

Rate of reinfections after SARS-CoV-2 primary infection in the population of an Italian province: a cohort study

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ABSTRACT

Background Current data suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfections are rare, but no information are available on minors and after 12 months of follow-up.

Methods This retrospective cohort study included all the population of an Italian Province, diagnosed with a SARS-CoV-2 infection from March 2020 to May 2021. The primary outcome was the incidence of a reinfection, defined as a new positive polymerase chain reaction (PCR) test occurring ≥ 90 days after complete resolution of the first infection, and data were retrieved from the official datasets (coronavirus disease 2019 [COVID-19], demographic, hospital and co-pay exemption) of the Local Health Unit (LHU) of Pescara.

Results After an average of 201 days of follow-up (max. 414), we recorded 24 reinfections ≥ 90 days after the resolution of the first 7173 infections (0.33%). Four reinfections required hospitalization, one was lethal. Most of the reinfections ($n = 13$) occurred 6–9 months after the resolution of the first infection; no new infection was detected 12 or more months later and among the 832 minors.

Conclusions This study confirms previous findings on a low risk of SARS-CoV-2 reinfection. If confirmed, these findings suggest that more targeted restriction policies can be applied to the subjects that recovered after a first infection.

Keywords COVID-19, Italy, reinfection, relapse, SARS-CoV-2

Introduction

A precise estimation of the extent and length of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection in previously infected individuals is essential to optimize restriction and vaccination policies.¹ A few studies reported consistently reassuring results, suggesting that a secondary infection is rare both among health-care workers and in the general population, occurring in $<1\%$ of individuals who previously tested positive for SARS-CoV-2.^{2–6} However, no data have been provided separately for the minors, and the length of follow-up never exceeded twelve months. We carried out a cohort study on the entire population of an Italian province, estimating the rate of SARS-CoV-2 reinfection, by age-class, in the first 15 months of the pandemic.

Methods

This retrospective cohort study included all the subjects aged ≥ 1 year who were resident in the Province of Pescara, Italy on 1 January 2020, diagnosed with a SARS-CoV-2 infection (either asymptomatic or symptomatic and requiring hospital admission in coronavirus disease 2019 [COVID-19] wards) from 3 March 2020 (date of the first positive real-time

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polymerase chain reaction—RT-PCR—test) to 90 days before 21 May 2021 (date of data extraction and end of follow-up).

Baseline-positive subjects were identified with PCR samples, tested through nasopharyngeal swabs by the accredited laboratories of Pescara Local Health Unit. The primary outcome was the incidence of a reinfection, defined as a new positive PCR test occurring ≥ 90 days after complete resolution of the first infection, and with ≥ 2 consecutive negative test results between episodes.⁶ Data sources and extraction criteria are reported in the supplemental online appendix.

The research protocol was approved by the Ethics Committee of the Emilia-Romagna Region (protocol code 556/2021/Oss/UniFe). The manuscript was prepared according to the STROBE (strengthening the reporting of observational studies in epidemiology) statement.⁷

Results

A total of 18 034 residents in Pescara Province had ≥ 1 positive RT-PCR sample from 3 March 2020 to 21 May 2021. Of them, 1990 were tested and followed by healthcare facilities placed outside the Province, and could thus not be included because follow-up data could have been missing. Also, all the subjects who were younger than 1 year ($n = 65$), had < 90 days of follow-up between complete resolution and follow-up end ($n = 8471$), or deceased within 90 days after the resolution of the first infection ($n = 335$), were excluded from the analyses.

Therefore, the final sample consisted of 7173 residents (Table 1; mean age: 46.3 ± 21.8 years; 48.0% males). Of them, 1478 (20.6%) were diagnosed with ≥ 1 comorbidity over the previous 10 years, and 1783 (24.9%) had received at least the first dose of a COVID-19 vaccine as of 21 May 2021.

After an average of 201 days of follow-up (min. 90; max 414), a total of 24 participants had a new positive RT-PCR test (0.33% of the sample). Four of the reinfected subjects (0.06%) had a symptomatic COVID-19 requiring hospitalization, and one died (a 77-year-old woman).

Most of the reinfections ($n = 13$) occurred 6–9 months after the resolution of the first infection; no new infection was detected 12 or more months later and among the subjects aged < 18 years.

The characteristics of the 24 reinfected individuals are reported in Table S1. The mean age and the proportion of subjects with ≥ 1 comorbidity were substantially higher among those who were reinfected than those who were not (mean age: 54.5 ± 18.4 versus 46.3 ± 21.8 years and 41.7% versus 20.6%, respectively). Nine of the reinfected subjects received a first vaccine dose (and four were fully immunized) during the follow-up, but after the onset of the new infection.

Overall, the primary SARS-CoV-2 infection occurred before the immunization in all but four subjects, who had a positive test result 3–13 days following the first vaccine dose.

Discussion

Main findings of this study

During the first 15 months of SARS-CoV-2 pandemic, in the general population of an Italian Province, we observed a 0.33% reinfection rate among the subjects who recovered from a previous infection (symptomatic or asymptomatic). Most of the episodes were asymptomatic or paucisymptomatic, and only one subject deceased after the second infection (0.01%).

What is already known on this topic

Overall, these findings are in line with the available literature,^{3–6,8} suggesting that the natural immunity confers substantial protection in the first months after the primary infection: all the published cohort studies reported reinfection rates lower than 1%,^{3–6} and the only Italian study, on a sample of 1579 positive subjects, reported a virtually identical reinfection rate (0.32%).⁶ However, this is the first study with a follow-up longer than 12 months, and the first to provide data separately for the minors: notably, no reinfections were recorded after 12 months of follow-up, and none of the 832 included minors experienced a reinfection.

What this study adds

These findings may have major implications for the management of the pandemic: indeed, the low risk of reinfection strongly supports the strategies of several governments that, during the first phase of the vaccination campaign, characterized by a shortage of vaccines, opted to postpone the immunization of those who were previously infected,⁹ and are considering these subjects as a low-risk category, able to receive the newly established COVID pass, such as vaccinated individuals or subjects with a negative test within the last 48 h.¹⁰ Also, in the current debate on the most appropriate non-pharmaceutical anti-contagion policies for the next waves of the pandemic,⁶ some targeted, less stringent quarantine measures may be applied to the individuals who recovered from the first infection, especially if their age is lower than 18 years. As an example, in Italy, the individuals who have been infected and recovered, have been included among those who can request the EU digital COVID certificate (so-called ‘Green Pass’, which is mandatory to access many social and professional activities), with no need of vaccination or nasopharyngeal swabs (Italian Minister of Health:

Table 1 Characteristics of the sample and incidence of reinfections^a

	Overall sample
	(n = 7173)
Mean age in years (SD)	46.3 (21.8)
Age-class in years, % (n)	
< 18	11.6 (832)
18–59	61.0 (4378)
≥60	27.4 (1963)
Male gender, % (n)	48.0 (3444)
Comorbidities or risk factors, % (n) ^b	
Diabetes	5.7 (406)
Hypertension	12.4 (891)
Major cardiovascular diseases	6.4 (460)
COPD	3.2 (231)
Kidney disease	2.1 (149)
Cancer	4.2 (301)
At least one of the above	20.6 (1478)
First dose of SARS-CoV-2 vaccine ^c	24.9 (1783)
Outcomes	
Reinfection, % (n)	0.33 (24)
Reinfection and hospitalization, % (n)	0.06 (4)
Hospitalizations after the second infection, % (n/N)	16.7 (4/24)
Reinfection and deaths, % (n)	0.01 (1)
Follow-up, mean (SD)	
Days from resolution to the end of follow-up, without reinfection (n = 7149)	181 (90)
Days from resolution to reinfection (n = 24)	201 (61)
% of reinfections by time after first infection resolution (n/N)	
3–6 months after resolution	0.13 (7/5510)
6–9 months after resolution	2.22 (13/585)
9–12 months after resolution	0.81 (4/495)
≥12 months after resolution	0.00 (0/918)

SD = Standard deviation; n/N = Number of subjects with the outcome/Total number of subjects.

^aA reinfection was defined as a new positive PCR test occurring ≥ 90 days after complete resolution of the first infection, and with at least two consecutive negative test results between episodes.

^bSubjects with the selected comorbidities/risk factors in the Regional co-pay exemption database (Italian 'Esenzioni Ticket' file) or an hospital admission in the last ten years (from the Italian SDO database of administrative discharge abstracts) with the following ICD-9-CM codes in any diagnosis field: 250.xx (diabetes); 401.xx-405.xx (hypertension); 410.xx-412.xx or 414.xx-415.xx or 428.xx or 433.xx-436.xx (major cardiovascular or cerebrovascular diseases); 491.xx-493.xx (chronic obstructive pulmonary diseases—COPD); 580.xx-589.xx (kidney diseases); 140.xx-172.xx or 174.xx-208.xx (cancers).

^cOf the 1783 participants who received the first vaccine dose during the follow-up, 1779 were immunized after the first positive nasopharyngeal swab; only four subjects were immunized before the first positive test.

<https://www.dgc.gov.it/web/>). In the same country, however, all the population is still requested to maintain social distance, avoid mass gatherings and wear masks indoor. These measures will certainly help lowering the infection rate, in turn decreasing the absolute number of reinfections.^{11,12}

Finally, given the lack of data on the long-term duration of both the natural immunity and that conferred by the vaccines,¹³ the absence of reinfections after twelve months

of follow-up is certainly reassuring and may suggest a longer protection than the nine months currently recommended for the COVID pass.¹⁰

Limitations of this study

Clearly, the findings on both minors and immunity duration are inevitably preliminary and require confirmation from specifically designed prospective population studies, which

may also evaluate the extent and degree of protection against the emerging viral variants.

In conclusion, our study confirms previous findings on a low risk of SARS-CoV-2 reinfection. More targeted restriction policies can be applied to the subjects that recovered after a first infection.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

- 1 European Centre for Disease Prevention and Control. *Reinfection with SARS-CoV-2: Considerations for Public Health Response*. Stockholm: ECDC, 2020.
- 2 Hall VJ, Foulkes S, Charlett A *et al*. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet* 2021;**397**:1459–69.
- 3 Hansen CH, Michlmayr D, Gubbels SM *et al*. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* 2021;**397**:1204–12.
- 4 Harvey RA, Rassen JA, Kabelac CA *et al*. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. *JAMA Intern Med* 2021;**181**:672–9.
- 5 Lumley SF, O'Donnell D, Stoesser NE *et al*. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2021;**384**:533–40.
- 6 Vitale J, Mumoli N, Clerici P *et al*. Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy. *JAMA Intern Med* 2021. <https://doi.org/10.1001/jamainternmed.2021.2959>.
- 7 von Elm E, Altman DG, Egger M *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;**335**:806–8.
- 8 Abu-Raddad LJ, Chemaitelly H, Coyle P *et al*. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine* 2021;**35**:100861.
- 9 Health Policy Watch. *People Who Have Had COVID Can Delay Vaccine Up To 6 Months, Says WHO*. 2021 (5 July 2021, date last accessed); Available from: <https://healthpolicy-watch.news/covid-vaccine-delay-six-months-who/>.
- 10 Italian Ministry of Health. *EU Digital COVID Certificate*. 2021 (5 July, date last accessed 2021); Available from: <https://www.dgc.gov.it/web/>.
- 11 Boccia S, Cascini F, McKee M, Ricciardi W. How the Italian NHS is fighting against the COVID-19 emergency. *Front Public Health* 2020;**8**:167.
- 12 Gatto M, Bertuzzo E, Mari L *et al*. Spread and dynamics of the COVID-19 epidemic in Italy: Effects of emergency containment measures. *Proc Natl Acad Sci U S A* 2020;**117**:10484–91.
- 13 Flacco ME, Soldato G, Acuti Martellucci C *et al*. Interim Estimates of COVID-19 Vaccine Effectiveness in a Mass Vaccination Setting: Data from an Italian Province. *Vaccines (Basel)* 2021;**9**:628.