



## Laboratory-confirmed SARS-CoV-2 reinfection in the population treated at social security

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### ABSTRACT

The scientific community has questioned whether reinfection with SARS-CoV-2 is possible. Gradually, cases of reinfection have been documented. In Mexico, people with SARS-CoV-2 reinfection have not been officially identified. To allow a retrospective investigation of patients with PCR-confirmed SARS-CoV-2 and to identify how reinfected with this virus occurs in a population that requires medical attention. A retrospective search of the epidemiological surveillance system was performed to identify people who met the clinical criteria based on laboratory diagnosis of SARS-CoV-2 and temporality to identify cases of reinfection. Clinical information was collected from clinical records. Seven people with two separate COVID-19 events were identified in medical units in Quintana Roo, Mexico between April and December 2020. The overall median interval between the two events was 156 days (61–191 days). Six people were health workers, and one was a member of the general population. This is one of the first reports of reinfection in health personnel in Mexico, revealing that the frequency of reinfection is low among positive cases and that the interval between infection episodes was three months. There are several scenarios in the natural history of the disease that must be considered based on adequate anamnesis with a clinical-epidemiological approach to determine the correct diagnostic category.

### 1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging viral disease. It was initially called 2019 NCoV and is caused by a type 2 coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2) [1]. SARS-CoV-2 is a zoonotic agent that was initially related to several incidental hosts [2,3].

In Mexico, at the beginning of January 2020, a Preventive Notice of Travel to China for Pneumonia of Unknown Etiology was issued [4]; days later, on February 27, the first positive case was identified in Mexico City, and the country's health authorities decided to initiate phase one of the emergency response [5]. Subsequently, the first suspected cases were reported by the Mexican Institute of Social Security (IMSS) in the states of Hidalgo and Mexico, and the first confirmed case was reported at a third-level social security facility in Mexico City.

COVID-19 is characterized by different patterns of disease progression that suggest various host immune responses [6,7]. The scientific

community has questioned whether reinfection by this agent is possible. Some cases were initially documented in Hong Kong [8], the Netherlands and Belgium [9], Ecuador [10] and the USA [11]. One death from reinfection has even been reported in the Netherlands [12]. Among symptomatic people, various intervals between infection events have been reported, with a range from 43 to 142 days; and the average interval is 85.3 days [13]. In Mexico, COVID-19 reinfections have not been officially reported [14]. Similarly, epidemiological surveillance of this disease in Mexico does not include the determination of antibodies [15]. Because the IMSS serves an important proportion of the Mexican population, the COVID-19 pandemic represents an important challenge that could persist for the medium or long term if there are no effective strategies for reducing this problem. Currently, there are few documented cases of reinfection throughout the world, with heterogeneous intervals between events for each patient [13]. The presence of this phenomenon would have a negative impact on the individual at the psychological level and on the host environment and economy.

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Quintana Roo, Mexico is a national and international tourist destination that offers wide mobility. Although tourist and economic activities were restricted at the beginning of the pandemic, as time passed, there was flexibility to allow for a return to the “new normal”. Therefore, the objective of the present study is to conduct a retrospective investigation of patients with PCR-confirmed SARS-CoV-2 infection and to identify reinfections with this virus in a population that required medical attention at the medical units of the IMSS in Quintana Roo in 2020.

## 2. Material and methods

### 2.1. General description of the study

Patient data was obtained from the database of the Online Notification System for Epidemiological Surveillance (SINOLAVE, by its acronym in Spanish), an epidemiological surveillance system that operates in all IMSS medical units. People who were registered more than one occasion between February and December 2020 were identified by the date of symptom onset based on their social security number, full name, age, date of notification and onset of symptoms. Those who had positive laboratory results for SARS-CoV-2 for all their events were retained. A search for these patients in the Epidemiological Control System for the Laboratory was performed to collect the results for subsequent (follow-up) samples. Finally, a review of the electronic clinical records was performed to obtain complete information about the clinical conditions of the patients' care. The intervals between events were determined by the date of symptom onset.

Excluded were a) patients treated at the medical units of the IMSS with only one notification, and b) patients treated at the medical units of the IMSS with more than one notification who met any of the following exclusion conditions: no sample, a rejected sample, a positive result for an infection other than SARS-CoV-2 or a negative result for SARS-CoV-2. We eliminated patients who, despite having received care at the medical units of the IMSS on more than one occasion during 2020, did not have available clinical records.

### 2.2. Criteria for reinfection

Reinfection was primarily determined by the identification of a second event in the SINOLAVE. The following criteria were established for identifying a reinfection event: a) a temporal parameter of an interval of at least 40 days between the onset of symptoms of the first infection and the second infection, with clinical improvement between each event; b) a laboratory parameter, with positive SARS-CoV-2 results reports for each event; and c) a clinical parameter, evidenced by the remission of the clinical manifestations of infection.

### 2.3. Data collection and manipulation

The special epidemiological surveillance system is operated through an online platform that is exclusive to the institution and requires a username and password with a user profile. This study was submitted as a research protocol to the National Committee for Scientific Research of the IMSS and was approved on January 30, 2020, with the registration number R-2021-785-013.

## 3. Results

### 3.1. General findings

Between April and December 2020, seven patients who were managed at the first and second levels of care. The overall median interval between infection events was 156 days (61–191 days). Six of the identified patients were health workers, and one was a member of the general population. In terms of place of residence, two lived in the municipality of Cozumel, and five lived in Benito Juárez. The median

age was 35 years (22–57 years). The median interval between symptom onset and seeking medical attention was two days (range: 0 to 9). A chronological detailing of the laboratory results is presented in [Table 1](#). All cases without a history of vaccination against COVID-19; since the vaccination program in Mexico began in December 2020.

### 3.2. Case 1

Physician aged 48 years, with asthma and right pulmonary lobectomy in childhood due to the presence of bullae. The patient was in a domestic partnership. A total of 160 days elapsed between the two infection events. The first event began on April 23, 2020; that day, the patient sought medical attention for headache, cough, sudden onset, odynophagia, general malaise, myalgia and arthralgia. He noted that he had contact with COVID-19 cases in his workplace. A sample was positive for SARS-CoV-2 by PCR; a second pharyngeal sample was collected that was negative for SARS-CoV-2. The second event occurred on September 30, 2020; the clinical manifestations were the same as for the first event, with the addition of prostration and abdominal pain. On October 5, a sample of pharyngeal exudate was taken and was positive for SARS-CoV-2. The patient initially received ambulatory management with paracetamol and supplemental oxygen and transrectal ozone therapy at home. Subsequently, on October 8, he was admitted to the hospital in Playa del Carmen. During the stay, he remained in a prone position and received oxygen via the Puritan system with 80% FiO<sub>2</sub>, reaching 98% saturation. The patient was maintained in the intermittent prone position with a progressive decrease of FiO<sub>2</sub> to 40% and a saturation of 96–98%. On October 13, with 96% oxygen saturation via nasal cannula at 3 L/min, the patient was discharged to go home with medical disability.

### 3.3. Case 2

Nurse aged 32 years, without comorbidities and with an interval of 71 days between events. The symptoms of the first event started on June 12 and included fever, headache, cough, odynophagia, myalgia and arthralgia. Three days later, the patient sought medical attention at his workplace. Pharyngeal/nasopharyngeal exudate was collected and tested positive for COVID-19. The patient reported contact with another case at his workplace and was treated with penicillin sodium and paracetamol. From June 19 to 29, the patient received daily telephone follow-up; June 29, medical disability was extended for eight more days. On June 26, a negative SARS-CoV-2 result was obtained from a second sample. The patient presented for the second event on August 22; he sought medical attention at a second-level hospital in Playa del Carmen three days after the onset of symptoms, which were the same as for the first event with the addition of rhinorrhea, chills, diarrhea, and chest pain. Samples of pharyngeal and nasopharyngeal exudate were taken on August 25 and three days later, and the laboratory results were positive for COVID-19. He was placed on disability for eight days and was referred for physical medicine and rehabilitation.

### 3.4. Case 3

Medical assistant, 42 years old, residing in Cozumel. The patient experienced fever and cough beginning on April 9, followed by headache, myalgia, chills and chest pain. On April 22, a sample of pharyngeal exudate was taken, and a SARS-CoV-2-positive result was returned on April 27. The patient suffered from systemic arterial hypertension. On May 13, a second (follow-up) sample was collected and also tested positive. The third sample, taken on May 23, was negative for the virus. The second event occurred 156 days later. Symptoms began on September 12 and were managed on an outpatient basis. On September 14, samples of pharyngeal and nasopharyngeal exudate were collected, and a positive result was returned four days later. Clinical improvement was observed.

**Table 1**  
General description of the results of the positive cases of COVID-19.

Case	Specimen A		Specimen B	Specimen C	Specimen D		Interval (days)
	Onset of symptoms	Date and result	Date and result	Date of collection	Onset of symptoms	Date and result	
Case 1	4/23/2020	4/29/2020 Positive CT 34.79	5/14/2020 Negative	Not collected	9/30/2020	10/5/2020 Positive CT 27.3	160
Case 2	6/12/2020	6/15/2020 Positive CT 25.36	6/26/2020 Negative	Not collected	8/22/2020	8/25/2020 Positive CT 36.46	71
Case 3	4/9/2020	4/22/2020 Positive	5/13/2020 Positive CT 37.42	5/23/2020 Negative	9/12/2020	9/14/2020 Positive CT 17.08	156
Case 4	4/23/2020	4/25/2020 Positive CT 36.2	6/8/2020 Negative	Not collected	10/23/2020	10/23/2020 Positive CT 33.81	183
Case 5	10/31/2020	11/4/2020 Positive CT 32.83	12/8/2020 Negative	1/9/2021 RAT Negative	12/31/2020	1/11/2021 Positive CT 31.44	61
Case 6	6/23/2020	6/25/2020 Positive CT 16.74	7/9/2020 Negative	Not collected	9/19/2020	9/21/2020 Positive CT 35.51	88
Case 7	6/19/2020	6/24/2020 Positive CT 26.28	7/2/2020 Negative	Not collected	12/27/2020	12/30/2020 Positive CT 33.84	191

RAT: Rapid antigen test for SARS-CoV-2.

### 3.5. Case 4

Physician, 33 years of age, with no basic comorbidities. Her symptoms began on April 23, 2020, and were characterized by sudden onset, cough, headache, odynophagia, rhinorrhea and abdominal and chest pain. On April 25, the first pharyngeal exudate sample was taken; it came back positive for SARS-CoV-2 on April 29. On June 8, a second (follow-up) sample returned a negative result. The second episode occurred 183 days after the onset of symptoms of the first episode. Symptoms began on October 23, 2020, and were characterized by cough, odynophagia, myalgia and arthralgia, and the patient was granted eight days of medical disability. On October 28, a pharyngeal/nasopharyngeal exudate sample was taken, and after two days, it came back positive for SARS-CoV-2 by PCR. The patient's medical history included a brother who died of COVID-19. Her illness was managed on an outpatient basis, and she was on medical disability for 13 days.

### 3.6. Case 5

Physician, 35 years old, with no related underlying diseases. Symptoms began on October 31, 2020, with headache, odynophagia, myalgia and arthralgia. On October 3, she sought medical attention at the Family Medicine Unit. The following day, a sample of pharyngeal/nasopharyngeal exudate was collected, and positive results were returned on November 5. Four days of leave were requested. From November 10 to 14, follow-up was conducted by telephone; the patient had symptoms but no alarming signs. On December 18, another sample was taken, which was negative. The patient had previously presented clinical improvement; however, she was entered the epidemiological surveillance system again on December 11 for a return of symptoms, which showed clinical improvement. On December 31, she again experienced symptoms, including fever, cough, nausea, myalgia, arthralgia, rhinorrhea, anosmia and dysgeusia. She had a sister who had tested positive for SARS-CoV-2. On January 9, a pharyngeal/nasopharyngeal sample was taken; two days later, PCR testing indicated that it was positive for SARS-CoV-2. That day, an exudate sample was taken for rapid antigen determination, which was negative. Sixty-one days elapsed between the events.

### 3.7. Case 6

Nurse in the adult intensive care unit, 22 years old, without comorbidities. The first event began with symptoms on June 23, 2020, including fever, cough, myalgia and difficulty breathing. After two days, the patient sought medical attention; a sample of pharyngeal/nasopharyngeal exudate was taken, and on June 27, a positive SARS-CoV-2 result was reported. The patient was granted work disability for 11

days. She showed clinical improvement, and on July 9, a PCR test was negative for COVID-19. She returned to work. The second episode began 88 days later, on September 19, 2020, with the sudden presentation of fever, cough, headache, diarrhea, and chest pain. She went to the hospital three days later for medical attention. A sample of pharyngeal/nasopharyngeal exudate was taken, it was found positive for SARS-CoV-2. On October 22, a pharyngeal exudate sample was found negative for SARS-CoV-2.

### 3.8. Case 7

Male, aged 57 years, with obesity and systemic arterial hypertension. The first event began on June 19, 2020, and was characterized by cough, headache, myalgia, diarrhea and irritability. The same day, he went to the hospital for evaluation. A pharyngeal exudate sample was taken on June 24, and two days later, the sample was found positive. The patient reported having been in contact with suspected cases at his workplace. On July 2, a control sample was found negative for the virus. The second episode occurred 191 days later, on December 27, 2020, and the patient presented at the same medical unit he had gone to for the first episode. The clinical manifestations were cough, odynophagia and rhinorrhea. On December 30, the patient sought medical attention; a pharyngeal/nasopharyngeal exudate sample was taken, and on January 3, 2021, PCR testing was SARS-CoV-2. The patient presented clinical improvement.

## 4. Discussion

We report seven patients who presented with two separate COVID-19 events at medical units in Quintana Roo. On October 27, 2020, the Pan American Health Organization (PAHO) published provisional guidelines for the detection of reinfection with SARS-CoV-2 [16]. These guidelines define reinfection in people with and without symptoms who had a positive result for an event, followed by another positive result for a new event  $\geq 90$  days later provided that prolonged shedding of the virus has been ruled out, and in people who have a positive SARS-CoV-2 result  $\geq 45$  days after the first infection provided that prolonged shedding of the virus and a previous positive result for SARS-CoV-2 or viral RNA from another agent has been ruled out. Using the provisional criteria of the PAHO, we identified seven cases with a median interval of 156 days (61–191 days) between events and a negative test to rule out prolonged shedding. The interval between events required for a case to be considered a reinfection is still not well defined; clarification of the operational definition of reinfection is ongoing [16,17] and while some authors suggest an interval of 80 days [18], intervals as long as 201 days have been recommended [17]. Of the 19,483 suspected cases reported in the social security system of Quintana Roo, 4459 had positive laboratory results for SARS-CoV-2, and seven patients with SARS-CoV-2 reinfection

were identified. This represents 0.16% of positive cases, which is less than the proportion reported in a study performed in Mexico that included 258 cases of reinfection (0.26%) [19]. However, the previous study did not consider a laboratory criterion of negative results, and the interval between episodes was as short as 28 days from the onset of symptoms; thus, some events may have been second episodes of symptoms and not reinfections. In this sense, there are several publications that use different categories and terms for this phenomenon: reinfection [19,20] recurrence or relapse [21] and second episode [15] with precise criteria for each term. Second episodes are those with a second documented SARS-CoV-2 infection and a history of laboratory-confirmed infection but with no negative result between the two episodes, which is required for a case to be considered a reinfection. For all of these diagnostic categories, prolonged shedding of the virus must be excluded. However, what is currently controversial is the criterion of temporality between one episode and another. Although relapse occurs in people with less than 45 days between one event and another, despite having presented clinical improvement, Piri defines relapse as testing positive for the virus for more than two weeks and with worsening clinical manifestations [21]. A meta-analysis of 2568 individuals revealed that interval for recurrence was 35.4 days; however, it has been proposed that recurrence is different from reinfection [22].

Murillo et al. reported that the majority of reinfection cases were under 50 years of age. This is consistent with the findings of the present study, in which the seven reported patients had a median age of 35 years. However, the majority of the patients were health workers who were in contact with patients with suspected COVID-19, and while an increased risk of infection by contact *per se* must be excluded, the total time the patients received care must also be considered [23]. In this sense, the present case report had a predominance of health personnel; given that Mexico was affected by the pandemic from its beginning until the third quarter of 2020, it was recommended that at least two samples be taken from health personnel: one to allow an initial diagnosis and another follow-up sample to determine their readiness to return to work [24].

The results of the meta-analysis of studies on reinfection indicated that a second positive PCR result should not always be considered reinfection or reactivation of the disease because there may be false negative scenarios when discharging patients or examining those who do meet the criteria for hospital discharge [20]. Nonetheless, these scenarios are possible, and adequate anamnesis with a clinical-epidemiological approach should be performed to determine the correct category. Additionally, health personnel are at increased risk of infection due to the learning curve associated with proper use of personal protective equipment, the duration of exposure to confirmed cases of SARS-CoV-2, the physical and mental fatigue that can lead to errors in personal protection measures and the risk of contagion in the community [23]. One limitation was that a laboratory study was not carried out to identify a variant of the virus.

Finally, this is one of the first reports of reinfection in health personnel in Mexico. The findings reveal that the frequency of reinfection is low among positive cases and identifies an interval of three months between infection episodes. Similarly, the study shows that there are several categories that are used synonymously but incorrectly.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.rmcr.2021.101493>.

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