

Original research article

Incidence of recurrent SARS-CoV-2 infections during the COVID19 pandemic in Madina, Saudi Arabia

Abstract

Background

SARS-CoV-2 infections emerged in China and spread globally causing the Corona virus disease 2019 (COVID19) pandemic. Dispersed reports from different countries reported the possibility of the incidence of SARS-CoV-2 reinfection in individual reported cases. The aim of this report was, therefore, to document several recurrent infection cases in Saudi Arabia to furtherly augment this body of evidence.

Methods

The study was conducted retrospectively from October 2020 to October 2021. The study included patients who had experienced multiple COVID-19 infections, which were confirmed through qPCR tests. There was a minimum gap of three months between each infection, and the patients had tested negative after each infection. Personal or phone interviews were conducted with the patients.

Results

In total, 10 cases (7 males and 3 females) of COVID19 recurrent infections were reported with an average age of 34.1 years. The most common symptoms included fever, headache, body aches, sore throat, cough, diarrhea. With the exception of one case that required hospitalization during the third infection and one case of miscarriage during the first infection, all reported cases were mild. The average duration of illness for the first infection was 13.9 days, while for the second infection, it was 12.9 days. Only one patient reported being vaccinated before his second course of infection.

Conclusion

Infection with COVID-19 does not provide life-long protection. The possibility of recurrent and repeated reinfection with COVID-19 was presented in several cases especially in healthcare

workers, indicating that screening of COVID19 infection in hospitals and healthcare centers is essential.

Key words:

COVID-19; SARS-CoV-2; reinfection; recurrence; case

UNDER PEER REVIEW

Introduction

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection, also known as the new corona virus disease 2019 (COVID-19), was declared as a worldwide pandemic in the year 2020 (Ren, 2020 #420). COVID-19 was first reported in December 2019 in Wuhan, China, and spread progressively throughout China and then to the whole world (Li, 2020 #421). Many questions remain without an answer until now. A main concern is the possibility of being infected more than once with SARS-CoV-2. It remains unclear how well and how long the immune responses protect the host from reinfection. However, for some viruses, the first infection can provide lifelong immunity; for seasonal coronaviruses, protective immunity is short-lived (Siggins, 2021 #422).

Reports of COVID-19 reinfection have emerged from various countries across the globe. In several instances, individuals who had previously recovered from COVID-19 experienced a recurrence of symptoms and tested positive for SARS-CoV-2 again. These reinfection cases have occurred in individuals of different age groups, with varying severity of symptoms, and in both immunocompromised and immunocompetent individuals (Malhotra, 2022 #419).

COVID-19 high capacity for human-to-human transmission is alarming. During the course of the COVID-19 disease, no antiviral agent has yet shown reasonable efficiency, however, few antiviral drugs showed some promise [1,2]. Currently, only few individuals had serological data from the first infection while some had pre-existing antibody (IgM) against SARS-CoV-2. While differences in the viral genome sequences of the various isolates is an excellent method to identify if an individual was reinfected, it does not indicate that the second infection was due to immune evasion. A recent case study report has shown that reinfection with different variants of SARS-CoV-2 may occur, however, it was a single case study [3]. Indeed, primary infection of Rhesus macaques with SARS-CoV-2 was shown to stimulate an immune response which can prevent infection after a second exposure to the virus, nonetheless, the endurance of the immune response was only measured short-term [4]. To date, there are few case reports on reinfection including six cases reported in the United Kingdom (UK) [5], 14 cases in France [6,7], and 3 cases in China [8]. From Saudi Arabia, further four cases were reported [9]. In some arguments within the scientific community, reactivation of a latent infection was also suggested. There is currently some evidence that SARS-CoV-2 variant can emerge as a result of immune evasion. Reports about cases of primary illness due to infection followed by a discrete secondary infection or

illness with the same biological agent remains scarce and uncertain. Reports of secondary infection events with SARS-CoV-2 have been published from Hong Kong, Netherlands, Belgium, and Ecuador with only a limited number of patients. Negative results between two consecutive infections were missing in a number of these studies, which does not help rule out the possibility that those patients may not have recovered from the initial infection at the first place. Therefore, more evidence is required to better understand the nature of reinfection with COVID-19 to protect healthcare workers and the population from being re-infected twice with SARS-CoV-2.

Methods

This was a retrospective study aiming to investigate the possibility of multiple infection with SARS-CoV-2. After obtaining ethical clearance (No. COPTU-REC-13-20210401), patients with multiple COVID-19 infections during the period starting October 2020 until October 2021 were allocated. Identified patients were interviewed personally or through the phone and informed consent was taken from each patient. The consent was in Arabic language, explaining the research plan, benefits, risks, and information regarding the researchers. A clear statement of patients' rights was included with an option to agree or refuse to participate. Researchers filled in a questionnaire covering several questions; age, sex, occupation, and the date of the initiation of symptoms, date of first qPCR positive and negative results, number of days during which the symptoms persisted, symptoms and isolation (home or hospital) for each infection course. Enrolment criteria included all COVID19 patients who were infected with SARS-CoV-2 more than once as confirmed with quantitative real-time polymerase chain reaction (qPCR) tests, with at least three months between infection, and a negative test after each infection. Real-time PCR results were obtained along with patients' history and previous positive and negative tests of COVID19. For each patient, his/her first infection with COVID19 was compared to the second infection to evaluate symptoms and disease severity. All measures were taken to preserve the integrity and privacy of the data. All subjects were assigned a study identification number and stayed anonymous while information which identifies patients were not used.

Results

Case 1

The first case was for a 48-year-old male working as a receptionist in the COVID19 referral hospital in Madinah. He was first diagnosed with positive SARS-CoV-2 qPCR result on the 24th of May 2020, and the CT value was 32.6. He had symptoms for 2-3 days prior to the first positive PCR result. During this course of infection, he had fever, generalized bone ache, cough and diarrhea which he reported to have persisted for around two weeks. He was in home quarantine until he obtained his first negative result on the 3rd of July 2020. The second infection occurred around six months later, as he tested positive for SARS-CoV-2 on the 23rd of November 2020. He reported more severe symptoms than his first illness, including fever (38.5° C), cough, muscle pain, diarrhea, and headache. He was isolated at home for two weeks.

Case 2

The patient was a 32-year-old female nurse working at the ophthalmology department in the COVID19 referral hospital in Madinah. She was also taking some shifts at the visual triage reception of the outpatient clinics. She was first diagnosed with COVID19 by qPCR on the 18th of July 2020 and reported that she had been ill for around 10 days. She had her first negative PCR result on the 1st of August 2020. The symptoms were severe, including fever, nausea and vomiting, diarrhea, bone aches, headache, severe back pain, and loss of smell and taste. Additionally, the patient was pregnant and suffered miscarriage while she was at home isolation. Her second course of infection was diagnosed with a positive qPCR test on the 8th of November 2020 and the duration was ten days as reported by the patient. She did not have another PCR, as home isolation until the disappearance of the symptoms was enough at that time. Her symptoms in the second infection were reported by her as 'moderate' as compared to the first infection. The symptoms she displayed in the second infection included fever, bone aches, back pain, abdominal cramps, headache, and pharyngitis.

Case 3

A 47-year-old male was diagnosed with positive COVID19 three times. The first occasion, was on the 15th of October 2020. The patient was complaining of abdominal pain, diarrhea, chest pain followed by breathing difficulties and fever. The symptomatic duration of the first course of infection was 21 days and the patient was in home quarantine. The second infection was diagnosed on the 15th of December 2020 and lasted for seven days. The symptoms included

cough, fever and chest pain and he was assigned to stay home for quarantine again. The third time occurred on the 30th of March 2021, and the respiratory symptoms were severe. The symptoms included chest pain, persistent cough, fever, low oxygen saturation and a heart attack due to myocardial infarction. The patient was hospitalized for around a month and stayed at home for a further month to retain his respiration back to normal and regain his energy.

Case 4

A 33-year-old female was first diagnosed with COVID-19 infection returning a positive qPCR test on the 23rd of October 2020. Her symptoms started two days earlier, as she was complaining of severe headache, cough, dryness in the throat, fatigue, and malaise. She was isolated at home and her first negative qPCR result was on the 14th of November 2020. After around seven months her second infection was confirmed on the 13th of May 2021 after one day of the symptom's appearance, and she reported that her symptoms in the second infection were less severe compared to the first infection. Symptoms during the second course of infection included headache, cough, dry mouth, and easy fatigability. She was isolated at home until her symptoms disappeared.

Case 5

A 30-year-old male physician was diagnosed with COVID-19 by qPCR on the 31st of March 2020 but he already had symptoms for one day before. The patient reported his symptoms as pain in the throat without fever. After 19 days of isolation in a hotel, the patient had his first qPCR negative results on the 18th of April 2020. The second course of COVID-19 infection which occurred around six months after the first infection was diagnosed on the 24th of October 2020 by qPCR. His symptoms in the second infection were generalized bone aches, diarrhea, and cough. He was isolated at home until he obtained his first negative result on the 23rd of November 2020.

Case 6

A 42-year-old male physician was first diagnosed with COVID-19 by qPCR on the 19th of May 2020 but he did not have any symptoms. After eight days of hospital isolation, he had his first negative qPCR result on the 19th of November 2020. His second infection was diagnosed by qPCR on the 15th of July 2021, as he reported having fever and runny nose and he did not take another

qPCR test in his second infection as his symptoms resolved. The patient was given a self-isolation period before returning to work. Of note, the patient was vaccinated with the second dose of AstraZeneca vaccine on the 2nd of February.

Case 7

A 15-year-old male was first diagnosed with COVID-19 on the 3rd of January 2021. His symptoms included diarrhea, common cold-like symptoms, jointspain, and headache. His symptoms were mild and lasted for ten days **during which** he required home isolation. The second infection was diagnosed on the 6th of February 2021 **with a positive qPCR test**, suffering from common cold symptoms and headache. He was isolated at home for seven days until the symptoms resolved.

Case 8

A 23-year-old male was first diagnosed with COVID19 on the 7th of July 2020. His symptoms included fever, severe sore throat, and loss of taste and smell. The duration of the disease was 10 days. On the 2nd of January 2021 he was diagnosed positive for COVID19 for the second time, he had sore throat with no fever and his symptoms lasted for 7 days. In both incidents he was assigned to home isolation by healthcare authorities.

Case 9

The first course of infection in a 48-year-old female was **reported** on the 23rd of May 2020. She was allocated to a hotel room isolation for 14 days. Her symptoms **included** loss of smell and taste, drowsiness, and disorientation. The second time she tested positive was on the 1st of May 2021. She obtained her first negative result after 14 days from her positive qPCR result. **She reported that her** symptoms were more severe on the second infection, including fever, sore throat, difficulty in respiration and disorientation.

Case 10

A 23-year-old male who was diagnosed with positive qPCR test on the 22nd of November 2020. He was isolated at home until he obtained his negative COVID19 test result after ten days. His symptoms were mainly sore throat with fever and loss of smell and taste. The second time he tested positive for COVID19 was on the 7th of August 2021 with mild symptoms including only

sore throat. He was isolated at home for seven days as he obtained his first negative COVID19 qPCR result. A brief description of cases is shown in Table 1.

Table 1:

CASE NO.	SYMPTOMS	DURATION OF SYMPTOMS	ISOLATION	NOTES
CASE 1 AGE: 48 GENDER: MALE OCCUPATION: HOSPITAL RECEPTIONIST				
FIRST INFECTION	Fever, generalized body pain, cough and diarrhea	14 days	Home	
SECOND INFECTION	Fever, cough, muscle pain, diarrhea, and headache	14 days	Home	
CASE 2 AGE: 32 GENDER: FEMALE OCCUPATION: NURSE				
FIRST INFECTION	Fever, nausea and vomiting, diarrhea, body pain, headache, severe back pain, and loss of smell and taste and miscarriage.	10 days	Home	Pregnant
SECOND INFECTION	Fever, body pain, back pain, abdominal cramps, headache, and pharyngitis	10 days	Home	
CASE 3 AGE: 47 GENDER: MALE				
FIRST INFECTION	Abdominal pain, diarrhea, chest pain followed by breathing difficulties and fever	21 days	Home	
SECOND INFECTION	Cough, fever and chest pain	7 days	Home	
THIRD INFECTION	Chest pain, persistent cough, fever, low oxygen saturation and a heart attack due to blood clotting events	60 days	Hospital and Home	
CASE 4 AGE: 33 GENDER : FEMALE				
FIRST INFECTION	Severe headache, cough, dryness in the throat, fatigue, and malaise	23 days	Home	
SECOND INFECTION	Headache, cough, dry throat, and tiredness		Home	
CASE 5 AGE:30 GENDER: MALE				

FIRST INFECTION	Pain in the throat without fever	19 days	Hotel	
SECOND INFECTION	Generalized body pain, diarrhea, and cough	31 days	Home	
CASE 6 AGE: 42 GENDER: MALE				
FIRST INFECTION	Without symptoms	8 days	Hospital	
SECOND INFECTION	Fever and runny nose	14 days	Home	vaccinated 2nd dose
CASE 7 AGE: 15 GENDER: MALE				
FIRST INFECTION	diarrhea, common cold-like symptoms, joint pain, and headache	10 days	Home	
SECOND INFECTION	common cold symptoms and headache	7 days	Home	
CASE 8 AGE: 23 GENDER: MALE				
FRIST INFECTION	fever, severe sore throat, and loss of taste and smell	10 days	Home	
SECOND INFECTION	sore throat with no fever	7 days	Home	
CASE 9 AGE: 48 GENDER: FEMALE				
FIRST INFECTION	loss of smell and taste, drowsiness, and disorientation	14 days	Hotel	
SECOND INFECTION	fever, sore throat, difficulty in respiration and disorientation	14 days	Home	
CASE 10 AGE: 23 GENDER: MALE				
FIRST INFECTION	mainly sore throat with fever and loss of smell and taste	10 days	Home	
SECOND INFECTION	sore throat	7 days	Home	

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Discussion

Since the emergence of the novel coronavirus, SARS-CoV-2, our understanding of its dynamics and the immune response it elicits has evolved. While initial assumptions suggested that infection with COVID-19 would confer long-lasting immunity, increasing evidence has demonstrated the possibility of reinfection (Vora, 2021 #417)(Gupta, 2021 #418). This one of the first reports of reinfection with SARS-CoV-2 in Saudi Arabia, although few reports have shown some cases in other countries. Cases from the city of Madinah in Saudi Arabia were investigated from the database records. Therefore, this study aimed at reporting the possible cases of reinfection with COVID19 more than once after recovering and obtaining negative PCR results. Obtaining a negative PCR result was one of the criteria for the inclusion of cases in this report. This was an important criterion to rule out any possibility that the initial viral infection persisted, asymptotically, for months. Also, the time between two infections is an essential information, as cases of reinfection twice within less than 3 months can be criticized for the same reason. Of note, case 3 had only two months period between first and second infections. The patient did not have a negative result in between, however, he was included in this study because he had a third infection which was separated by more than three months from the second infection. In this case, the patient did not perform a qPCR test because the regulation at that time was that the patient is considered recovered and can return to work after three days with no symptoms. Of note, this was the only case added to this series of cases which was not in Madinah. Although the number of cases reported does not represent a large percentage from the overall cases count in the area, still, it confirms the possibility of reinfection and confirms the fact that immunization after first exposure is mostly variable between different individuals. Regarding case 2, the first infection resulted in miscarriage in the first infection of a female nurse. Of note, premature labor and preeclampsia were also reported in previous reports [10].

COVID-19 reinfections have exhibited distinct characteristics. Reinfection cases often occur months after the initial infection, with some studies reporting an average interval of around 3-6 months. In many cases, the symptoms observed during reinfection have been milder compared to the initial infection. However, severe reinfections have also been documented, emphasizing the unpredictable nature of the disease (Jain, 2021 #416). The use of neutralizing monoclonal antibodies was shown to have beneficial effects [11], while IgG and memory B cells specific to the spike protein of SARS-CoV-2 were detectable after six months of infection, showing that an

immune memory can help protect from a second infection, however, CD4+ and CD8+ cells were shown to decline within a range of 3 to 5 months [12].

Because of the lack of knowledge about the pathogen, the front-line healthcare workers were most affected. Additionally, the period of exposure to such a threat is prolonged for healthcare professionals who spend long hours at work, with higher possibility of getting exposed to the virus which can be transmitted by direct contact [13] or airborne routes. For sure, personal protecting equipment [2] can help, however, this differs from one hospital to another and from one country to other countries around the world. Most of the cases reported here were healthcare workers, showing that surveillance of COVID19 infection in hospitals and healthcare centers is essential to protect them.

Animal models were used to study the possibility of reinfection with SRAS-CoV-2, however, clinical data from COVID19 patients is more relevant. This is because the immune response is different, as evident from a recent work by Bao et al (2020) showing that reinfection does not occur in rhesus macaques[14]. Additionally, the angiotensin converting enzyme 2 receptor (ACE2) reported as the gateway for viral entry to human cells [15] is expressed differentially in experimental animals [16], and the SARS-CoV-2 manifestations can be different from humans.

Conclusion

The results suggest that immunity acquired from a COVID-19 infection may not guarantee lifelong protection. There have been reported instances of recurring and repeated reinfection with COVID-19, particularly among healthcare workers. This highlights the importance of conducting regular screenings for COVID-19 infection in hospitals and healthcare facilities.

Authors contributions

Authors' Contribution Statement:

Hossein Mostafa Elbadawy, Amin Khaled Khattab, and Fahad Dakilallah Aljohani were involved in the conceptualization and design of the study. They contributed to data collection, analysis, and interpretation. Mekky Abouzied, Mohannad A Bahlaq, and Khalid Abdelkarim Abdalla participated in the data collection, performing laboratory tests, and data analysis. Sultan Hamid M. Aljohani, Heba M. Eltahir, Rania K. Alharbi, and Talal Aljumaidi contributed to the data interpretation, statistical analysis, and critically reviewing the manuscript for important

intellectual content. Amr Maher Galal, Muayad Albadrani, Mohannad A. Almikhlaifi, and Ahmed Aldhafiri assisted in data collection, literature review, and drafting the manuscript. All authors reviewed and approved the final version of the manuscript for submission and take responsibility for the accuracy and integrity of the work presented in the article.

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