*Short Communication*

# Vaccination and Younger Age Are Associated with Recurrent Laboratory-Confirmed Symptomatic SARS-Cov-2 Infections

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**Abstract:** Background: Repeated SARS-CoV-2 infections are plausible and related published data are scarce. We aimed to identify factors associated with the risk of recurrent (three episodes) laboratory-confirmed symptomatic SARS-CoV-2 infections. Methods: A retrospective cohort study was conducted and 1,700 healthcare workers were enrolled. We used risk ratios (RR) and 95% confidence intervals (CI) to evaluate factors associated with symptomatic SARS-CoV-2 infections. Results: We identified 14 participants with recurrent illness episodes. Therefore, the incidence rate was 8.5 per 10,000 person-months. In multiple model, vaccinated adults (vs. unvaccinated, RR = 1.05 [1.03 - 1.06]) and those with a severe first illness episode (vs mild disease, RR = 1.05 [1.01 - 1.10]) were at increased risk for repeated symptomatic SARS-CoV-2 reinfections. Increasing age showed a protective effect (per each additional year of age: RR = 0.98 [0.97 - 0.99]). Conclusions: Our results suggest that recurrent SARS-CoV-2 infections are rare events in adults and they seem to be determined, partially, by vaccination status and age.

**Keywords:** COVID-19; SARS-CoV-2; Reinfection

## 1. Introduction

Evidence derived from observational studies shows that patients who have recovered from coronavirus disease 2019 (COVID-19) by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can develop natural immunity [1]. However, a high varia-

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bility in antibodies titers has been documented and healthcare workers seem to be at high reinfection risk [2].

In addition, and even when effecting to preventing severe disease-related outcomes [3], waning immunity after COVID-19 vaccination has been documented at months from vaccination in all the vaccines which use is widespread [4].

Under these considerations, having repeated SARS-CoV-2 infections is plausible but related published data are scarce [5]. The aim of this study was to identify factors associated with recurrent (three disease episodes) laboratory-confirmed symptomatic SARS-CoV-2 infections.

## 2. Materials and Methods

A retrospective and dynamic cohort study was conducted in a province of Mexico. The state of Colima (≈ 732 thousand inhabitants), where the study took place, is located in Western region of the country and on the central Pacific coast. Adults (aged 18 years or older) employed (as nurses, physicians or others) by the Mexican Institute of Social Security (IMSS, the Spanish acronym) at any of its healthcare settings (n = 13) located all across the state, were eligible.

Participants were integrated into the study sample at the date of recovery of the first illness episode and were followed until the start of a new COVID-19 episode, if applicable. Enrolled subjects contributed again to rate denominators once they fully recovered from the last disease episode or until September 30, 2022, when the follow-up ended.

Participants were classified as nurses (n = 378), physicians (n = 258) or other (n = 1,064). This latter was integrated, in general, by administrative or health personnel without direct patient care.

The main outcome was repeated symptomatic infection (three laboratory-confirmed COVID-19 episodes) by the SAR-CoV-2 occurring during the study period (March 2020 - September 2022; 30 months). Reinfection was defined by a positive RT-PCR or rapid antigen test, in patients with respiratory symptoms, at least 90 days after full clinical recovery (disappearance of respiratory symptoms) from a COVID-19 episode [6]. Subjects with < 90 days between two positive tests were considered as persistent infections.

The COVID-19 cases were identified by using data from an institutional system for the epidemiological surveillance of respiratory viral pathogens, which use is mandatory for the process of incapacity for work during illness recovery.

Clinical and epidemiological data of interest were retrieved from the medical files of participants. Participants were categorized according to the number of SARS-CoV-2 infections (1-2 vs. 3 episodes). Summary statistics were computed and we used risk ratios (RR) and 95% confidence intervals (CI), estimated through generalized linear regression models, to evaluate factors associated with the risk of repeated symptomatic reinfection.

## 3. Results

A total of 1,700 individuals were enrolled for a total follow-up of 16,474 person-months. We identified 14 participants with three laboratory-positive COVID-19 episodes. Therefore, the overall rate of multiple symptomatic infections in the study sample was 8.5 per 10,000 person-months. All the recurrent cases had no severe symptoms.

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The mean time (± standard deviation) to second infection (first reinfection) was 292 ± 103 days, and the interval to third infection was 131 ± 34 days.

When compared with subjects with 2 or fewer COVID-19 episodes, those with 3 episodes were younger (mean ± standard deviation: 30.8 ± 5.6 vs. 37.1 ± 8.1 years, p = 0.004) and were more likely to be fully COVID-19 vaccinated (57.1% vs. 8.5%, p < 0.001) or to have had a severe first-episode (7.1% vs. 1.0%, p = 0.026). Most of the participants with recurrent infections (64.3%, n = 9/14) were administrative or health personnel without direct patient care. The remaining cases were nurses and none of them were physicians. A broader description of the study sample, according to the reinfection status, is presented in Table 1.

**Table 1.** Characteristics of the study sample for selected variables, Mexico 2020 - 2022

| Characteristic | Overall (n = 1,700) | | Number of COVID-19 episodes | | | | p |
|---|---|---|---|---|---|---|---|
| | | | One or two (n = 1,686) | | Three (n = 14) | | |
| **Gender** | | | | | | | |
| Female | 1,079 | (63.5) | 1,069 | (63.4) | 10 | (71.4) | 0.535 |
| Male | 621 | (36.5) | 617 | (36.6) | 4 | (28.6) | |
| **Age (years)** [a] | 37.1 ± 8.1 | | 37.1 ± 8.1 | | 30.8 ± 5.6 | | 0.004 |
| **Age group** | | | | | | | |
| < 20 | 2 | (0.1) | 2 | (0.1) | 0 | (0) | 0.007 |
| 20-29 | 300 | (17.7) | 292 | (17.3) | 8 | (57.2) | |
| 30-39 | 826 | (48.6) | 821 | (48.7) | 5 | (35.7) | |
| 40-49 | 440 | (25.8) | 439 | (26.0) | 1 | (7.1) | |
| 50-59 | 119 | (7.0) | 119 | (7.1) | 0 | (0) | |
| 60+ | 13 | (0.8) | 13 | (0.8) | 0 | (0) | |
| **COVID-19 vaccination status** | | | | | | | |
| Unvaccinated | 1,545 | (90.9) | 1,539 | (91.3) | 6 | (42.9) | < 0.001 |
| Vaccinated | 155 | (9.1) | 147 | (8.7) | 8 | (57.1) | |
| **Severity of the first COVID-19 episode** | | | | | | | |
| Mild | 1,682 | (98.9) | 1,669 | (99.0) | 13 | (92.9) | 0.026 |
| Severe | 18 | (1.1) | 17 | (1.0) | 1 | (7.1) | |
| **Activity in healthcare services** | | | | | | | |
| Other | 1,064 | (62.6) | 1,055 | (62.6) | 9 | (64.3) | 0.192 |
| Nurse | 378 | (22.2) | 373 | (22.1) | 5 | (35.7) | |
| Physician | 258 | (15.2) | 258 | (15.3) | 0 | (0) | |
| **Personal history of:** | | | | | | | |
| **Obesity (BMI 30 or above)** | | | | | | | |
| No | 1,451 | (85.4) | 1,441 | (85.5) | 10 | (71.4) | 0.139 |
| Yes | 249 | (14.6) | 245 | (14.5) | 4 | (28.6) | |
| **Arterial hypertension** | | | | | | | |
| No | 1,572 | (92.5) | 1,559 | (92.5) | 13 | (92.9) | 0.956 |
| Yes | 128 | (7.5) | 127 | (7.5) | 1 | (7.1) | |
| **Type 2 diabetes mellitus** | | | | | | | |
| No | 1,632 | (96.0) | 1,618 | (96.0) | 14 | (100) | 0.443 |
| Yes | 68 | (4.0) | 68 | (4.0) | 0 | (0) | |
| **Asthma** | | | | | | | |
| No | 1,647 | (96.9) | 1,633 | (96.9) | 14 | (100) | 0.500 |
| Yes | 53 | (3.1) | 53 | (3.1) | 0 | (0) | |

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Abbreviations: COVID-19, coronavirus disease 2019; BMI, body mass index.
Note: The absolute and relative (%) frequencies are presented, except if other is specified.
[a] Arithmetic mean ± standard deviation.

In the multiple regression model (Table 2), fully COVID-19 vaccinated adults (vs. unvaccinated, RR = 1.05 [1.03 - 1.06]) and those with a severe first illness episode (vs mild disease, RR = 1.05 [1.01 - 1.10]) were at increased risk for repeated symptomatic SARS-CoV-2 reinfections. Increasing age showed a protective effect (per each additional year of age: RR = 0.98 [0.97 - 0.99]).

**Table 2.** Factors associated with the risk of multiple (3 or above) SARS-CoV-2 symptomatic reinfections, Mexico 2020 - 2022

| Characteristic | RR (95% CI), p | | | |
|---|---|---|---|---|
| | Bivariate analysis | | Multiple analysis | |
| **Gender** | | | | |
| Female | Ref. | | Ref. | |
| Male | 0.99 (0.98 - 1.01) | 0.535 | 0.99 (0.98 - 1.01) | 0.878 |
| **Age (years)** | 0.98 (0.97 - 0.99) | 0.004 | 0.98 (0.97 - 0.99) | 0.008 |
| **COVID-19 vaccination status** | | | | |
| Unvaccinated | Ref. | | Ref. | |
| Vaccinated | 1.05 (1.02 - 1.06) | < 0.001 | 1.05 (1.03 - 1.06) | < 0.001 |
| **Obesity (BMI 30 or above)** | | | | |
| No | Ref. | | Ref. | |
| Yes | 1.01 (0.99 - 1.03) | 0.139 | 1.01 (0.99 - 1.02) | 0.187 |
| **Severity of the first COVID-19 episode** | | | | |
| Mild | Ref. | | Ref. | |
| Severe | 1.05 (1.01 - 1.09) | 0.025 | 1.05 (1.01 - 1.10) | 0.020 |
| **Activity in healthcare services** | | | | |
| Other | Ref. | | Ref. | |
| Nurse | 1.00 (0.99 - 1.02) | 0.378 | 1.01 (0.99 - 1.02) | 0.434 |
| Physician | 0.99 (0.98 - 1.00) | 0.177 | 0.99 (0.98 - 1.01) | 0.467 |

Abbreviations: COVID-19, coronavirus disease 2019; BMI, body mass index.
Note: The absolute and relative (%) frequencies are presented, except if other is specified.
[a] Arithmetic mean ± standard deviation.

## 4. Discussion

We characterized healthcare workers who have had multiple symptomatic and laboratory-positive SARS-CoV-2 infections. Our results suggest that having three COVID-19 episodes was infrequent (about 8 cases per 1,000) in the study sample and that vaccinated and younger participants were more likely to be reinfected.

A previously published study, and where healthcare professionals were enrolled, identified 11 cases of multiple SARS-CoV-2 reinfections (thrice infected) among 73 thousand participants [5]. In this study, the multiple reinfection cases were also young workers (mean age: 27 years; total range: 22 to 56 years). Published data has documented age mediated differences in COVID-19 risk-taking, and a lower risk perception for self and other has been observed in younger adults [7].

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We also observed a 5% (95% CI 3-6%) increase in reinfection risk among vaccinated participants. This latter may be closely related to the high perceived efficacy of the COVID-19 vaccines which is likely further reduce adherence to other non-pharmaceutical interventions focusing in the prevention of respiratory viral spread [8]. Thus, this may be an example of the Peltzman effect where the risk perception decreases after safety measures have been implemented [9].

Interestingly, individuals who recovered from severe disease at primary infection showed a higher reinfection risk when compared whit those who present mild symptoms (RR = 1.05, 95% CI 1.01 - 1.10). Similar findings had been published and may be related to increased perceived benefits from taking risks [10].

The potential limitations of the study must be cited. First, only workers from a specific healthcare institution were recruited. Therefore, even when their profiles are highly heterogeneous, they may not be entirely representative of the source population. Second, there is no genomic information for the infections. So we were unable to determine which variant or subvariant was causing the infection, and a more infectious variant able to evade vaccine-derived or natural immunity [11] would lead to a higher prevalence of infection at the time of the epidemic wave caused by that variant.

Third, previously infected or immunized individuals may be less likely to develop symptomatic infections later on (they may be reinfected but have a milder or asymptomatic illness) [12]. Consequently, they may not be tested and these reinfections are not detected. And fourth, younger adults are more likely to have far more social contacts (and therefore potential sources of infection or opportunities to spread infection) than older adults [13]. This latter may also be determining the higher reinfection rates observed in younger participants.

## 5. Conclusions

Our results suggest that recurrent SARS-CoV-2 infections are rare events and seem to be determined, at least partially, by vaccination status and age.

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**Data Availability Statement:** The data that support the findings of this study are not openly available and are available from the corresponding author upon reasonable request.

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**Conflicts of Interest:** The authors declare no conflict of interest.

## References


1. Petráš M. Highly Effective Naturally Acquired Protection Against COVID-19 Persists for at Least 1 Year: A Meta-Analysis. J Am Med Dir Assoc. 2021;22(11):2263-2265. https://doi.org/10.1016/j.jamda.2021.08.042
2. Murillo-Zamora E, Trujillo X, Huerta M, Ríos-Silva M, et al. Symptomatic SARS-COV-2 reinfection: healthcare workers and immunosuppressed individuals at high risk. BMC Infect Dis. 2021;21(1):923. https://doi.org/10.1186/s12879-021-06643-1
3. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-594. https://doi.org/10.1056/NEJMoa2108891
4. Hernandez-Suarez C, Murillo-Zamora E. Waning immunity to SARS-CoV-2 following vaccination or infection. Front Med (Lausanne). 2022;9:972083. https://doi.org/10.3389/fmed.2022.972083
5. Swift MD, Hainy CM, Sampathkumar P, et al. Multiple SARS-CoV-2 Reinfections: A Case Series of Thrice-Infected Individuals. Mayo Clin Proc. 2022;97(5):1021-1023. https://doi.org/10.1016/j.mayocp.2022.03.003
6. Nguyen NN, Houhamdi L, Hoang VT, et al. SARS-CoV-2 reinfection and COVID-19 severity. Emerg Microbes Infect. 2022;11(1):894-901. https://doi.org/10.1080/22221751.2022.2052358
7. Wolfe K, Sirota M, Clarke ADF. Age differences in COVID-19 risk-taking, and the relationship with risk attitude and numerical ability. R Soc Open Sci. 2021;8(9):201445. https://doi.org/10.1098/rsos.201445
8. Trogen B, Caplan A. Risk Compensation and COVID-19 Vaccines. Ann Intern Med. 2021;174(6):858-859. https://doi.org/10.7326/M20-8251
9. Kaim A, Saban M. Are we suffering from the Peltzman effect? Risk perception among recovered and vaccinated people during the COVID-19 pandemic in Israel. Public Health. 2022;209:19-22. https://doi.org/10.1016/j.puhe.2022.05.018
10. Tsai CI, Zeng Y. Risky but alluring: Severe COVID-19 pandemic influence increases risk taking. J Exp Psychol Appl. 2021;27(4):679-694. https://doi.org/10.1037/xap0000380
11. Mistry P, Barmania F, Mellet J, et al. SARS-CoV-2 Variants, Vaccines, and Host Immunity. Front Immunol. 2022 Jan 3;12:809244. https://doi.org/10.3389/fimmu.2021.809244
12. Ayoubkhani D, Bermingham C, Pouwels KB, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. BMJ. 2022;377:e069676. https://doi.org/10.1136/bmj-2021-069676
13. Juvonen J, Lessard LM, Kline NG, et al. Young Adult Adaptability to the Social Challenges of the COVID-19 Pandemic: The Protective Role of Friendships. J Youth Adolesc. 2022;51(3):585-597. https://doi.org/10.1007/s10964-022-01573-w