strain, including D614G | Mild | N/A | N/A |
| 2. Abu-Raddad LJ et al. [35]—case 33        | 2021 | Qatar           | 40–44-year-old man | 71 | 11 SNVs compared to initial infection strain, including D614G | Mild | N/A | N/A |
| 3. Abu-Raddad LJ et al. [35]—case 20        | 2021 | Qatar           | 45–49-year-old woman | 88 | 3 SNVs compared to initial infection strain, including D614G | Mild | N/A | ROCHE elecsys anti-SARS-CoV-2 negative at time of reinfection |
| 4. Abu-Raddad LJ et al. [35]—case 44        | 2021 | Qatar           | 25–29-year-old woman | 55 | 1 SNVs compared to initial infection strain, including D614G | Mild | N/A | N/A |
| 5. Adrielle dos Santos L et al. [36]         | 2021 | Brazil          | 44-year-old healthcare man with systemic arterial hypertension, obesity | 53 | Clade B.1.1.28 | 20A Mild | Dry cough, dyspnea, dysgeusia, diarrhea, asthenia, sneezing/runny nose | N/A |
| 6. Aguilar-Shea AL et al. [37]               | 2021 | Spain           | 39-year-old healthcare man | 290 | N/A | | Sore throat, fever, general malaise, nasal congestion, tachycardia, chest pain, loss of smell and taste | Rapid antibody test: positive |
| 7. Ahmadian S et al. [38]                    | 2021 | Iran            | 36-year-old healthcare man | 60 | N/A | | Lethargy, fatigue, shortness of breath, headache, fever, chills | N/A |
| 8. Ahmed A et al. [39]                      | 2021 | Pakistan        | Healthcare worker man | 118 | N/A | | Arthralgia, weakness, anosmia, ageusia | N/A |
| 9. Ahmed A et al. [39]                      | 2021 | Pakistan        | Healthcare worker man | 86 | N/A | | Fever, sore throat, dry cough | N/A |
### Table 2. Cont.

| Authors                  | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection |
|--------------------------|------|-----------------|---------|-----------------------------------------------|----------------------|-------------------|-----------------------------------------------|
| 10. Ak R et al. [40]     | 2021 | Pakistan        | 40-year-old male | 94                               | N/A                          | Mild Fever      | N/A                                           |
| 11. Aldossary B et al. [41] | 2021 | Bahrain         | 47-year-old woman without comorbidities | 60                               | N/A                          | Mild Mild respiratory tract symptoms | N/A                                           |
| 12. Ali A. et al. [42]   | 2020 | Iran            | Patient 1 | 20s year age range, male                     | 89 **                        | N/A                          | 6.7 IgG (s/ca) after recovery |
| 13. Ali A. et al. [42]   | 2020 | Iran            | Patient 2 | 30s year age range, female                    | 55 **                        | N/A                          | 10.3 IgG (s/ca) after recovery |
| 14. Ali A. et al. [42]   | 2020 | Iran            | Patient 5  | 40s year age range, male                     | 55 **                        | N/A                          | 15.5 IgG (s/ca) after recovery |
| 15. Ali A. et al. [42]   | 2020 | Iran            | Patient 8  | 50s year age range, male                     | 46 **                        | N/A                          | 10.3 IgG (s/ca) after recovery |
| 16. Ali A. et al. [42]   | 2020 | Iran            | Patient 9  | 50s year age range, female                    | 53 **                        | N/A                          | 5.35 IgG (s/ca) after recovery |
| 17. Ali A. et al. [42]   | 2020 | Iran            | Patient 11 | 40s year age range, male                     | 76 **                        | N/A                          | 7.22 IgG (s/ca) after recovery |
| 18. Ali A. et al. [42]   | 2020 | Iran            | Patient 12 | 40s year age range, female                    | 45 **                        | N/A                          | 11.2 IgG (s/ca) after recovery |
| 19. Ali A. et al. [42]   | 2020 | Iran            | Patient 14 | 40s year age range, male                     | 50 **                        | N/A                          | 12.51 IgG (s/ca) after recovery |
| 20. Ali A. et al. [42]   | 2020 | Iran            | Patient 16 | 40s year age range, male                     | 62 **                        | N/A                          | 7.11 IgG (s/ca) after recovery |
| Authors   | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                                                                 |
|-----------|------|-----------------|---------|--------------------------------------------------|----------------------|----------|----------------------------------------------------------------------------|
| 21. Ali A. et al. [42] | 2020 | Iran            | Patient 17 | 40s year age range, female | 49 **                 | N/A      | Mild Fever, worse Fever, loss of taste and smell, myalgia                 |
| 22. Ali A. et al. [42] | 2020 | Iran            | Patient 18 | 40s year age range, male | 72 **                 | N/A      | Mild Fever, worse Fever, loss of taste and smell, myalgia, cough         |
| 23. Ali A. et al. [42] | 2020 | Iran            | Patient 20 | 30s year age range, male | 59 **                 | N/A      | Mild Fever, worse Fever, loss of taste and smell, myalgia, cough         |
| 24. Ali A. et al. [42] | 2020 | Iran            | Patient 22 | 50s year age range, male | 53 **                 | N/A      | Mild Fever, worse Fever, myalgia                                        |
| 25. Ali A. et al. [42] | 2020 | Iran            | Patient 23 | 20s year age range, male | 49 **                 | N/A      | Mild Fever, worse Fever, loss of taste and smell, myalgia, cough         |
| 26. Ali A. et al. [42] | 2020 | Iran            | Patient 24 | 40s year age range, female | 52 **                 | N/A      | Mild Fever, worse Loss of taste and smell, myalgia                       |
| 27. Ali A. et al. [42] | 2020 | Iran            | Patient 25 | 20s year age range, female | 54 **                 | N/A      | Mild Fever, mild Fever, cough                                           |
| 28. Ali A. et al. [42] | 2020 | Iran            | Patient 26 | 30s year age range, male | 138 **                | N/A      | Moderate Fever, loss of taste and smell, myalgia, cough                 |
| 29. AlFehaidi A et al. [43] | 2020 | Qatar           | Patient 27 | 46-year-old woman with mild asthma | 80                    | N/A      | Mild Sore throat                                                         |
|           |      |                 |          |                                                  |                      |          | Moderate Chest pain, fever, sore throat, body pain, cough, mild dyspnea |
| Authors                          | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection                           |
|---------------------------------|------|-----------------|---------|--------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 30. Alshukairi AN et al. [44]   | 2021 | Saudi Arabia    | 51-year-old woman with autologous hematopoietic stem cell transplantation for follicular non-Hodgkin lymphoma | 160                  | 19B                                 | Mild Fever, cough, malaise, and headache                                          | Negative COVID-19 serology after 1st infection and reinfection          |
| 31. Amikishiyes S et al. [16]   | 2021 | Turkey          | 34-year-old man with chronic glomerulonephritis | >150                 | N/A                                 | Mild Asymptomatic                                                                  | N/A                                                                        |
| 32. Amorin MR et al. [45]       | 2021 | Brazil          | 35-year-old healthcare worker woman              | 55                   | N/A                                 | Mild Fever, headache, chills, sneezing, coryza, myalgia                           | N/A                                                                        |
| 33. Amorin MR et al. [45]       | 2021 | Brazil          | 61-year-old healthcare worker woman with chronic bronchitis | 170                  | N/A                                 | Mild Headache, cough, myalgia, odynophagia, coryza, diarrhea, ageusia              | N/A                                                                        |
| 34. Amorin MR et al. [45]       | 2021 | Brazil          | 40-year-old healthcare worker woman              | 131                  | N/A                                 | Mild Odynophagia, sneezing, coryza, diarrhea, ageusia, anosmia                     | N/A                                                                        |
| 35. Amorin MR et al. [45]       | 2021 | Brazil          | 40-year-old healthcare worker woman              | 148                  | N/A                                 | Mild Fever, headache, myalgia, dry cough, vomiting, malaise                       | N/A                                                                        |
| 36. Arteaga-Livias K et al.     | 2021 | Peru            | 42-year-old healthcare worker woman              | 107                  | N/A                                 | Mild Odynophagia, dry cough, myalgia, malaise, coryza, headache                   | IgM and IgG+                                                              |
| 37. Atici S et al. [47]         | 2021 | Turkey          | 46-year-old healthcare worker man                | 114                  | N/A                                 | Moderate Fever, sore throat, headache, cough, weakness, nausea and diarrhea, bilateral ground glass opacities and peribronchial thickening predominating on the right lung | N/A                                                                        |

Table 2. Cont.
| Authors           | Year | Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------|------|---------|---------|-------------------------------------------------|-----------------------|---------------------------------------------------------------------------------|-----------------------------------------------|
| 38. Atici S et al. [47] | 2021 | Turkey  | 47-year-old healthcare worker woman | 128 | N/A | Mild: Myalgia, headache and abdominal pain started without fever and cough       | Worse: Sore throat, headache and myalgia, fever, cough and mild respiratory symptoms, ground glass opacities and subpleural nodule on the left lung base consistent with COVID-19 on chest CT imagine |
| 39. Awada H et al. [48] | 2021 | Lebanon | 27-year-old man | 56 | N/A | Mild: Fever, chills, diffuse arthralgia, myalgia, headache, back pain          | Milder: Fever, headache |
| 40. Bader N et al. [49] | 2021 | USA     | 73-year-old man with obesity, chronic obstructive pulmonary disease, pancreatic insufficiency, type II diabetes mellitus | 60 | N/A | Mild: Shortness of breath                                                     | Worse: Dyspnea, fevers, confusion with worsening clinical situation and intubation |
| 41. Baiswar S et al. [50] | 2021 | USA     | 28-year-old male with diabetes mellitus type 1, hypertension, and end-stage renal disease on hemodialysis with multiple past admissions for diabetic ketoacidosis and uncontrolled hypertension | 122 | N/A | Mild: Nausea and vomiting                                                     | Worse: Headaches and altered mental status, left-hand weakness. The patient became unresponsive and was intubated for airway protection > cerebrovascular accident |
Table 2. Cont.

| Authors                  | Year | Country | Patient                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19                  | Symptoms                                                                 | Antibody after First Infection or Reinfection |
|--------------------------|------|---------|-------------------------------------------------------------------------|-----------------------------------------------|------------------------|--------------------------|--------------------------------------------------------------------------|-----------------------------------------------|
| Bellesso M et al. [51]   | 2021 | Brazil  | 76-year-old female with end-stage kidney disease related to lambda light chain multiple myeloma | 126                                           | N/A                    | Moderate                 | Hip pain, confusion, respiratory distress                                | N/A                                           |
| Bongiovanni M. [52]      | 2020 | Italy   | 48-year-old nurse female                                                 | 90                                            | N/A                    | Mild                     | Dry cough, mild fever                                                   | LIASON® SARS-CoV-2 S1/S2 IgG+ 30 Au/mL        |
| Bonifacio LP et al. [53] | 2020 | Brazil  | 24-year-old white female without comorbidities                           | 76                                            | N/A                    | Worse                    | Moderate                    | IgG+ 102.9 Au/mL                                                          |
| Borgogna C et al. [54]   | 2021 | Italy   | 52-year-old man with transitional cell carcinoma of the renal pelvis     | 110                                           | Clade 20B and Pangolin lineage B.1.1 | Mild                      | Cough, fever                                                           | Very low levels of IgG anti-SARS-CoV-2 Spike protein, positive IgG anti-SARS-CoV-2 N protein |

Clade 20B and Pangolin lineage B.1.1

Mild

Cough, fever

Very low levels of IgG anti-SARS-CoV-2 Spike protein, positive IgG anti-SARS-CoV-2 N protein
| Authors | Year | Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms | Antibody after First Infection or Reinfection |
|---------|------|---------|---------|------------------------------------------------|-----------------------|----------|----------|-----------------------------------------------|
| 46. Brehm TT et al. [55] | 2021 | Germany | 27-year-old female nurse | 282 | HH-24.I (19A) | Mild | Fever, chills, dyspnea | IgG anti-SARS-CoV-2 Spike protein: 40 AU/mL in July 2020, 15 AU/mL in September 2020 |
| 47. Buddingh EP et al. [56] | 2021 | The Netherlands | 16-year-old girl | 390 | Classic | Moderate | High fever, mild conjunctivitis, malaise, chest pain, coughing, abdominal pain and diarrhea. She was diagnosed with myocarditis, shock and had high inflammatory parameters. | IgG SARS-CoV-2 was negative (Abbott SARS-CoV-2 IgG; Abbott Laboratories) |
| 48. Caralis P. [57] | 2021 | USA | 60 with diabetes | 72 | N/A | Mild | Acute renal failure | |
| 49. Caralis P. [57] | 2021 | USA | 27 with psoriatic arthritis | 79 | N/A | Mild | Fever, flu-like | IgG+ |
| 50. Caralis P. [57] | 2021 | USA | 33 year-old woman with allergic rhinitis | 172 | N/A | Mild | Fever, cough, diarrhea | IgG+ |
| 51. Caralis P. [57] | 2021 | USA | 71 with renal/liver transplant HIV, diabetes | 93 | N/A | Moderate | Fever, pneumonia, respiratory insufficiency | |
| 52. Caralis P. [57] | 2021 | USA | 72 with pulmonary/cardiac sarcoidosis | 111 | N/A | Mild | Dyspnea, fatigue, headache | |
| 53. Cavanagaugh AM et al. [58] | 2021 | USA | M (80–89 years old) | 101 | N/A | Mild | Lethargy, decreased appetite, dry cough for 14 days | |
### Table 2. Cont.

| Authors                          | Year | Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                                                                 | Antibody after First Infection or Reinfection |
|----------------------------------|------|---------|---------|--------------------------------------------------|-----------------------|----------|---------------------------------------------------------------------------|-----------------------------------------------|
| 54. Cavanagaugh AM et al. [58]    | 2021 | USA     | F (80–89 years old) | 103                                              | N/A                   |          | Asymptomatic, asymptomatic, worse | Congestion, respiratory failure and death     | N/A                                           |
| 55. Cavanagaugh AM et al. [58]    | 2021 | USA     | F (60–69 years old) | 109                                              | N/A                   |          | Mild nausea                                                               | N/A                                           |
| 56. Cavanagaugh AM et al. [58]    | 2021 | USA     | F (70–79 years old) | 109                                              | N/A                   |          | Mild Cough, sore throat, loss of appetite, malaise, muscle aches for 17 days | N/A                                           |
| 57. Cavanagaugh AM et al. [58]    | 2021 | USA     | Female (90–99 years old) | 110                                              | N/A                   |          | Asymptomatic, asymptomatic, milder | Loss of appetite, malaise, muscle aches for 12 days | N/A                                           |
| 58. Colson P et al. [59]          | 2021 | France  | 70-year-old man | 105                                              | 20A E2, 34 nucleotide differences |          | Asymptomatic, during a systematic screening | IgG+ on D26                                    |
| 59. Das P et al. [60] case 1      | 2021 | Bangladesh | A 35–49-year-old man with hypertension | 98                                              | N/A                   |          | Mild | Fever, cough                                                                 |                                             |
| 60. Das P et al. [60] case 2      | 2021 | Bangladesh | A 35–49-year-old researcher woman | 92                                              | N/A                   |          | Milder | Fever, cough, cold                                                        |                                             |
| 61. Das P et al. [60] case 3      | 2021 | Bangladesh | 35–49 hypertensive physician | 94                                              | N/A                   |          | Milder | Sore throat, fever, cough, headache                                       |                                             |
| 62. Das P et al. [60] case 4      | 2021 | Bangladesh | 35–49 man with asthma | 93                                              | N/A                   |          | Mild | Fever, headache, sore throat                                               |                                             |
| 63. Das P et al. [60] case 5      | 2021 | Bangladesh | 35–49-year-old health worker woman with hypertension, hypothyroidism | 131                                              | N/A                   |          | Worse | Chest pain, headache, sore throat, hospitalized                            |                                             |
| Authors                          | Year | Country | Patient Age and Gender | Patient Comorbidities | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                                                                 | Antibody after First Infection or Reinfection |
|---------------------------------|------|---------|------------------------|-----------------------|-------------------------------------------------|-----------------------|----------|---------------------------------------------------------------------------|-------------------------------------------------|
| 64. Daw MA et al. [61]          | 2021 | Libya   | 52-year-old healthy male |                       | 72                                               | N/A                   | Mild     | Cough, sore throat, fever, myalgias, headache                             | N/A                                             |
| 65. De Brito C. et al. [62]     | 2020 | Brazil  | 40-year-old male doctor |                       | 46                                               | N/A                   | Moderate | Fever, cough, sore throat, fatigue, myalgia, headache, diarrhea          | IgG and IgM– 42 days after 1 infection           |
| 66. Diaz Y et al. [63]          | 2021 | Panama  | 36-year-old man         | without comorbidities | 181                                              | A.2.4                 | Mild     | Myalgia, chest pain, fever, cephaelea, rhinorrea, hypsomia, ageusia       |                                                |
| 67. Dimeglio C et al. [64]      | 2021 | France  | 25-year-old female      | healthcare worker     | >90                                              | N/A                   | Asymptomatic | Asymptomatic | Fever, rhinorrea, dyspnea, chest pain, anosmia, asthenia, myalgia, eye pain, pharyngitis; not hospitalized | Yes, neutralizing antibodies |
| 68. Dimeglio C et al. [64]      | 2021 | France  | 40-year-old female      | healthcare worker     | >90                                              | N/A                   | Asymptomatic | Asymptomatic | No neutralizing antibodies                                                  | No neutralizing antibodies |
| 69. Dimeglio C et al. [64]      | 2021 | France  | 46-year-old female      | healthcare worker     | >90                                              | N/A                   | Moderate | Fever, rhinorrea, cough, dyspnea, chest pain, intestinal disorders, dysgeusia, anosmia, asthenia, headache, myalgia, not hospitalized | Yes, neutralizing antibodies |
| 70. Dimeglio C et al. [64]      | 2021 | France  | 31-year-old male        | healthcare worker     | >90                                              | N/A                   | Mild     | Anosmia; not hospitalized                                                 | Yes, neutralizing antibodies |

The table continues...
| Authors                  | Year | Patient Country       | Patient Details                                      | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                  | Antibody after First Infection or Reinfection |
|-------------------------|------|-----------------------|------------------------------------------------------|--------------------------------------------------|-----------------------|-------------------------------------|-----------------------------------------------|
| Dimeglio C et al. [64]  | 2021 | France                | 50-year-old female healthcare worker                | >90                                              | N/A                   | Asymptomatic                        | Yes, neutralizing antibodies                 |
| Dobano C et al. [65]    | 2021 | Spain                 | 29-year-old female healthcare worker                | 212                                              | N/A                   | Mild                                | Yes, neutralizing antibodies                 |
| Dobano C et al. [65]    | 2021 | Spain                 | 41-year-old female healthcare worker                | 154                                              | N/A                   | Mild                                | Seronegative after 1st infection, seroconverted after re-infection |
| Dobano C et al. [65]    | 2021 | Spain                 | 58-year-old female healthcare worker                | 58                                               | N/A                   | Mild                                | Unknown after 1st infection, seropositive after reinfection |
| Dobano C et al. [65]    | 2021 | Spain                 | 44-year-old female healthcare worker                | 211                                              | N/A                   | Mild                                | Seropositive after 1st infection with antibody low-level |
| Duggan NM et al. [66]   | 2020 | USA                   | 82-year-old male with Parkinson, insulin-dependent diabetes, chronic kidney disease, hypertension | 48                                               | N/A                   | Severe with intubation              | Fever, shortness of breath, hypoxia, pneumonia |
| Elzein F et al. [67]    | 2021 | Saudi Arabia          | 51-year-old man without comorbidities               | 58                                               | N/A                   | Severe without intubation           | Fever, hypoxia, hypotension, tachycardia, pneumonia |
| Elzein F et al. [67]    | 2021 | Saudi Arabia          | 55-year-old man with relapsed NHL                   | 31                                               | N/A                   | Mild                                | Fever, cough, generalized weakness, and shortness of breath, bilateral diffuse patchy airspace disease while a CT scan revealed bilateral patchy 4 central and peripheral ground glass opacities most likely related to COVID-19 |
| Elzien F et al. [67]    | 2021 | Saudi Arabia          | 60-year-old man with diabetes mellitus, hypertension, ischemic heart disease | 27                                               | N/A                   | Mild                                | 0.01 SARS-CoV-2 IgG (Abbot) index negative during second admission |

7.04 SARS-CoV-2 IgG (Abbot) during second admission
| Authors                          | Year  | Country          | Patient Details                                      | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19   | Symptoms                                      | Antibody after First Infection or Reinfection |
|---------------------------------|-------|------------------|------------------------------------------------------|--------------------------------------------------|------------------------|------------|-----------------------------------------------|------------------------------------------------|
| 80. Elzein F et al. [67]         | 2021  | Saudi Arabia     | 48-year-old woman with metastatic breast cancer      | 85                                               |                        | Moderate   | Pneumonia                                     | N/A                                             |
|                                 |       |                  |                                                      |                                                  |                        | Mild       | Fever, shortness of breath                    |                                                 |
| 81. Fageeh H et al. [68]         | 2021  | Saudi Arabia     | 24-year-old male dental student                      | 90                                               | N/A                    | Mild       | N/A                                           |                                                 |
|                                 |       |                  |                                                      |                                                  |                        | Mild       | Mild—long term care facility                 | N/A                                             |
| 82. Fabianova K et al. [69]—case 1 | 2021  | Czech Republic   | 60-year-old man with diabetes                        | 177                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 83. Fabianova K et al. [69]—case 2 | 2021  | Czech Republic   | 75-year-old man with diabetes, cardiovascular disease | 102                                              | N/A                    | Severe     | N/A                                           |                                                 |
| 84. Fabianova K et al. [69]—case 3 | 2021  | Czech Republic   | 72-year-old man with malignity                       | 205                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 85. Fabianova K et al. [69]—case 4 | 2021  | Czech Republic   | 62-year-old woman with asthma                        | 137                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 86. Fabianova K et al. [69]—case 5 | 2021  | Czech Republic   | 57-year-old woman without comorbidities              | 203                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 87. Fabianova K et al. [69]—case 6 | 2021  | Czech Republic   | 56-year-old woman without comorbidities              | 216                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 88. Fabianova K et al. [69]—case 7 | 2021  | Czech Republic   | 55-year-old man without comorbidities                | 212                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 89. Fabianova K et al. [69]—case 8 | 2021  | Czech Republic   | 53-year-old man without comorbidities                | 214                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 90. Fabianova K et al. [69]—case 9 | 2021  | Czech Republic   | 50-year-old woman with malignity                     | 197                                              | N/A                    | Mild       | N/A                                           |                                                 |
| 91. Fabianova K et al. [69]—case 10 | 2021  | Czech Republic   | 49-year-old woman without comorbidities              | 195                                              | N/A                    | Mild       | N/A                                           |                                                 |
| Authors                          | Year | Country             | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms          | Antibody after First Infection or Reinfection |
|---------------------------------|------|---------------------|---------|--------------------------------------------------|-----------------------|----------|-------------------|-----------------------------------------------|
| Fabianova K et al. [69]—case 11 | 2021 | Czech Republic      | 49-year-old woman without comorbidities | 200                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 12 | 2021 | Czech Republic      | 47-year-old man without comorbidities | 141                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 13 | 2021 | Czech Republic      | 47-year-old man without comorbidities | 206                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 14 | 2021 | Czech Republic      | 46-year-old man without comorbidities | 154                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 15 | 2021 | Czech Republic      | 46-year-old woman without comorbidities | 231                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 16 | 2021 | Czech Republic      | 45-year-old woman without comorbidities | 101                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 17 | 2021 | Czech Republic      | 45-year-old woman with diabetes, chronic pulmonary disease, allergy | 196                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 18 | 2021 | Czech Republic      | 45-year-old woman with cardiovascular disease | 211                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 19 | 2021 | Czech Republic      | 44-year-old woman with hypertension | 169                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 20 | 2021 | Czech Republic      | 44-year-old man without comorbidities | 224                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 21 | 2021 | Czech Republic      | 42-year-old woman without comorbidities | 206                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 22 | 2021 | Czech Republic      | 39-year-old woman without comorbidities | 229                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 23 | 2021 | Czech Republic      | 34-year-old man without comorbidities | 158                  | N/A         | Mild               | Mild—home                                     |
| Fabianova K et al. [69]—case 24 | 2021 | Czech Republic      | 30-year-old woman without comorbidities | 219                  | N/A         | Mild               | Mild—home                                     |
Table 2. Cont.

| Authors                  | Year | Patient Country | Patient                          | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection |
|--------------------------|------|-----------------|----------------------------------|------------------------------------------------|-----------------------|-------------------|-----------------------------------------------|
| 106. Fabianova K et al.  | 2021 | Czech Republic  | 29-year-old woman without comorbidities | 139                                           | N/A                   | Mild              | N/A                                           |
| 107. Fabianova K et al.  | 2021 | Czech Republic  | 27-year-old woman without comorbidities | 172                                           | N/A                   | Mild              | N/A                                           |
| 108. Fabianova K et al.  | 2021 | Czech Republic  | 27-year-old woman without comorbidities | 215                                           | N/A                   | Mild              | N/A                                           |
| 109. Fabianova K et al.  | 2021 | Czech Republic  | 25-year-old man without comorbidities | 222                                           | N/A                   | Mild              | N/A                                           |
| 110. Fernandez AC et al. | 2021 | Portugal         | 28-year-old man with asthma        | 285                                           | N/A                   | Asymptomatic      | Fever, chills, sneezing                      |
| 111. Ferrante L et al.   | 2021 | Brazil           | 24-year-old woman without comorbidities | 109                                           | N/A                   | Asymptomatic      | No IgG antibodies after first infection      |
| 112. Fintelman-Rodrigues N et al. | 2021 | Brazil          | 54-year-old man without comorbidities | 65                                            | N/A                   | Mild              | IgM, IgA, IgG detected <1:4                 |
| 113. Fintelman-Rodrigues N et al. | 2021 | Brazil          | 57-year-old woman with discoid lupus erythematos | 61                                            | N/A                   | Mild              | IgM, IgA, IgG detected <1:4                 |
| 114. Fintelman-Rodrigues N et al. | 2021 | Brazil          | 34-year-old man without comorbidities | 64                                            | N/A                   | Asymptomatic      | IgM, IgA, IgG detected <1:4                 |
| 115. Fintelman-Rodrigues N et al. | 2021 | Brazil          | 34-year-old woman without comorbidities | 60                                            | N/A                   | Mild              | IgM, IgA, IgG detected <1:4                 |
| Authors | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection |
|---------|------|-----------------|---------|-----------------------------------------------|----------------------|-----------------|---------------------------------------------|
| 116. Fonseca V et al. [73] | 2021 | Brazil | 29-year-old health care worker man without comorbidities | 225 | B.1.1.28 Spike D614G | 116 | Fever, myalgia, cough, sore throat, diarrhea | IgG negative 180 days after the 1st infection |
| 117. Garduno-Orbe B et al. [74] | 2021 | Mexico | 40-year-old healthcare worker woman with hypertension, smoking | 134 | N/A | 117 | Mild | Fever, dry cough, nasal drainage, dyspnea, myalgia, arthralgia, headache, anosmia, dysgeusia, decreased oxygen saturation up to 84%, maculopapular rash on the upper and lower limbs, chest, face, neck |
| | | | | | | | Moderate | Sneezing, runny nose, myalgia, arthralgia, fever, dry cough, headache, dyspnea, emphysema of the right lung |
| | | | | | | | Worse | Nasal congestion, myalgia, arthralgia, chills, headache, dry cough, dysgeusia, anosmia, maculopapular exanthema, insomnia |
| 118. Garduno-Orbe B et al. [74] | 2021 | Mexico | 49-year-old health care worker woman with hypothyroidism | 129 | N/A | 118 | Mild | Headache, dry cough, odynophagia, myalgia, dysgeusia, conjunctivitis |
| 119. Garduno-Orbe B et al. [74] | 2021 | Mexico | 53-year-old health care worker man without comorbidities | 107 | N/A | 119 | Mild | Fever, dyspnea, pneumonia |
| | | | | | | | Moderate | Fever, chills, anosmia, dysgeusia dry cough, rhinorrhea, general malaise, chest pain |
| | | | | | | | Worse | Odynophagia, dry cough, nasopharyngeal exudate |
| 120. Garduno-Orbe B et al. [74] | 2021 | Mexico | 52-year-old health care worker man without comorbidities | 82 | N/A | 120 | Mild | Myalgia, arthralgia, dry cough, dyspnea, odynophagia, pneumonia> intensive care for hypoxia |
| 121. Garg J et al. [75] | 2021 | India | 30-year-old health care worker man without comorbidities | 90 | N/A | 121 | Mild | Fever | 30 days after initial diagnosis IgG antibody negativity |
| | | | | | | | Moderate | Fever, severe myalgia, anosmia, loss of taste |
| | | | | | | | Worse | 30 days after reinfection diagnosis IgG antibody positivity |
| Authors                  | Year | Country | Patient Description                                      | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19                  | Symptoms                                      | Antibody after First Infection or Reinfection |
|-------------------------|------|---------|----------------------------------------------------------|-------------------------------------------------|-----------------------|---------------------------|-----------------------------------------------|-----------------------------------------------|
| 122. Garvey MI et al. [76] | 2021 | UK      | 92-year-old man with dementia                           | 207                                             | 1st wave              | Moderate                  | Pyrexia, dry cough, shortness of breath, bilateral pneumonia | B.1.177 (Spain variant) Moderate Lethargy, persistent cough, pyrexia, pneumonia |
| 123. Garvey MI et al. [76] | 2021 | UK      | 84-year-old man with dementia and Paget’s disease       | 224                                             | 1st wave              | Mild                      | Lethargy, confusion, headache, fatigue         | B.1.177 (Spain variant) Mild Positive |
| 124. Garvey MI et al. [76] | 2021 | UK      | 59-year-old man with end stage renal failure            | 236                                             | 1st wave              | Mild                      | Cough, fluctuating temperature                 | B.1.1.7 (Kent variant) none None |
| 125. Goel N et al. [77]   | 2021 | USA     | 59-year-old man with end stage renal failure and hemodialysis | 59                                              | N/A                   | Moderate                  | Cough, fever, pneumonia > hospitalization     | SARS-CoV-2 IgG antibody positive after re-infection |
| 126. Goldman JD et al. [30] | 2020 | USA (Washington) | Sexagenarian (age between 60 and 69) with emphysema and hypertension | 140                                             | Clade 19B             | Severe                    | Fever, chills, productive cough, dyspnea, chest pain | Clade 20A harboring the spike variant D614G Severe, but milder than first Dyspnea, dry cough, weakness |
| 127. Gulati K et al. [78] | 2021 | UK      | 61-year-old south Asian with immunosuppression for ANCA-associated vasculitis | 180                                             | N/A                   | Severe                    | Dry cough, dyspnea, fever, myalgia, kidney dysfunction, pneumonia | N/A |
| 128. Gupta V et al. [79]  | 2020 | India   | 25-year-old male healthcare worker                     | 108                                             | 9 SNVs compared to initial infection (19A first infection-20A second infection) | Asymptomatic          | Asymptomatic, with higher viral load            | N/A |
| 129. Gupta V et al. [79]  | 2020 | India   | 28-year-old female healthcare worker                   | 111                                             | 10 SNVs compared to initial infection, mutation 22882T > G (S:N440K) within the receptor binding domain found in the second episode | Asymptomatic          | Asymptomatic, with higher viral load            | N/A |
Table 2. Cont.

| Authors                  | Year | Country | Patient Details                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|--------------------------|------|---------|--------------------------------------------------------------------------------|---------------------------------------------------|-----------------------|---------------------------------------------------------------------------------|---------------------------------------------|
| Habadi MI et al. [80]    | 2021 | SAU     | 44-year-old woman healthcare worker                                          | 108                                               | N/A                   | Moderate Fever, chills, severe sore throat, fatigue                             | N/A                                         |
| Habadi MI et al. [80]    | 2021 | SAU     | 35-year-old heavy male smoker                                                  | 94                                                | N/A                   | Asymptomatic Fever, cough, body ache, abdominal pain, loss of taste            | N/A                                         |
| Hanif M et al. [81]      | 2020 | Pakistan| 58-year-old cardiac surgeon male without comorbidities                        | 55                                                | N/A                   | Hospitalized for 14 days Fever >39 °C, headache, muscle aches                   | N/A                                         |
| Harrington D et al. [82] | 2021 | UK      | 78-year-old man with type 2 diabetes mellitus, diabetic nephropathy, chronic obstructive pulmonary diseases, sleep apnea, ischemic heart disease | 250                                               | Lineage B.2 with no mutations in the S region | Discharged home Mild illness | SARS-CoV-2 antibodies (using the Roche anti-SARS-CoV-2 IgM/IgG assay detecting antibodies targeting viral nucleocapsid “N” antigen) were detectable on 6 occasions between 4 June 2020 and 13 November 2020 with no evidence of antibody waning seen |
| Hayes B et al. [83]      | 2021 | USA     | 30-year-old female healthcare worker with idiopathic thrombocytopenic purpura, pancreatitis, GERD, anxiety, recurrent pneumonia | 183                                               | N/A                   | Mild Fever, fatigue, sore throat, nasal congestion, dry cough, chest tightness | After 1st infection anti-SARS-CoV-2 IgG were negative |
| Hunsinger HP et al. [84] | 2021 | USA     | 81-year-old woman with immunosuppression for rheumatoid arthritis             | 62                                                | N/A                   | Moderate Cough, shortness of breath, oxygen requirement                         | N/A                                         |
| Hussein NR, Musa DH et al. [85] | 2021 | Iraq    | 39-year-old man with hypertension                                              | 112                                               | N/A                   | Moderate Fever, dry cough, hypoxemia                                           | SARS-CoV-2 2 months after discharge |
|                         |      |         |                                                                                |                                                   |                       | Mild Fever, not hypoxemia                                                      |                                             |
| Authors                        | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection |
|-------------------------------|------|-----------------|---------|-------------------------------------------------|-----------------------|------------------|-----------------------------------------------|
| Hussein NR, Rashad BH et al. [86]—case 1 | 2021 | Iraq            | 32-year-old man | 82 | N/A | Mild | Myalgia, fever | N/A |
| Hussein NR, Rashad BH et al. [86]—case 2 | 2021 | Iraq            | 40-year-old man | 50 | N/A | Severe | Fever, loss of smell, myalgia, dyspnea | N/A |
| Hussein NR, Rashad BH et al. [86]—case 3 | 2021 | Iraq            | 46-year-old man | 74 | N/A | Mild | Fever, sore throat | N/A |
| Hussein NR, Rashad BH et al. [86]—case 4 | 2021 | Iraq            | 39-year-old man | 122 | N/A | Moderate | Fever, sore throat, loss of taste and smell | N/A |
| Hussein NR, Rashad BH et al. [86]—case 5 | 2021 | Iraq            | 32-year-old woman | 174 | N/A | Mild | Fever, dry cough, loss of smell, sore throat | N/A |
| Hussein NR, Rashad BH et al. [86]—case 6 | 2021 | Iraq            | 44-year-old man with colon cancer | 51 | N/A | Mild | Fever, myalgia | N/A |
| Hussein NR, Rashad BH et al. [86]—case 7 | 2021 | Iraq            | 26-year-old woman | 84 | N/A | Mild | Headache, sweating, loss of taste | N/A |
| Hussein NR, Rashad BH et al. [86]—case 8 | 2021 | Iraq            | 26-year-old woman | 84 | N/A | Mild | Headache, loss of taste | N/A |
| Hussein NR, Rashad BH et al. [86]—case 9 | 2021 | Iraq            | 36-year-old woman with diabetes | 51 | N/A | Mild | Headache, fever | N/A |
| Hussein NR, Rashad BH et al. [86]—case 10 | 2021 | Iraq            | 34-year-old man | 49 | N/A | Severe | Fever, myalgia, headache, anorexia | N/A |
| Hussein NR, Rashad BH et al. [86]—case 11 | 2021 | Iraq            | 79-year-old woman with heart failure and hypertension | 58 | N/A | Severe | Fever, dyspnea | N/A |
| Ibrahim M et al. [87] | 2021 | USA | 59-year-old Caucasian male with Hodgkin lymphoma | 150 | N/A | Moderate | Shortness of breath, dry cough, tachycardia, oxygen desaturation to 85% | N/A |
|                               |      |                 |          |                                                 |                       |                  | Chills, worsening shortness of breath, productive cough, fever, tachycardia, hypoxemia | N/A |
### Table 2. Cont.

| Authors                  | Year | Country | Patient                          | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection                                                                 |
|--------------------------|------|---------|----------------------------------|--------------------------------------------------|-----------------------|-------------------|----------------------------------------------------------------------------------------------------------------|
| Inada M et al. [88]      | 2021 | Japan   | 58-year-old with mild dyslipidemia | 105                                              | N/A                   | Moderate          | Fever, bilateral pneumonia After 1st episode IC50 of neutralizing antibodies anti-SARS-CoV-2 was 50.0 microg/mL |
| Jain A et al. [89]       | 2020 | India   | 21-year-old female               | 50                                               | N/A                   | Asymptomatic      | Asymptomatic After 2nd episode IC50 of neutralizing antibodies anti-SARS-CoV-2 was 14.8 microg/mL          |
| Kapoor R et al. [90]     | 2021 | India   | 39-year-old male with multiple myeloma | 84                                              | N/A                   | Asymptomatic      | Asymptomatic Severe High grade fever, chills, shortness of breath, bilateral pneumonia                      |
| Kapoor R et al. [90]     | 2021 | India   | 33-year-old male with T cell acute lymphoblastic leukemia | 60                                              | N/A                   | Severe            | Fever, cough, pneumonia                                     |
| Kapoor R et al. [90]     | 2021 | India   | 26-year-old male with Philadelphia chromosome positive acute lymphoblastic leukemia | 91                                              | N/A                   | Asymptomatic      | Severe Headache, vomiting, high grade fever, pneumonia                                                      |
| Krishna VN et al. [91]   | 2021 | USA     | 70-year-old man with hypertension, diabetes mellitus, coronary artery disease | 45                                              | N/A                   | Asymptomatic      | Asymptomatic Worse Shortness of breath, cough, chest pain, myalgias COVID-19 IgG positive after 1st infection |
| Krishna VN et al. [91]   | 2021 | USA     | Late 50s woman with hypertension, hepatitis C, heart failure | 75                                              | N/A                   | Asymptomatic      | Asymptomatic Worse Fever, myalgias, sore throat                                                            |
| Klein J et al. [31]*     | 2021 | USA     | 66-year-old man with bipolar disorder, end-stage renal disease due to lithium toxicity and renal transplantation | 210                                             | Clade B.1.280         | Clade B.1         | Mild Fever, fatigue, dry cough Failure of humoral immunity with defective response of the neutralizing antibodies after primary infection |
### Table 2. Cont.

| Authors                        | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms | Antibody after First Infection or Reinfection |
|-------------------------------|------|-----------------|---------|--------------------------------------------------|-----------------------|----------|----------|-----------------------------------------------|
| Kulkarni O et al. [92]        | 2021 | India           | 61-year-old male healthcare worker | 75                   | 20B clade | Asymptomatic | Asymptomatic | N/A                                    |
| Larson D et al. [93]          | 2020 | USA (Virginia)  | 42-year-old man military healthcare provider | 64                   | Lineage B.1.26 | Moderate, clinical resolution in 10 days | Cough, fever, myalgia | N/A                                    |
| Lechien JR et al. [94]        | 2020 | France          | 42-year-old Parisian male          | 7 months             | N/A       | Home-managed | Dyspnea, fever, headache, diarrhea, abdominal pain, ageusia, total less of smell | IgG 2 months after |
| Lechien JR et al. [94]        | 2020 | Spain           | 38-year-old Spanish healthcare worker female | 6 months             | N/A       | Moderate—hospitalized for 7 days | Dyspnea, fever, headache, diarrhea, loss of smell | N/A                                    |
| Lee JS et al. [95]            | 2020 | South Korea     | 21-year-old healthy woman          | 26                   | Clade V—found in Asia and Europe | Hospitalized with few symptoms | Sore throat | Clade G—found in south Korea | Mild | Cough, sore throat | IgG+                                      |
| Loconsole D et al. [96]       | 2021 | Italy           | 41-year-old healthcare worker woman | 289                  | 20B       | Mild | Fever, arthralgia, headache, diarrhea, anosmia, ageusia | IgG positive after 1st infection and after 2nd infection |
| Loh SY et al.                 | 2021 | UK              | 55-year-old man with X-linked agammaglobulinaemia | 56                   | N/A       | Moderate | Purulent sputum, fever, breathlessness, fever, headache, myalgia, chest tightness | N/A                                    |
| Luciani M et al. [97]         | 2020 | Italy           | 69-year-old man, heavy smoker with classic Hodgkin’s lymphoma with mixed cellularity | 131                  | N/A       | Moderate with 3 months of hospitalization | Pneumonia, fever, diarrhea | IgG+ 50 days after hospitalization |
|                              |      |                 |                                    |                      |           | Moderate with 64 days of hospitalization | Fever, dyspnea, anemia, leukopenia, pneumonia | N/A                                    |
| Authors                        | Year | Patient Country | Patient       | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------------------|------|-----------------|---------------|---------------------------------------------------|-----------------------|----------------------------------------------------------------------------------|-----------------------------------------------|
| Mahajan NN et al. [98]—Case 2 | 2021 | India           | 33-year-old man | 90                                                | N/A                   | Mild Sore throat                                                                 | N/A                                           |
| Mahajan NN et al. [98]—Case 3 | 2021 | India           | 27-year-old man | 69                                                | N/A                   | Asymptomatic                                                                    | N/A                                           |
| Mahajan NN et al. [98]—Case 4 | 2021 | India           | 48-year-old woman | 97                                               | N/A                   | Mild Myalgia                                                                    | N/A                                           |
| Mahajan NN et al. [98]—Case 5 | 2021 | India           | 26-year-old woman | 55                                               | N/A                   | Mild Fever, myalgia                                                              | N/A                                           |
| Mahajan NN et al. [98]—Case 6 | 2021 | India           | 25-year-old man | 89                                                | N/A                   | Mild Fever, sore throat, myalgia and loss of smell and taste                    | N/A                                           |
| Mahajan NN et al. [98]—Case 7 | 2021 | India           | 31-year-old man | 70                                                | N/A                   | Asymptomatic                                                                    | N/A                                           |
| Mahajan NN et al. [98]—Case 8 | 2021 | India           | 51-year-old woman | 157                                              | N/A                   | Asymptomatic                                                                    | N/A                                           |
| Marquez L et al. [99]         | 2021 | USA             | 16-year-old woman with end-stage renal disease | 90                                                | B.1.2                 | Mild Sore throat, fatigue, nasal congestion, rhinorrhea, dry cough              | IgM+ and IgG – after the 2nd infection         |
| Massanella M et al. [100]     | 2021 | Spain           | 62-year-old male healthcare worker with previous history of mild asthma, hypertension, dyslipidemia, liver steatosis, hyperuricemia, and overweight (body mass index ≥ 30 kg/m²) | 158                  | B.1.79 (G)                        | Mild Fever of 38 °C, diarrhea, anemia, dysgeusia, cough, intense asthenia, and arthromyalgia | After reinfection weak immune response, with marginal humoral and specific T-cell responses against SARS-CoV-2. All antibody isotypes tested as well as SARS-CoV-2 neutralizing antibodies increased sharply after day 8 post symptoms. A slight increase of T-cell responses was observed at day 19 after symptom onset |
### Table 2. Cont.

| Authors                        | Year | Patient Country | Patient Details                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19               | Symptoms                                      | Antibody after First Infection or Reinfection |
|--------------------------------|------|-----------------|---------------------------------------------------------------------------------|-------------------------------------------------|-----------------------|------------------------|------------------------------------------------|-----------------------------------------------|
| 174. Mohseni M et al. [101]    | 2021 | USA             | 53-year-old female with liver transplant in 2010 due to alcoholic cirrhosis, hypertension, hypothyroidism, anxiety, and chronic kidney disease | 90                                               | N/A                   | Severe                 | Severe Encephalopathy due to her COVID-19       | N/A                                           |
|                                |      |                 |                                                                                  |                                                  |                       | Mild                   | Nausea, vomiting, diarrhea, and myalgias         |                                               |
| 175. Mulder et al. [102]       | 2020 | Denmark         | 89-year-old immunocompromised woman (Waldestrom macroglobulinemia)               | 59                                               | The 2 strains differed at 10 nucleotide positions in ORF1a (4), ORF1b (2), spike (2), ORF3A (1), M (1) genes | Hospitalized for 5 days                      | Fever, severe cough, persisting fatigue        | IgM-                                          |
|                                |      |                 |                                                                                  |                                                  |                       | Hospitalized for 5 days                      | Fever, cough, dyspnea > death after 2 weeks    | N/A                                           |
| 176. Munos Mendoza J et al.    | 2020 | USA             | 51-year-old African American male with hypertension and hemodialysis history     | 2 months                                         | N/A                   | Asymptomatic            | Positive for NAAT and IgG at a routine control during hemodialysis | IgM-, IgG+                                      |
|                                |      |                 |                                                                                  |                                                  |                       | Severe, hospitalized with non-invasive positive pressure mechanical ventilation | Fever 38.3 °C, severe dyspnea, pneumonia       | IgG+, IgM+, IgA+                                |
| 177. Nachmias V. et al. [104]  | 2020 | Israel          | 22-year-old woman without comorbidities                                        | 111                                              | N/A                   | Mild                   | Mild with home back after 23 days               | IgG+                                          |
|                                |      |                 |                                                                                  |                                                  |                       | Asymptomatic            | Fever, cough                                      |                                               |
| 178. Naveca F et al.—case 1   | 2021 | Brazil          | 29-year-old                                                                      | 281                                              | 20A                   | Mild                   | Fever, myalgia, cough, sore throat, nausea, and back pain |                                               |
|                                |      |                 |                                                                                  |                                                  | 20J (P1)              | Mild                   | Fever, cough, sore throat, diarrhea, anosmia, ageusia, headache, runny nose, and resting pulse oximetry of 97% |                                               |
| 179. Naveca F et al.—case 2   | 2021 | Brazil          | 50-year-old                                                                      | 153                                              | 20B                   | Mild                   | Fever, cough, and tiredness                       |                                               |
|                                |      |                 |                                                                                  |                                                  | 20J (P1)              | Mild                   | Cough, headache, and runny nose                  |                                               |
| 180. Naveca F et al.—case 3   | 2021 | Brazil          | 40-year-old woman                                                               | 282                                              | 20A                   | Mild                   | Fever, headache, chest pain, and weakness        |                                               |
|                                |      |                 |                                                                                  |                                                  | 20J (P1)              | Mild                   | Sore throat and running nose                     |                                               |
| Authors                       | Year | Patient Country | Patient Description                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------------------|------|----------------|-------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------|--------------------------------------------------------------------------------|-----------------------------------------------|
| Nazar N et al. [106]          | 2020 | India          | 26-year-old man healthcare worker                                                   | 97                                               | N/A                   | Asymptomatic, Asymptomatic                                                        | N/A                                           |
| Nicholson EG et al. [107]—case 1 | 2021 | USA            | 46-year-old man with hypertension, gastroesophageal reflux disease, plantar fasciitis | >90                                              | N/A                   | Mild, Fever, myalgias, sore throat, chills, headaches, nausea, shortness of breath | SARS-CoV–2 IgG testing 1st test: 1:4096 (BCM laboratory) |
| Nicholson EG et al. [107]—case 2 | 2021 | USA            | 27-year-old woman                                                                 | >90                                              | N/A                   | Mild, Congestion, fatigue, loss of taste, loss of smell, headache                 | N/A                                           |
| Nicholson EG et al. [107]—case 3 | 2021 | USA            | 53-year-old man with hypertension, sleep apnea                                       | >90                                              | N/A                   | Mild, Cough, congestion, loss of taste, loss of smell                             | SARS-CoV–2 IgG testing 2nd test: 1:2048 (BCM laboratory) |
| Nicholson EG et al. [107]—case 4 | 2021 | USA            | 66-year-old woman with diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, congestive heart failure, renal disease, gout, hypertension | >90                                              | N/A                   | Mild, Fatigue                                                                     | N/A                                           |
| Nicholson EG et al. [107]—case 5 | 2021 | USA            | 73-year-old woman with hypertension, hyperlipidemia, depression                      | >90                                              | N/A                   | Mild, Cough, shortness of breath, congestion, abdominal pain, nausea, vomiting, headache | N/A                                           |
| Nicholson EG et al. [107]—case 6 | 2021 | USA            | 42-year-old woman with breast cancer                                                | >90                                              | N/A                   | Mild, Cough, shortness of breath, fatigue, loss of taste, loss of smell, headache, fever | SARS-CoV–2 IgG testing 1st test: 1:4096 (BCM laboratory) |
| Authors | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms | Antibody after First Infection or Reinfection |
|---------|------|-----------------|---------|-----------------------------------------------|-----------------------|----------|----------|-----------------------------------------------|
| 188. Nicholson EG et al. [107]—case 7 | 2021 | USA | 36-year-old man | >90 | N/A | Mild | Cough, fatigue, nausea, loss of smell, fever | SARS-CoV–2 IgG testing 1st test: 1:4096 (BCM laboratory), 2nd test: 1:4096 (BCM laboratory) |
| 189. Nonaka CKV et al. [108] | 2021 | Brazil | 45-year-old woman | 147 | Lineage B.1.1.35 with S:G1219C mutation | Mild | Diarrhea, myalgia, asthenia, odynophagia for 7 days | N/A |
| 190. Novoa W et al. [109] | 2021 | Colombia | 44-year-old male, healthcare worker | 103 | N/A | Asymptomatic | Asymptomatic | N/A |
| 191. Ozaras R et al. [110] | 2020 | Turkey | 23-year-old woman | 116 | N/A | Moderate | Headache, malaise, ageusia, muscle fatigue, insomnia, mild dyspnea, shortness of breath | N/A |
| 192. Pow T et al. [111] | 2021 | USA | 40-year-old man | 89 | N/A | Asymptomatic | Asymptomatic | N/A |
| 193. Prado-Vivar B et al. [28] | 2020 | Ecuador | 46-year-old man | 63 | Nextstrain 20A/GISAID B.1.p9 lineage | Mild | Intense headache, drowsiness | IgM+ IgG+ on D27 of initial infection |
| 194. Quiroga B et al. [112] | 2021 | Spain | 60-year-old male, with chronic kidney disease (CKD) due to focal and segmental glomerulosclerosis that received his first kidney transplant 2004 | 149 | N/A | Moderate | Odynophagia, nasal congestion, fever 39 °C, back pain, productive cough, dyspnea | IgM+ IgG+ on D28 |
| 195. Ramirez JD et al. [113]—case 3 | 2021 | Colombia | 54-year-old woman with hypertension, gastritis, arthritis | 33 | B.1.1.269 | Milder | Fever, cough, odynophagia, fatigue | N/A |
| Authors | Year | Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms | Antibody after First Infection or Reinfection |
|---------|------|---------|---------|--------------------------------------------------|-----------------------|----------|----------|-----------------------------------------------|
| Rani PR et al. [114] | 2021 | India | 47-year-old man | 46 | 15 genetic variants with 22882T > G (Spike N440K) | Asymptomatic | Asymptomatic | N/A |
| Resende PC et al. [115] | 2021 | Brazil | 37-year-old healthcare worker woman | 116 | B.1.1.33 | Mild | Headache, runny nose, diarrhea, myalgia | IgG+ after re-infection |
| Rodriguez-Espinosa D et al. [116] | 2021 | Spain | 76-year-old man with hypertension, biological aortic heart valve replacement, and end-stage kidney disease secondary to autosomal dominant polycystic kidney disease | 58 | Asymptomatic | Asymptomatic | Fever, cough, and shortness of breath, bilateral pneumonia > death 18 days after admission | IgG and IgM to SARS-CoV-2 tested negative after 1st and 2nd episode |
| Romano CM et al. [117] | 2021 | Brazil | 26-year-old woman | 128 | Non-VOC virus | Mild | Dry cough, dizziness, headache, fatigue, stuffy nose, back pain, loss of taste, nausea, diarrhea | |
| Salcin S et al. [118] | 2021 | USA | 62-year-old woman with hypertension, hypothyroidism, chronic lower back pain | 90 | N/A | Worse with intubation twice | Tachypnea, hypoxia, pneumonia | N/A |
| Salehi-Vaziri M et al. [119] | 2021 | Iran | 42-year-old man | 128 | 20G with 11 mutations | Mild | Cough, headache, severe diarrhea | IgG and IgM negative |
| | | | | | 20G with 17 mutations | Mild | Body pain, shortness of breath, headache, anosmia | IgG and IgM negative |
| Authors                        | Year | Country  | Patient Age   | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                        | Antibody after First Infection or Reinfection                                                                 |
|-------------------------------|------|----------|----------------|-----------------------------------------------|-----------------------|----------|--------------------------------|----------------------------------------------------------------------------------------------------------------|
| 202. Salehi-Vaziri M et al.  | 2021 | Iran     | 32-year-old woman | 63                                      | D614G mutation       | Worse    | Severe cough, fever            | The antibody titration was achieved positive by the rapid test (sensitivity 72%, specificity: 76%) for IgM (At the time of second infection, IgG titration was assessed as 4.89 AU/mL which after two months turned to a significant raise (over ELISA reader standard range). |
| 203. Salehi-Vaziri M et al.  | 2021 | Iran     | 54-year-old man  | 156                                     | L139L non-synonymous mutation | Mild     | Fatigue, anxiety, chest pain, cough, fever | IgM and IgG were detected in the first incidence, and he was being followed up to the second virus presentation. In the whole duration between two incidences, IgG test was positive. Antibody titration at the time of second infection showed that IgG level was 5.25 IU/mL which increased to 27.5 IU/mL after about 2 weeks. |
| 204. Salehi-Vaziri M et al.  | 2021 | Iran     | 42-year-old man  | 111                                      | N/A                   | Mild     | Shortness of breath, sore throat, shaking chills, pain, diarrhea | The IgG titration was 17.5 IU/mL which decreased to 6.5 IU/mL after almost 2 weeks. |
| 205. Salzer HJF [121]        | 2021 | Austria  | 95-year old man with dementia, hypertension, total thyroidectomy | 124                      | N/A                   | Mild     | Fever, leukopenia               | N/A                                                                                                            |
| 206. Sanyang B et al. [122]  | 2021 | Gambia   | 31-year-old woman without comorbidities | 145                      | B1                    | Mild     | Mild                            | B1.1.74                                                                                                         |
| 207. Sanyang B et al. [122]  | 2021 | Gambia   | 36-year-old woman without comorbidities | 184                      | B.1                   | Worse    | Mild                            | B.1.235 Asymptomatic                                                                                             |
| Authors                  | Year | Patient Country | Patient                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                     | Antibody after First Infection or Reinfection |
|-------------------------|------|-----------------|-------------------------------------------------------------------------|--------------------------------------------------|-----------------------|----------------------------------------|-----------------------------------------------|
| Scarpati G et al. [123] | 2021 | Italy           | 63-year-old healthcare man with type II diabetes, atrial fibrillation, chronic obstructive pulmonary disease | 299                                              | Clade 20A             | Asymptomatic                           | Clade 20E                                      |
|                         |      |                 |                                                                         |                                                  |                       |                                        | Shortness of breath with rapid worsening of clinical presentation and recovering in intensive care unit > death |
| Selhorst P et al. [124] | 2020 | Belgium         | 39-year-old female immunocompetent healthcare worker                    | 185                                              | Different clades: 19A | Mild                                   | IgG+                                         |
|                         |      |                 |                                                                         |                                                  | 20A                   | Milder                                 | IgM and IgG+                                   |
|                         |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Selvaraj V. et al. [125]| 2020 | USA             | 70-year-old male with obesity, neuropathy, asthma, obstructive sleep apnea, hypertension | 7 months                                         | Hospitalized          | Worsening shortness of breath, tachypneic, mild, patchy mid and lower lung airspace disease bilaterally | SARS-CoV-2 IgG−                                 |
|                         |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Sen MK et al. [126]     | 2020 | India           | 78-year-old man with coronary artery disease                           | 57                                               | N/A                   | Mild                                   | N/A                                          |
|                         |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Sevillano G et al. [127]| 2021 | Ecuador         | 28-year-old man                                                         | 102                                              | B.1.1                 | Mild                                   | IgM and IgG negative after 1st infection |
|                         |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Sharma R et al. [13]    | 2020 | Qatar           | 57-year-old male with diabetes mellitus                                | 86                                               | N/A                   | Asymptomatic                           | N/A                                          |
|                         |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Shastri J et al. [128]  | 2021 | India           | 27-year-old male doctor                                                 | 66                                               | Lineage B.1            | Mild, 2 days of symptoms               | IgM and IgG+                                   |
| —Case A                 |      |                 |                                                                         |                                                  |                       |                                        |                                               |
|                         |      |                 |                                                                         |                                                  | Lineage B with 7 differences | Mild, worse than initial (1 week) | Abbott anti-NC IgG− on D5 of reinfection |
| Shastri J et al. [128]  | 2021 | India           | 31-year-old male doctor                                                 | 65                                               | Lineage B.1.1          | Asymptomatic                           | N/A                                          |
| —Case B                 |      |                 |                                                                         |                                                  |                       |                                        |                                               |
| Authors                  | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------------|------|-----------------|---------|--------------------------------------------------|-----------------------|----------|--------------------------------------------------------------------------|-----------------------------------------------|
| 216. Shastri J et al.   | 2021 | India           | 27-year-old male doctor | 19 | Lineage B.1.1 | Asymptomatic | Asymptomatic—screening prior going home to visit parents | N/A                                           |
|                         |      |                 |         |                                                  | Lineage B.1.1 with 9 SNPs compared to reference not present in initial infection strain including D614G | Mild | Fever, headache, myalgia not productive cough | IgG/IgM/IgA−                                   |
|                         |      |                 |         |                                                  | Lineage B.1.1 with 9 SNPs compared to reference not present in initial infection strain including D614G | Mild | Fever, myalgia, rhinitis, sore throat, not productive cough, fatigue | IgG/IgM/IgA−                                   |
| 217. Shastri J et al.   | 2021 | India           | 24-year-old woman nurse | 55 | Lineage B.1.1 | Mild, 5 days | Sore throat, rhinitis, myalgia | N/A                                           |
|                         |      |                 |         |                                                  | Lineage B.1.1 with 10 SNPs compared to reference not present in initial infection strain including D614G | Mild, worse than initial—3 weeks | Fever, myalgia, rhinitis, sore throat, not productive cough, fatigue | N/A                                           |
| 218. Shoar S et al.     | 2021 | USA             | 31-year-old healthcare worker man | 79 | N/A | N/A | N/A | N/A | N/A |
|                         |      |                 |         |                                                  | Severe | Malaise, cough, shortness of breath, anosmia, <2 saturation to 88%, pneumonia | N/A |
|                         |      |                 |         |                                                  | Milder | Malaise, aphthous gingival ulcer, desquamating palmar lesion, fever, myalgia | N/A |
| 219. Sicsic I et al.    | 2021 | USA             | 69-year-old woman with asthma, hypercholesteremia, hypertension, OSA (obstructive sleep apnea) | 70 | N/A | N/A | N/A | N/A | N/A |
|                         |      |                 |         |                                                  | Mild | Shortness of breath, dry cough, headache, fatigue, fevers | N/A |
|                         |      |                 |         |                                                  | Moderate | Cough, fever, ageusia | N/A |
| 220. Siqueira JD et al. | 2021 | Brazil          | 76-year-old woman with chronic renal failure and renal squamous cell carcinoma | 104 | 9 single nucleotide variations (SNVs) | Severe | Cough, fever, pneumonia | N/A |
|                         |      |                 |         |                                                  | Worse | Cough, fever, pneumonia > death | N/A |
| 221. Soares da Silva et al. | 2021 | Brazil          | 39-year-old man with chronic cardiovascular disease, diabetes mellitus | 101 | P.1 | Not reported | Not reported | N/A |
|                         |      |                 |         |                                                  | P.2 | Worse | Dyspnea, fatigue, respiratory distress > intubated > death 12 days after the onset of symptoms | N/A |
| 222. Staub T et al.     | 2021 | France          | Mid-20s healthcare worker man without comorbidities | >83 | November N/A | Asymptomatic | Asymptomatic | N/A |
|                         |      |                 |         |                                                  | B1.351—identified in December 2020 in South Africa | Worse | Cough | N/A |
| 223. Staub T et al.     | 2021 | France          | Mid-20s healthcare worker woman without comorbidities | 288 | April 2020—N/A | Mild | Fever, headache, chills, diarrhea, loss of taste and smell | N/A |
|                         |      |                 |         |                                                  | B1.351 | Milder | Fever, headache, chills | N/A |

Table 2. Cont.
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| Authors                          | Year | Patient Country | Patient                          | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms | Antibody after First Infection or Reinfection |
|----------------------------------|------|-----------------|----------------------------------|---------------------------------------------------|-----------------------|-------------------|-----------------------------------------------|
| 224. Staub T et al. [133]—case 4 | 2021 | France          | Late-20s healthcare worker woman without comorbidities | 90 | November 2020—N/A | Mild | Fever, muscle pain, headache, loss of taste and smell | N/A |
|                                   |      |                 |                                  |                                                   | B1.351               |                   |                                |
| 225. Takeda C et al. [134]       | 2020 | Brazil          | 29-year-old man healthcare professional without comorbidities | 53 | N/A               | Mild | Cough, muscle pain | N/A |
| Patient 1                         |      |                 |                                  |                                                   |                       |                   |                                |
|                                   |      |                 |                                  |                                                   |                       | Mild | Fever, anosmia, loss of taste | N/A |
| 226. Takeda C et al. [134]       | 2020 | Brazil          | 63-year-old man healthcare professional without comorbidities | 58 | N/A               | Mild | Diarrhea, fever | N/A |
| Patient 2                         |      |                 |                                  |                                                   |                       |                   |                                |
|                                   |      |                 |                                  |                                                   |                       | Mild | Hypoxemia, fever | N/A |
| 227. Takeda C et al. [134]       | 2020 | Brazil          | 40-year-old woman healthcare professional with ankylosing spondylitis and asthma | 70 | N/A               | Moderate | Fever, Pneumonia, myalgia | Not specified |
| Patient 3                         |      |                 |                                  |                                                   |                       | Mild | Anosmia, fever | Not specified |
| 228. Takeda C et al. [134]       | 2020 | Brazil          | 67-year-old man healthcare professional with obesity, apnea syndrome, rhinitis | 54 | N/A               | Mild | Coryza, arthralgia | Not specified |
| Patient 4                         |      |                 |                                  |                                                   |                       |                   |                                |
|                                   |      |                 |                                  |                                                   |                       |                   |                                |
| 229. Takeda C et al. [134]       | 2020 | Brazil          | 47-year-old man healthcare professional without comorbidities | 56 | N/A               | Mild | Myalgia, fever | Not specified |
| Patient 5                         |      |                 |                                  |                                                   |                       |                   |                                |
| 230. Takeda C et al. [134]       | 2020 | Brazil          | 31-year-old man healthcare professional without comorbidities | 57 | N/A               | Moderate | Hyoxemia, myalgia, diarrhea, fever | Not specified |
| Patient 6                         |      |                 |                                  |                                                   |                       |                   |                                |
| 231. Tang CY et al. [135]        | 2021 | USA             | Female in 20s with asthma, obesity, anxiety, depression | 19 | PANGOLIN A.3 lineage | Mild | Cough, chills, exertional dyspnea, sore throat, dizziness, rhinorrhea, fever | N/A |
|                                  |      |                 |                                  |                                                   |                       |                   |                                |
|                                  |      |                 |                                  |                                                   | PANGOLIN B.1.1 lineage | Milder |                                      |      |
| Authors                  | Year | Patient Country | Patient | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------------|------|-----------------|---------|--------------------------------------------------|-----------------------|----------------------------------------------------------------------------------|-----------------------------------------------|
| Tehrani HA et al. [136] | 2021 | Iran            | 15-year-old boy with acute myeloid leukemia M3 | 43                   | N/A       | Moderate, Cough, dyspnea, patchy infiltration in the left lung                  | IgG+ IgM–                                      |
|                         |      |                 |         |                                                   |                       | Severe, Fever, neutropenia, cough, myalgia and shivering, O2 saturation at 75%, pneumonia | IgG–                                          |
| Teka IA et al. [137]    | 2021 | Libya           | 18-year-old man                           | 80                   | N/A       | Mild, Fever, headache, sore throat, cough, shortness of breath, anosmia         | IgG positive after re-infection               |
|                         |      |                 |         |                                                   |                       | Worse, Fever, cough, muscle pain, dyspnea, hypoxia                              |                                               |
| Tillett RL et al. [27]  | 2020 | USA (Nevada)    | 25-year-old man without comorbidities     | 48                   | Clade 20C | Clade 20C with 11SNP mutation, Severe with hospitalization                      | Roche Elecsys Anti-SARS-CoV-2 IgM/IgG+ on D8 of reinfection |
|                         |      |                 |         |                                                   |                       | Sore throat, cough, headache, nausea, diarrhea                                  |                                               |
## Table 2. Cont.

| Authors                      | Year | Patient Country | Patient                        | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence                  | COVID-19       | Symptoms                                      | Antibody after First Infection or Reinfection                                                                 |
|------------------------------|------|-----------------|--------------------------------|--------------------------------------------------|----------------------------------------|---------------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| 235. To KK et al. [5,138,139] | 2020 | Hong Kong       | A 33-year-old male             | 142                                              | Nextstrain 19A/GISAID V/Pangolin lineage B.2 | Mild—hospitalized | Fever, headache, cough, sore throat          | IgG negativity by ELISA or microsphere based antibody assay 10 days post symptom onset; IgG positivity but IgM negativity by indirect immunofluorescence assay; neutralizing antibody presence 10 days post-symptom onset with conventional and pseudovirus-based neutralization tests (VNTs) |
| 236. Tomkins-Tinch C-H et al. [140] | 2021 | USA             | 61-year-old man with liver transplant due to chronic hepatitis B and C infections | 111                                              | Genome of 2nd episode differed by 11 to 12 single base substitutions | Mild | Fever, nausea, vomiting, cough              | Anti-SARS-CoV-2 assay positive after 2nd episode                                                                 |
| 237. Tomassini S et al. case 9 [141] | 2021 | UK              | 93-year-old British male with multiple myeloma, cognitive impairment | 55                                               | N/A                                    | 14 days—hospitalized | Lethargy, reduced appetite, diarrhea | Abbott Architect SARS-CoV-2 IgG+ on day 3; high affinity IgG                                               |
| Authors                          | Year | Patient Country | Patient Details                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|---------------------------------|------|-----------------|--------------------------------------------------------------------------------|--------------------------------------------------|-----------------------|--------------------------------------------------------------------------------|-----------------------------------------------|
| Tomassini S et al. case 24      | 2021 | UK              | 82-year-old British male with atrial fibrillation, congestive cardiac failure, abdominal aortic aneurism, lung cancer, diabetes | 87                                               | N/A                   | Mild—hospitalized, Fever, cough, sore throat, dyspnea, hemoptysis, hypoxia       | Abbott Architect SARS-CoV-2 IgG+ on D88. 92   |
| Torres DA et al.               | 2020 | Brazil          | 36-year-old female medical doctor without comorbidities                         | 87                                               | N/A                   | Milder Fever, cough, dyspnea                                                   | IgG—23 days after the onset, IgM/IgG—after 33 and 67 days from onset |
| Tuan J et al.                  | 2021 | USA             | 44-year-old Hispanic man with type 2 diabetes mellitus, obesity                | 4 months                                         | N/A                   | Severe with tracheostomy, Dyspnea, stridor, difficulty at breath,               | IgG+                                           |
| Ul-Haq Z et al.                | 2020 | Pakistan        | 41-year-old healthcare worker man                                              | 133                                             | N/A                   | Mild Fever, respiratory decompensation                                          | IgG+                                           |
| Van Elsland J et al.           | 2020 | Belgium         | 51-year-old woman with asthma                                                  | 93                                              | Pangolin Lineage B.1.1                                                    | Moderate Headache, myalgia, fever, cough, chest pain, dyspnea; some persisting symptoms for 5 weeks | Roche nucleocapsid IgG+ on D7 of reinfection |
| Vetter P et al.                | 2021 | Switzerland     | 36-year-old female physician                                                     | 205                                             | Lineage A; 11 nucleotide differences                                          | Milder with resolution in 1 week, Headache, cough, fatigue, rhinitis             | Positivity for anti-S1 IgG and anti-N Ig at 14th and at 30th days |

**Table 2.** Cont.
| Authors                  | Year | Patient Country | Patient Description                                                                 | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 Symptoms                                                                 | Antibody after First Infection or Reinfection |
|-------------------------|------|-----------------|-------------------------------------------------------------------------------------|-----------------------------------------------|----------------------|----------------------------------------------------------------------------------|-----------------------------------------------|
| 244. Vora T et al. [145] | 2021 | India           | 58-year-old woman with hypertension, hypothyroidism                                  | 120                                           | N/A                  | Mild Fever, generalized body ache, running nose, soreness of throat               | Total antibody and immunoglobulin G antibody test for COVID-19 were negative after first infection |
| 245. Vora T et al. [145] | 2021 | India           | 58-year-old woman with hypertension and hypothyroidism                              | 91                                            | N/A                  | Mild Low-grade intermittent fever, generalized body ache, running nose and soreness of throat | N/A                                           |
| 246. West J et al. [146] | 2021 | UK              | 25-year-old male UK doctor                                                          | 17                                            | N/A                  | Mild High-grade fevers, headache of 3-day duration, severe fatigue lasting 3 weeks | N/A                                           |
| 247. Yeleti R et al. [147]| 2021 | USA             | 25-year-old female medical student with vitiligo                                    | 120                                           | N/A                  | Asymptomatic                                                                    | Asymptomatic                                   |
|                        |      |                 |                                                                                     |                                                |                      | Severe Fever, abdominal pain, fatigue, vomiting and fulminant myocarditis with co-infection of parvovirus and SARS-CoV-2 | IgG+                                           |
| 248. Yu ALF et al. [148]| 2021 | Brazil          | 41-year-old woman with gastoplasty history                                           | 146                                           | B.1.1.33 lineage      | Mild Headache, myalgia, fatigue, fever, dry cough, shortness of breath, anosmia, loss of taste | N/A                                           |
|                        |      |                 |                                                                                     |                                                | B.1.1.28 lineage      | Mild Headache, myalgia, fatigue, fever, dry cough, shortness of breath, anosmia, loss of taste, diarrhea, loss of appetite, dizziness | N/A                                           |
| 249. Yu ALF et al. [148]| 2021 | Brazil          | 34-year-old healthcare worker woman with chronic respiratory disease                | 173                                           | B.1.1.28 lineage      | Mild Fever, cough, odynophagia, dyspnea                                           | N/A                                           |
|                        |      |                 |                                                                                     |                                                | P2                   | Mild Headache, running nose, fever, sore throat                                   | N/A                                           |
| 250. Zare F et al. [149]| 2021 | Iran            | 50-year-old man                                                                     | 230                                           | N/A                  | N/A                                                                              | N/A                                           |
| 251. Zare F et al. [149]| 2021 | Iran            | 81-year-old woman                                                                   | 234                                           | N/A                  | Moderate                                                                        | N/A                                           |
| 252. Zare F et al. [149]| 2021 | Iran            | 42-year-old woman                                                                   | 107                                           | N/A                  | Worse                                                                           | Death for COVID-19                            |
| 253. Zare F et al. [149]| 2021 | Iran            | 27-year-old man                                                                     | 115                                           | N/A                  | N/A                                                                              | N/A                                           |
Table 2. Cont.

| Authors                  | Year | Country  | Patient Age | Patient Gender | Interval Time between 1 Infection and Reinfection | Viral Genome Sequence | COVID-19 | Symptoms                                                                 | Antibody after First Infection or Reinfection |
|--------------------------|------|----------|-------------|----------------|--------------------------------------------------|-----------------------|----------|--------------------------------------------------------------------------|-----------------------------------------------|
| 254. F. Zare et al. [149] | 2021 | Iran     | 79-year-old man | Male           | 150                                              | N/A                   | Moderate | N/A                                                                        | N/A                                           |
|                          |      |          |             |                |                                                  |                       | Worse    | Death for COVID-19                                                        |                                               |
| 255. F. Zare et al. [149] | 2021 | Iran     | 86-year-old man | Male           | 164                                              | N/A                   | Moderate | N/A                                                                        | N/A                                           |
|                          |      |          |             |                |                                                  |                       | Worse    | Death for COVID-19                                                        |                                               |
| 256. F. Zare et al. [149] | 2021 | Iran     | 90-year-old woman | Female         | 130                                              | N/A                   | N/A      | N/A                                                                       | N/A                                           |
| 257. F. Zare et al. [149] | 2021 | Iran     | 13-year-old woman | Female         | 124                                              | N/A                   | N/A      | N/A                                                                       | N/A                                           |
| 258. K. Zhang et al. [150]| 2020 | China    | 33-year-old female | Female         | 59                                               | N/A                   | Moderate | Reduction of IgG+ to −                                                   | IgG+                                          |
|                          |      |          |             |                |                                                  |                       |          | IgG+                                                                      |                                               |
| 259. K. Zhang et al. [150]| 2020 | China    | 33-year-old female | Female         | 86                                               | N/A                   | Moderate | Reduction of IgG+ to weak+                                                | IgM+ and IgG+                                 |
|                          |      |          |             |                |                                                  |                       |          | IgM+ and IgG+                                                             |                                               |
| 260. N. Zucman et al. [151]| 2021 | South African | 58-year-old male with asthma | Male           | 120                                              | N/A                   | Mild     | Dyspnea, fever                                                            | IgG+                                          |
|                          |      |          |             |                |                                                  |                       |          | South African variant 501Y.V2                                             |                                               |
|                          |      |          |             |                |                                                  |                       |          | Dyspnea, fever, severe acute respiratory distress syndrome               |                                               |

* data from papers which are not certified by peer review, medRxiv or Research Square preprints. ** days from recovery not from 1 infection. NAAT: nasopharyngeal nucleic acid amplification test; AT: antibody test.
3.1. Demographic and Clinical Features of Reinfection Cases

Reinfection occurred across the world: 1 case from Austria, 1 from Bahrain, 5 from Bangladesh, 2 from Belgium, 31 from Brazil, 3 from China including 1 from Hong Kong, 2 from Colombia, 28 from the Czech Republic, 1 from Denmark, 2 from Ecuador, 10 from France, 2 from Gambia, 1 from Germany, 24 from India, 31 from Iran, 12 from Iraq, 1 from Israel, 5 from Italy, 1 from Japan, 1 from Lebanon, 1 from Libya, 4 from Mexico, 5 from Pakistan, 1 from Panama, 1 from Peru, 1 from Portugal, 6 from Qatar, 1 from South Korea, 1 from Switzerland, 8 from Saudi Arabia, 1 from South Africa, 9 from Spain, 1 from the Netherlands, 4 from Turkey, 9 from the United Kingdom, 42 from the United States of America (Figure 2).

Age was reported in 237 cases: 5/237 patients (2.1%) were between 0 and 20 years old, 95/237 (40%) between 21 and 40 years old, 83/237 (35%) between 41 and 60, 42/237 (17%) between 61 and 80, and 12/237 (5%) > 80 years old (Figure 3).

Gender was reported in 251/260 cases, among which 115/251 patients (45.8%) were female and 136/251 (54.2%) were male (Figure 4).
Gender was reported in 251/260 cases, with men constituting 54% and women 46%. Health care workers represented 25%, patients with comorbidities 35%, and health subjects 40% (Figure 4).

The main risk groups were healthcare workers and patients with comorbidities. In total, 66/260 cases (2.3%) occurred among high risk groups, including healthcare workers (HCWs), doctors, students and nursing resident. A total of 91 cases (35%) occurred among patients with comorbidities, 48 in men and 38 in woman (Figure 5).

In total, 60% of reinfection involved patients in risk groups.

The evolution of the reinfection episode itself was more severe in 92/260 (35.3%) cases with the death only in 14/260 cases (5.3%), 7/260 male (2.65%) and 7/260 females (2.65%); 8 of these had a neoplastic immune system diseases, or transplant or other important comorbidities and 3 were over 80 years old (Figure 6).
Notably, reinfection occurred among patients whose initial infections were both asymptomatic/mild, 80% (207/260), and moderate/severe, 20% (53/260). 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, which may be expected to confer protection. Additionally of note, the severity of the reinfection episode itself was less in 21/53 cases (40%). The observation that many reinfection cases were less severe than initial cases is interesting because it may suggest partial protection from disease [152] and argues against antibody-dependent immune enhancement, which can be seen with other viral pathogens. In the absence of routine surveillance, we would have expected a bias toward detection of symptomatic reinfection, underscoring the importance of prospective screening.

Another interesting datapoint is the detection of different clades or lineages detected by genome sequencing between initial infection and reinfection in 52/260 cases (20%). 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 or lineage, as this provides clear evidence of infection by a different virus [6]. 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.

3.2. Quality and Risk of Bias Assessment

Briefly, only 14 studies fulfilled the quality checklist. “Selection—Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?” checklist resulted unclear in most of the studies, because the patient selection method was unclear. In general, overall quality was satisfactory in all included studies.

4. Discussion

Since the first cases, a question has haunted all researchers: can a patient recovered from COVID-19 get sick again? The first confirmed case of reinfection occurred in a 33-year-old Caucasian man of Hong Kong, that was admitted to the hospital for COVID-19
on 23 March 2020 [5]. After two negative tests by RT-PCR on days 21 and 22 he was discharged from the hospital and resumed his usual work [5]. Serological controls after the first infection showed that he did not produce virus neutralizing antibodies [139]. On 15 August 2020 after a 1-week trip in Spain, the patient returned to Hong Kong and was submitted to a collection of a deep throat saliva sample for RT-PCR as border surveillance and resulted positive [5]. The patient was asymptomatic until the new negative test. The viruses from the first and the second infection were phylogenetically distinct and the virus of first infection had a truncation in the 58AA open reading frame 8 gene, that could be responsible immune evasion [138]. However T cells and mucosal immunity might have played an important role in resolving the second infection, even if there was the absence of primary neutralizing antibodies [139].

In October 2020, Tillett et al. reported the first confirmed case of SARS-CoV-2 reinfection in the USA [27]. A 25-year-old man from Nevada, without known immune disorders, had PCR-confirmed SARS-CoV-2 infection in April, 2020 (cycle threshold (Ct) value 35·24; specimen A) [27]. He recovered in quarantine, testing negative by RT-PCR at two consecutive timepoints thereafter [27]. However, 48 days after the initial test, the patient tested positive again by RT-PCR (Ct value 35·31; specimen B) [27]. Viral genome sequencing showed that both specimens A and B belonged to clade 20C, a predominant clade seen in northern Nevada [27]. The genome sequences of isolates from the first infection (specimen A) and reinfection (specimen B) differed significantly, making the chance of the virus being from the same infection very small [27]. The particularity of this report is that SARS-CoV-2 reinfection resulted in worse disease than the first infection, requiring oxygen support and hospitalization [27]. The patient had positive antibodies after the reinfection, but whether he had pre-existing antibody after the first infection is unknown [27]. Both cases reported from Nevada and Hong Kong seem to confirm the possibility that the reinfections are due to a different variant of SARS-CoV-2.

The first important question to be answered is: are all cases reported in the literature as reinfection by SARS-COV-2 true reinfections?

A distinction must be made between true reinfecion, relapsed infection, recurrence of positive (re-positive) nucleic acid detection [17,153], in fact one of the features of SARS-CoV-2 infection is prolonged virus shedding. Several studies reported persistent or recurrent elimination of viral RNA in nasopharyngeal samples starting from first contact with a positive subject [18–20]. Several explanations can exist in order to explain this phenomenon without it being a true reinfection. One possible explanation for testing positive after a previously negative result could be that the negative results after patient recovery were really false-negative results [154]. Literature reported that false-negative rates can be as high as 30% for SARS-CoV-2 PCR testing [155]. However, actually the KCDC (Korean Control Disease Center) determined recovery as two separate negative PCR results within 24 h [156]. In this way, patients positive after having two consecutive negative results would be positive for an increase in viral genetic material due to reinfection [156]. It is difficult to have two previous consecutive false-negative results [156]. Another possible explanation could be the contamination of the samples, but most testing centers are requiring testers to change personal protective equipment (e.g., gloves, gowns and masks) [156]. However, surely one of the main points to consider is the basis of PCR testing: the test is able to amplify nucleic acid in the sample, not fully active viral particles. The genetic material (RNA and DNA) left behind degrades over time [157]. Thus, positive PCR results after recovery may not necessarily signify reinfection, but rather the presence of leftover genetic material from previously active infection [156]. Therefore, a patient who retests positive for virus might not necessarily be experiencing a second, new SARS-CoV-2 infection [158]. True reinfection has criteria that must be considered, including isolation of the complete genome of the virus (and not just genomic fragments) in the second episode, identification of two different virus strains in two episodes of infection based on phylogenetic analysis; proof of virus infectivity in the second episode by virus isolation and evaluation of its cytopathic effect in cell culture; investigation of immune responses and their comparison in two episodes;
epidemiologic data such as re-exposure history to COVID-19 patient in the second event and timing between episodes, with a longer time interval between two episodes favoring the reinfection hypothesis [17,159]. To date, positive retesting more than 83 days after the first positive test, along with other criteria, favors confirmation of reinfection, even if Turner et al. recently reported a patient with prolonged viral RNA shedding lasting 87 days after the initial positive clinical PCR test and 97 days after the onset of symptoms, probably due to the poor CD8+ T cell response during the first three months of his illness [160].

In addition to the abovementioned reasons, the disease clinical data are also useful in confirming the second episode, although the second episode may be asymptomatic [17]. A time interval where the patient is free of clinical signs between the two episodes is also necessary. In conclusion, only cases with clinical symptoms and RT-PCR positivity after negative tests following recovery from COVID-19 could be considered true SARS-CoV-2 reinfections. Recently Raveendran et al. suggested an interesting approach in order to individuate the reasons for a persistent RT-PCR positivity (Figure 7) [161]. According to this flow chart it is possible to individuate cases of persistent RT-PCR positivity due to reinfection or to presence of dead viral fragment or to persistent viral shedding.

**Figure 7.** Flow diagram in order to determine the cause of persistent RT-PCR positivity for SARS-CoV-2, modified by Raveendran, A.V. et al. [161].

The second important question to be answered is: can SARS-CoV-2 re-infect a patient after recovery?

When any unwanted virus comes into contact with our body, also in the case of SARS-CoV-2 infection, most patients are able to develop specific antibodies neutralizing
the spike proteins of this virus [5]. A recent study of Pilz et al. pointed out that the relatively low tentative reinfection rate (40 cases in 14,840 COVID-19 survivors of first wave—0.27%) ensures a good protection after natural infection for SARS-CoV-2 [162]. However there are three main mechanisms for reinfection: the immune response can be ineffective, strain-specific, or short-lived [156].

Monoclonal antibodies formed against the SARS-CoV-2 virus target the Spike (S) glycoprotein component, the receptor-binding domain of the virion [156]. SARS-CoV-2, however, has been shown to develop “escape mutants,” or alterations, in the epitope of the S protein that contribute to host tropism and viral virulence [156]. Sui et al. reported that major variations exist in the S protein at positions 360, 479, and 487 [163]. They found that altering 1–2 amino acids at those positions led previously efficacious neutralizing antibodies to SARS-CoV-2 to a 20–50% reduction in binding capacity [163]. Theoretically, if SARS-CoV-2 is also able to form “escape mutants” in the S protein, IgG antibodies formed in patients may be less ineffective, though not completely, in neutralizing the virus [156]. This could mean that patients remain resistant to SARS-CoV-2 infection even after mutations, with antibody responses that are 50–80% efficacious [156].

Another possibility that could allow the reinfection of a patient is the duration of the body immune response [156]. Recent findings suggested that protective immunity does not occur in all infected individuals [164], supporting the possibility of reinfection [103], even if 93% of the infected produce neutralizing antibodies [165]. Their function is to prevent the virus from entering cells between 6 and 20 days after infection [166] with this mechanism: after the infection, B lymphocytes are activated and produce IgM, IgG and IgA antibodies. A subset of them (IgG and IgA) then manage to make the new viral particles harmless. The neutralizing antibodies, in turn, are accompanied by the activation of killer cells (T lymphocytes), specialized in recognizing and destroying the virus [167].

Seroconversion of IgM and IgG antibodies occurs the first week after onset of symptoms, seroconversion rates rise until the fourth week and decline thereafter, by the seventh week IgM antibodies are not detected in most cases, even if some reports showed IgM antibodies to persist for up to 8 months post-COVID-19 [168], whereas IgG antibodies persist longer for a period of time yet unknown [169]. Immunoglobulins alone are not truly sufficient to confer long-term immunity to coronavirus [156]. CD4+ T-cells and memory CD8+ T-cells with their products, such as effector cytokines and IFN-γ, are important in providing protection from coronavirus [170]. In fact, when the infection is over, in the following weeks or months, the antibodies drop: the virus is no longer there, they are no longer needed. However, the memory cells remain in the body, ready to intervene in case of need. All the studies so far show that a long-lasting immune response occurs. A very recent study carried out in collaboration between the Policlinico San Matteo in Pavia and the Karolinska Institute in Stockholm quantifies this “time” more precisely: memory cells persist for at least 6–8 months after infection [171]. Considering that the disease erupted just under a year ago, this is the maximum observation time possible to date, but it could be much longer [171]. Previous studies showed that virus-specific memory CD8+ T-cells were found to persist for up to 6 years after a SARS associated coronavirus infection, but memory B-cells and accompanying antibodies were undetectable at that time [172]. However Vetter et al. hypothesized that reinfection can be due to a loss of protection elicited after the first episode for a progressive reduction of protective antibody titers [144,173].

We can conclude that antibody formation and longevity of immunity in a subject could be dependent by the strain of virus, its severity and age of subject [174].

Khoshkam et al. tried to classify the recovered and immunized subjects in four categories:

1. Infected cases with very mild symptoms or asymptomatic without any humoral immune response or elicited memory.
2. Infected cases with mild to moderate symptoms with low humoral immunity and low cellular immunity.
(3) Infected cases with moderate or severe symptoms with highly activated humoral immunity and elicited memory.

(4) Infected cases with moderate or severe symptoms with highly activated humoral immunity and low cellular immunity [175].

They hypothesized that reinfection may happen in groups 1 and 2, which may also develop the severe disease in the future due to the absence or low levels of acquired immunity [175]. Individuals in group 3 are more protective against further exposures and they may show long-term immunity since they develop increased elicited memory in defense of SARS-CoV-2 [175]. The last group may show rapid response against reinfection; they may not be safe for longer periods because of the non-imprinted memory of immunity [175].

The question to be solved is whether these antibodies can neutralize each SARS-CoV-2 clade and guarantee immunity to subsequent contact. Reinfection from SARS-CoV-2 with a genetically distinct strain of SARS-CoV-2 is, in theory, possible in patients immediately after recovery from COVID-19. SARS-CoV-2 infection may not confer immunity against a different SARS-CoV-2 strain, so more research is needed. SARS-CoV-2, even if it is a virus similar to that of the flu, seems to have a more stable genome and the response that the immune system generates is towards several fragments of the viral proteins and not just one. In fact, the mutations observed so far (and, perhaps, also the new English variant, at least until proven otherwise) are not associated with a change in the severity of the disease.

The new variants are accumulating mutations in different spike domains, such as the alpha variant or B.1.1.7 lineage (also known as 501Y.V1 or VOC202012/01), the beta variant or B.1.351 lineage (501Y.V2), the gamma variant or P.1 lineage (501Y.V3) and the delta variant or B.1.617.2 lineage [176]. All these variants have cumulated at least nine non-synonymous mutations/deletions throughout the Spike coding region. For example, the case reported by Harrington et al. showed that anti-SARS-CoV-2 antibodies were still present shortly before onset of reinfection, with no evidence of antibody waning [82]. This may raise some concerns about immune evasion by the alpha variant, which is a concern with the high number of spike region mutations seen. However, the study has a bias: there were no assays for SARS-CoV-2 antibodies recognizing spike antigen in the second reinfection, while the tested antibodies recognized “N” antigen, so it is difficult to point out an evident role of antibodies in the reinfection. The 501Y.V2 variant, or beta variant, is characterized by eight mutations in the spike protein-coding sequences that can improve its ability to transmission [151]. The case reported by Zucman et al. showed that beta variant can be more aggressive than non-VOC SARS-CoV-2 [151]. The last, the delta variant, is characterized by P681R and L452R mutations that can help the delta variant spread. For all these reasons it is necessary to investigate urgently the possibility of these new variants to escape the vaccine action. The immune responses generated by mRNA and adenoviral vector-based vaccines are restricted to the Spike glycoprotein, so new variants with big antigenic drift could reduce their efficiency and determine a growing number of reinfections.

Another possibility that could allow the reinfection of a patient is the reactivation of dormant virus which is commonly seen in immunosuppressed patients with some viruses, such as Epstein Barr, cytomegalovirus and herpes groups [90], but it is necessary to sequence viral genome for differential diagnosis between viral reactivation or reinfection with a different strain.

For all these reasons, it is important to identify cases of reinfection to understand if the “immunological memory” affects the symptoms during a second infection, a crucial fact, in particular, to predict the effectiveness of the vaccination campaign. If in the second time the symptoms are generally reduced, as in the Hong Kong [5], Belgium and the Netherlands [29] patients, this suggests that the immune system is responding as it should. However, if symptoms are consistently more severe during a second COVID-19 attack, as in the case of the Nevada [27] or Ecuador [28] subjects, it may be that the immune system makes matters worse. The mechanisms that could account for a more severe secondary infection can only be speculated. First, a very high dose of virus might have led to the
second instance of infection and induced more severe disease [177]. Second, it is possible that reinfection was caused by a more virulent variant of the virus, or more virulent in this patient’s context [27]. Third, a mechanism of antibody-dependent enhancement might be the cause, a means by which specific Fc-bearing immune cells become infected with virus by binding to specific antibodies [27]. In fact, the clinical course of some severe COVID-19 cases has been worsened by abnormal immune responses that damage healthy tissue. Patients who experienced that problem during a first infection may have immune cells that are induced to respond disproportionately the second time too. Sometimes antibodies produced in response to SARS-CoV-2 can facilitate the virus during a second infection rather than fight it [178–184]. The phenomenon [185–189] is rare, but researchers have found worrying signs of it while trying to develop vaccines against the coronaviruses responsible for severe acute respiratory syndrome and Middle East respiratory syndrome [190] and against SARS-CoV-2 [191–194].

As researchers accumulate more examples of reinfection, the situation should become clearer. Depending on the criteria used, rates of reinfection can vary widely [195]. There are some reports about retrospective observational study such as that of Pilz et al. that reported 40 cases of tentative reinfection in Austria, but these data are limited by the lack of detailed clinical characteristics [162]. For this reason, in November 2020 the Centers for Disease Control and Prevention pointed out the following criteria to define reinfection with SARS-CoV-2: detection of SARS-CoV-2 RNA (with Ct values < 33 if detected by RT-PCR) >90 days after the first detection of viral RNA whether or not symptoms were present and paired respiratory specimens from each episode that belong to different clades of virus or have genomes with >2 nucleotide differences per month [32]. Cases in which detection of SARS-CoV-2 RNA is present >45 days to 89 days apart are considered reinfections if the second symptomatic episode had no obvious alternate explanation for the COVID-19-like symptoms or there was close contact with a person known to have laboratory diagnosed COVID-19 and paired specimens are available with the Ct values and sequence diversity noted above.

However, the ability to re-infect does not mean that a SARS-CoV-2 vaccine cannot be effective. Some vaccines, for example, require a “booster” dose to maintain protection. Learning more about reinfection could help researchers in developing truly effective vaccines by showing them which immune responses are important for maintaining immunity. For example, researchers may find that people become vulnerable to reinfection after antibodies drop below a certain level, and so they can modify vaccination strategies accordingly using a booster dose to maintain that level of antibodies. At a time when health authorities are grappling with the dizzying logistical difficulties of vaccinating the world population against SARS-CoV-2, the need for a booster injection is a necessity that complicates the management of the vaccination campaign, but it does not make long-term immunity from SARS-CoV-2 impossible. However, some researchers fear that vaccines will only reduce symptoms during a second infection, rather than prevent it altogether. While giving some advantages, this possibility could turn vaccinated individuals into asymptomatic carriers of SARS-CoV-2, putting vulnerable populations at risk. The elderly, for example, are among the most affected by COVID-19, but they tend not to respond well to vaccines. For all these reasons, it would be interesting to see data on how much virus SARS-CoV-2 reinfected individuals spread.

The real problem to be solved is, therefore, the duration of immunity conferred by a COVID-19 episode. There is evidence in the literature that the COVID-19 immune response is variable and patient-specific with respect to the development of antibodies and to antibody persistence in serum over time [146]. In considering the protective effect of antibodies against a reinfection, the evidence is still inadequate, and more research is necessary in order to clarify the interplay between the roles of adaptive and innate immunity. A recent study of Gudbjartsson et al. reported that Icelandic humoral response to SARS-CoV-2 infection was persistent within the 120-day timeframe used with a modest decline in antibody titers after 120 days [196]. Iyer et al. observed declining antibody
titers over 90 days, with “median times to sero-reversion of 71 and 49 days following symptom onset” [197].

The genetic analysis of all the new cases reported as reinfection would help in understanding if the reinfection would be due to a new infection by a different SARS-CoV-2 or a reinfection by the same virus for a decline of immune response, but unfortunately genomic analysis is not available for some of these cases.

5. Conclusions

All these findings are useful and contribute towards the role of vaccination in response to the COVID-19 infections. Collected data show a wide range of situations: spanning a broad distribution of ages, risk groups, baseline health status and reinfection severity compared to the initial infection. Reinfection occurred as early as 45 days or >300 days after the initial infection. Common explanations for reinfection can be either waning SARS-CoV-2 antibodies or the presence of viral escape mutations [198]. While several cases of SARS-CoV-2 reinfection did involve infection with a different clade, it is noteworthy that mutations were identified throughout the genomes and the frequency of mutations within the S gene was not elevated relative to the rest of the genome [199]. In addition, individuals with more severe reinfections did not have significantly greater frequency of S gene mutations [199]. Finally, the presence of rare mutations was uncommon in the re-infecting virus, which largely mirrored the contemporaneously circulating variants in the region of infection, as reported by Choudhary et al. [199]. Concerning the problem of recognizing reinfection and persistent infection, two factors generally differentiated them. First, reinfections have so far been largely described in immunocompetent individuals while the majority of persistent COVID cases have been in immunosuppressed patients [199]. Secondly, phylogenetic analysis can generally differentiate between reinfection and persistent infection, especially in cases where persistent infection allowed the longitudinal collection of >2 sequences [199]. Due to the reinfection cases with SARS-CoV-2, it is evident that the level of immunity is not 100% for all individuals. Reinfection with SARS-CoV-2 is a possibility in both vaccinated and unvaccinated individuals, because vaccines to the virus may not translate to total immunity [199]. Recently breakthrough infections were reported following mRNA vaccination in healthy subjects [200,201], despite evidence of effective immune response among the breakthrough subjects [202]. Another study reported that eight symptomatic SARS-CoV-2 infections occurred in fully vaccinated healthcare workers (incidence rate 4.7 per 100,000 person-days adjusted) [203]. This type of challenge was also observed during the process of vaccine preparation for influenza [204]. Even though several vaccines are ready, the presence of more than 80 genotypical variants of the virus, possibility of reinfection, and short duration of seropositivity for neutralizing antibodies raise the concern that vaccination may not result in an effective and long-term immunity against SARS-CoV-2. Furthermore, immunoglobulin levels may not correlate with viral shedding and risk of transmissibility of SARS-CoV-2 [205]. Additionally, the short duration of immunity against the virus may not allow for increasing homogeneity of affected populations in a non-specific time frame. These factors raise concerns that eliminating the COVID-19 pandemic may not be as feasible as once assumed and that we must rely more on prevention of transmission until more aspects of the virus and its pathogenicity are discovered. A recent study suggested that among persons with previous SARS-CoV-2 infection, full vaccination provides additional protection against reinfection [206]. In fact, among previously infected Kentucky residents, those who were not vaccinated were more than twice as likely to be reinfected compared with those with full vaccination [206]. Data from literature are comforting: out of hundreds of millions of people infected with the virus and then cured, only a few are reported cases of confirmed reinfection [199]. Despite the appearance of different variants of the virus, vaccines seem to help us for the near future. However, the presence of immunosuppressed or transplanted subjects requires us to continue to observe the precautionary rules useful to prevent the spread of the virus. In fact, it is imperative that all individuals, whether previously diagnosed with COVID-19 or not should take identical
precautions to avoid reinfection with SARS-CoV-2 till the time when community immunity had been achieved [207]. All eligible persons should be offered vaccination, including those with previous SARS-CoV-2 infection, to reduce their risk for future infection [206].

This report highlights how it is necessary to continue to observe all the prescriptions recently indicated in the literature [208–210] in order to avoid new contagion for all patients after healed from COVID-19 or asymptomatic positive, since the infection does not ensure complete immunity in 100% of cases.

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