

## Characteristics of a case-series of COVID-19 reinfection and its trend from 2020 to June 2022 in a general medicine office in Toledo (Spain)

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### Abstract

**Background:** Longitudinal data on SARS-CoV-2 re-infection are scarce.

**Objectives:** 1) Characterize COVID-19 reinfection cases clinically and epidemiologically; 2) Determine whether the risk of SARS-CoV-2 reinfection has altered over time in the context of the development of beta, delta, and omicron variants.

**Methods:** From March 1, 2020 to July 1, 2022, an observational, longitudinal, and prospective investigation of Covid-19 re-infections was done in a general medical practice in Toledo, Spain.

**Results:** There were 43 cases in total, including 45 reinfections (2 cases presented 2 reinfections). The average period between first infection and reinfection was 346 days (range: 95-813 days). The average age was 41 years (range: 17-70 years). 5% were over the age of 65. 56% were female. 14% belonged to an ethnic minority. 82% of reinfections occurred among individuals who had been vaccinated (19%, 28%, and 35% in those who had received one dose, two doses, and a booster, respectively). They were symptomatic in 96% of the cases. All cases of reinfection were minor, with nonspecific symptoms (discomfort, asthenia, myalgia, fever, arthralgia) predominating (39%). Chronic illnesses were present in 60% of reinfection cases, with the Genitourinary (19%), Endocrine (17%), and Respiratory (16%) systems predominately. Reinfections have been steadily growing since 2020, with 67% occurring in 2022.

**Conclusion:** We discovered evidence of a continual increase in the incidence of reinfections in Toledo, Spain, primarily beginning in January 2022, which is temporally congruent with the introduction of the omicron variety, indicating its improved ability to infect previously infected persons.

**Keywords:** COVID-19; SARS-CoV-2; COVID-19 Vaccine; Breakthrough Infection; Reinfections; Hybrid immunity; General Practice; Spain

### Introduction

Seasonal endemic coronaviruses, which cause the majority of respiratory tract infections in humans, are known to leave a short-lived protective immunity that normally lasts no more than one to two years (1).

However, the virus that causes coronavirus illness 2019 (covid-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a totally new form of coronavirus, and one of the major unknowns is immunity (2, 3). On the other hand, while vaccinations have shown short-term benefit against the severity of

SARS-CoV-2 infection, the longevity of this protection over longer time periods is unknown (4).

Several studies have revealed that people who have recovered from SARS-CoV-2 have a low rate of reinfection. However, there are still concerns about the strength and duration of such protection in comparison to vaccination (5). The appearance of SARS-CoV-2 lineages (alpha, beta, delta, and omicron variations) during the covid-19 pandemic has raised severe concerns about the durability of vaccine-induced immunity (5), despite the fact that it appears to be resistant to serious disease (6-8).

In summary, the protection provided by natural immunity, vaccination, or both against SARS-CoV-2 infection is unknown, and there are little longitudinal data on SARS-CoV-2 infection following previous infection and partial or full immunization (9). More research is needed to understand the causes and outcomes of re-infections (10) and how SARS-CoV-2 will become an endemic virus (11).

The purpose of this study was to characterize covid-19 reinfection cases clinically and epidemiologically, as well as to examine the evolution of SARS-CoV-2 reinfection over time in a population attended in a general medicine clinic in Toledo (Spain) from 2020 to July 2022, in the context of the appearance of the beta, delta, and omicron variants.

## Material and methods

From March 1, 2020 to July 1, 2022, an observational, longitudinal, and prospective study of covid-19 re-infections was conducted in a general medicine office in Toledo, Spain, with a list of 2,000 patients > 14 years of age (in Spain, general practitioners (GPs) care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP). GPs in Spain work under the public National Health System and serve as the entry point for all patients into the system; each person is assigned a GP (12).

## Outcomes of interest

1. Clinically and epidemiologically defined covid-19 reinfection cases
2. Determined whether the risk of SARS-CoV-2 reinfection has altered over time in the study community as a result of the introduction of beta, delta, and omicron variants.

## Definition of reinfection

SARS-CoV-2 reinfection was traditionally characterized as an infection that occurred at least 90 days after the first infection (13-18).

## Diagnosis of covid-19

PCR oropharyngeal swab tests or antigen testing were used to make the diagnosis. A symptomatic confirmed case with active infection was defined as any person having a clinical picture of sudden onset acute respiratory infection of any severity, including fever, cough, or shortness of breath. According to clinical criteria, other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest discomfort, or headache were also regarded signs of suspected SARS-CoV-2 infection; and a positive PCR or quick antigen test (17, 19).

## Definition of vaccinated 2 doses

To be considered a case of covid-19 that has received two doses of vaccine, the following criteria were met:

That they received two vaccine doses separated by at least 19 days if the first dose was BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech), 21 days if the first dose was ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca), or 25 days if the last dose was mRNA-1273 vaccine (Spikevax, formerly covid-19 Moderna), and that at least 7 days have passed since the last dose of BNT162b2 mRNA vaccine (Comirnaty), or 14 days if the last dose was of ChAdOx1 nCoV-19 vaccine (Vaxzevria) or mRNA-1273 vaccine (Spikevax). People who received a Janssen vaccine (Johnson & Johnson vaccine) dose more than 14 days ago were likewise regarded completely immunized. In the heterologous regimen that employed Vaxzevria (Oxford / AstraZeneca) in the first dose and mRNA vaccines in the second, it was regarded fully vaccinated after 7 days if the second dose was Comirnaty, or after 14 days if the Moderna vaccine was used (20).

## Definition of homologous or heterologous booster

Regardless of the vaccine used in the original vaccination, any mRNA vaccine was utilized to provide the booster dose (21).

## Collected variables

-Age and gender  
 -Covid-19 reinfection symptoms  
 -Chronic diseases (defined as "any alteration or deviation from normal that has one or more of the following characteristics: is permanent, leaves residual impairment, is caused by a non-reversible pathological alteration, necessitates special training of the patient for rehabilitation, and/or can be expected to necessitate a long period of control, observation, or

treatment" (22), (23). -Patients who have at least one chronic ailment -Time elapsed between first covid-19 infection and reinfection with covid-19 -Social-occupancy class (professional, intermediate, non-manual skilled, manual skilled, partly skilled, unskilled occupations, other -students, armed forces, and people whose occupation is inadequately described, according to the Registrar General's classification of occupations and social status code) (24, 25)

-If they were members of the medical staff  
 -Family problems and low-income households based on genogram and GP experience for continuity of care and family knowledge (genogram is a schematic model of the structure and processes of a family, which included the family structure, life cycle and family relational patterns). It was formerly assumed that "complex" genograms produce psychosocial problems in families. In this fashion, "family issues" were classified as families having a "complex genogram." The criteria of "low-income household" were based on the family doctor who performed the genogram previously and has been in the same practice for over 30 years (26-29).

-An ethnic minority is defined as a "human group with cultural, linguistic, racial, and geographical values that is numerically inferior to the majority group."

-Severity of disease: Primary infection and reinfection (mild cases: clinical symptoms are mild, and no manifestation of pneumonia can be seen on images; moderate cases: with symptoms such as fever and respiratory tract symptoms, and the manifestation of pneumonia can be seen on imaging tests; and severe cases: respiratory distress, respiratory rate 30 breaths/min; pulse oxygen saturation 93% with room air at rest; arterial partial pressure of oxygen / oxygen concentration  $\leq$  300 mmHg) (19). To make comparisons easier, moderate and severe instances were combined.

-Vaccinated with one dose, two doses, and a booster, but not against covid-19.

## Results

There were 43 cases in total, including 45 reinfections (2 cases presented 2 reinfections: 2 women aged 17 and 19 years, with 2 and 1 dose of the vaccine, respectively). The average time from primary infection to reinfection (or second re-infection) was 346 days (range: 95-813 days). The average age was 41 years (range: 17-70 years). 5% were above the age of 65, and 2% were under the age of 18. 56% were female. 14% belonged to an ethnic minority. 82% of reinfections occurred among individuals who had been vaccinated (19%, 28%, and 35% in those who had received one dose, two doses, and a booster,

respectively). They were symptomatic in 96% of the cases. General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) predominated (39%), followed by Respiratory (cough, dyspnea, chest pain) (27%) and ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistaxis) (25%). Chronic illnesses were present in 60% of reinfection cases, with the Genitourinary (19%), Endocrine (17%), and Respiratory system (16%) groups predominating (Tables 1, 2, 3, and 4). Reinfections have been steadily growing since 2020, with 67% occurring in 2022. (Figure 1).

## Discussion

Our research showed evidence of a significant and ongoing rise in the chance of reinfection. We discovered that 82% of reinfections occurred in vaccinated persons (19%, 28%, and 35%, respectively, in those vaccinated with 1 dose, 2 doses, and booster). 96% were symptomatic, with general symptoms, followed by respiratory and ENT problems. All of the reinfections were minor. 60% of reinfection cases had chronic illnesses.

Throughout the epidemic, multiple SARS-CoV-2 variants with genetic changes from the original virus sequence have been described. (31). From March to April 2020, the A strain of the coronavirus predominated in Spain, particularly in SEC7 and SEC8, but from July to December 2020, the 20E (EU1) variety predominated (32, 33). The alpha version predominated in the January 2021 era, and from the summer-autumn of 2021, there was a very substantial increase in the delta variant and a significant decline in the Alpha variant (34, 35). With great population vaccination coverage, the delta variant had nearly absolute hegemony of the circulation in November 2021. Despite evidence that covid-19 vaccinations are slightly less effective against the delta form, they appear to provide protection against serious illness (36). In our investigation, we discovered that circulating delta variants were associated with a greater risk of reinfection when compared to the original strain. In March 2022, the BA.2 lineage of the omicron version of Covid-19 predominated in Spain, while the alpha variant's prevalence was waning (37, 38). In our study, we discovered a higher risk of reinfection associated with circulating omicron variants, clearly higher than previously reported for delta, and compared to the ancestral strain, which corresponds with what was previously reported about its greater ability to infect previously infected individuals (39).

**Table 1.** Characteristics of COVID-19 reinfection cases

<b>VARIABLES</b>	<b>COVID-19 REINFECTION N=43</b>
Mean age (Arithmetic mean +- Standard deviation; Range)	41.34 +- 14.34 (Range: 17-70 years)
>= 65 years	2 (5)
14-65 years	40 (93)
= < 18 years	1 (2)
Women	24 (56)
Social-occupancy class of patients (people with some type of labor specialization)	15 (35)
Complex family/ Problems in the family context	3 (7)
Low income household	4 (9)
Ethnic minority	6 (14)
Vaccinated 1 dose	8 (19)
Vaccinated 2 dose	12 (28)
Vaccinated with booster (3 doses)	15 (35)
Not vaccinated	8 (18)
Health Care Workers	7 (2)
Moderate-severe severity of reinfection	0
Moderate-severe severity of primary infection	3 (pneumonias) (7)
Chronic diseases presence	26 (60)

( ): Denotes percentages

**Table 2.** Other characteristics of COVID-19 reinfection cases

<b>Variables</b>	<b>COVID-19 Reinfection (N= 45 reinfections)</b>
Symptomatic COVID-19 reinfection	43 (96)
Asymptomatic COVID-19 reinfection	2 (4)
Days of covid-19 from primary infection (or first reinfection) to reinfection (or second reinfection) (Arithmetic mean +- Standard deviation; Range)	346.75 +- 175.09 (Range: 95-813 days )
Reinfection in 2020	1 (2)
Reinfection in 2021	14 (33)
Reinfection in 2022	30 (67)

( ): Denotes percentages

**Table 3. Symptoms COVID-19 reinfection cases**

Symptoms COVID-19 reinfection* according to WHO, ICD-10 groups	COVID-19 Reinfection N=43
General (discomfort, asthenia, myalgia, fever, arthralgias)	44 (39)
Respiratory (cough, dyspnoea, chest pain)	31 (27)
ENT (Anosmia / ageusia, odynophagia, rhinorrhoea, pharyngeal dryness-mucus, epistaxis)	29 (25)
Digestive (anorexia, nausea / vomiting, diarrhoea, abdominal pain)	3 (3)
Neurological (headache, dizziness, mental confusion -brain fog)	7 (6)
Psychiatric (Anxiety, insomnia)	0
Skin (chilblains, flictenas, rash)	0
Total symptoms*	114 (100)

( ): Denotes percentages

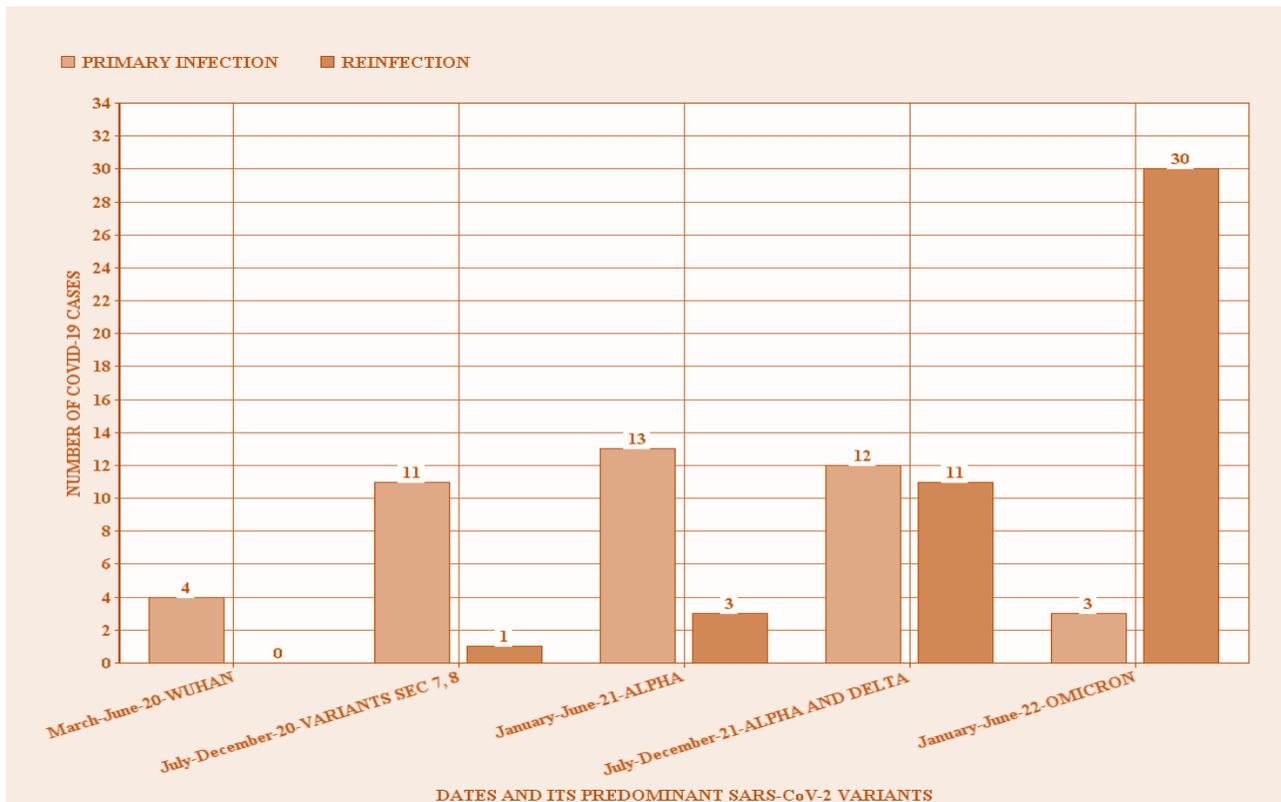
\* Patients could have more than one symptom. The percentages are over the total of symptoms

**Table 4. Chronic diseases in COVID-19 reinfection cases**

Chronic diseases* according to WHO, ICD-10 groups	COVID-19 Reinfection N=43
-I Infectious	0
-II Neoplasms	1 (2)
-III Diseases of the blood	0
-IV Endocrine	12 (17)
-V Mental	5 (7)
-VI-VIII Nervous and Senses	5 (7)
-IX Circulatory system	5 (7)
-X Respiratory system	11 (16)
-XI Digestive system	4 (6)
-XII Diseases of the skin	5 (7)
-XIII Musculo-skeletal	8 (12)
-XIV Genitourinary	13 (19)
TOTAL chronic diseases**	69 (100)

( ): Denotes percentages;

\*Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases of symptomatic and asymptomatic patients



**Figure 1.** Trend in number of COVID-19 cases with primary infection and with reinfection

The average period from first infection to reinfection in our study was 346 days (range: 95-813 days). This appears to be consistent with prior posts; the issue arises with the introduction of new variations in relation to the natural protection offered by a previous infection (40-42). Adults 65 and older are at a higher risk of reinfection with SARS-CoV-2, according to reports (43). In our series, however, 56% of the participants were female. A low likelihood of reinfection following earlier SARS-CoV-2 infection, as well as increased vaccination progress among women and individuals without prior infection, has been described elsewhere (9). Although patients infected with delta are at danger of developing serious lung disease, infection with omicron frequently results in milder symptoms, particularly in vaccinated individuals (44). In line with prior investigations, we discovered that all occurrences of reinfection were mild (45). Strong data currently indicates that those with various health issues are at a higher risk (46). According to other studies, the only symptoms

associated with a positive result in reinfections are sore throat and rhinitis (47).

Our research had some limitations. 1. The infectious lineages were not sequenced. As a result, it cannot be completely ruled out that a case's recurrence corresponds to a reactivation of the strain involved in its first episode (48, 49); 2. The number of cases was relatively small; 3. Asymptomatic cases may have been missed; 4. Preventive behaviors associated with transmission were not analyzed and may have been different during the study periods; 5. The study has the strength of its longitudinal design, which is typical of general medical work.

**Conclusion**

From March 1, 2020 to July 1, 2022, we discovered evidence of a modestly increased risk of reinfection linked with the circulating delta variant, and a significant increase temporally connected with the development of the omicron variant, all compared to the original Wuhan lineage. The omicron version has

a greater ability to infect previously infected persons; however, all incidences of reinfection were minor, indicating that the vaccines are still extremely successful in preventing hospitalizations and deaths.

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