



Primary Infection and Reinfection COVID-19 from October 2023 to October 2024 in a General Medicine Office in Toledo, Spain

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Abstract

Background: The clinical-epidemiological differences between primary infections vs. reinfections of COVID-19 are not known.

Objective: Compare primary infections vs. reinfections of COVID-19 from October 1, 2023 to October 1, 2024.

Methods: An observational, longitudinal and prospective case series study of adult patients with COVID-19 infections in general medicine from October 1, 2023 to October 1, 2024. Descriptive epidemiological analysis considered a set of selected demographic and clinical features.

Results: 39 primary COVID-19 infections and 15 COVID-19 reinfections from October 2023 to October 2024 were included. The reinfections compared to the primary infections were younger patients, more women, less severe, in more complex families, with more cases in ethnic minority people, more general symptoms, less otorhinolaryngological, more chronic nervous and senses and musculoskeletal diseases and with fewer vaccinated with 4th and 5th dose. However, no statistically significant differences were found in any of these variables, except for the higher frequency of reinfections in socio-health care workers (5% in primary infections vs. 27% in reinfections; Fisher exact test statistic=0.0439).

Conclusion: In the context of a general medicine consultation in Toledo (Spain) from October 2023 to October 2024 (omicron variant was dominant), reinfections vs. primary infections were significantly more frequent in socio-health care workers. There are probably no clinical-epidemiological differences between cases of reinfection and primary infection. It is suggested that interventions and vaccines against COVID-19 should focus on healthcare workers. Although our results should be taken with caution due to the small number of COVID-19 cases included.

Keywords: COVID-19; SARS-CoV-2; Reinfection; COVID-19 vaccines; Epidemiological characteristic; Secondary analysis; General practice

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Introduction

The clinical-epidemiological characteristics of Coronavirus Disease 2019 (COVID-19) have evolved over the five years since its detection. The causative agent, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), has evolved, giving rise to different variants that have been predominant over time, resulting in different degrees of virulence, pathogenicity, immunogenicity, transmissibility

and immunity-depleting capacity. These changes in the virus, together with the effectiveness of vaccines, treatment medications, intensive diagnostic testing and contact tracing of cases at the beginning of the pandemic, to no testing, tracing or case counting in the current endemic phase, changes in other public health measures such as mandatory masks and social distancing and accompanying societal changes, may result in different clinical aspects over time from its pandemic onset to the current endemic evolution



[1].

The problem of reinfections became significantly more frequent when Omicron emerged and its more infectious subvariants became dominant in December 2022 [2,3]. As of December 17, 2023, more than 772 million confirmed cases had been documented. Although WHO admits that reporting and surveillance centers have decreased and vaccination centers have shrunk, been dismantled or closed and all these leads to an incomplete picture and we should unfortunately expect more cases than officially reported [4]. For the large and growing number of people who have suffered a first infection, the question of whether a second infection carries additional risks is important [5].

As COVID-19 evolves, so does the scientific understanding of the immunity generated by vaccines based on messenger RNA (mRNA) technology, such as those from Pfizer-BioNTech and Moderna. Since their initial distribution, these vaccines have proven effective in reducing severe cases of the disease and preventing hospitalizations, which was essential in the early stages of the global health crisis. However, recent studies indicate that the immunity conferred by these vaccines wanes over time, leading the centers for disease control and prevention to recommend periodic booster doses for certain vulnerable groups, especially older people and people with compromised immune systems. The persistent need for additional doses raises questions about the durability of immunity generated by mRNA vaccines, even among people who had experienced both infection and vaccination (with hybrid immunity). There is no indication that mRNA vaccines are not working, but there could be something particular about the virus that prevents the body from maintaining high levels of immunity in the long term, as well as the high mutation rate of SARS-CoV-2 and its constant presence throughout the year (not seasonal) are also factors related to low levels of immunity in this scenario, the number of reinfections is expected to increase [6,7].

In any case, for those who have had a previous infection, vaccination often adds greater protection, especially against reinfections that lead to hospitalization [8]. But, the clinical impact of reinfection is not yet fully understood. In general, reinfections have been reported to be clinically less severe than initial SARS-CoV-2 infections, but clinical-epidemiological trends in reinfections have not been characterized [2,9,10].

In this context, an important question is what are the clinical-epidemiological differences of reinfections in relation to initial infections. To better understand these differences, we present a longitudinal and prospective study of cases of primary infection and reinfection of adult people in general medicine from October 1, 2023-October 1, 2024.

Materials and Methods

Design and emplacement

This study compares data from two previous observational, longitudinal and prospective studies of

COVID-19 reinfections from March, 2020 to October, 2024, already published [11,12]. Both studies were conducted on the same population: patients saw in a general medicine office in Toledo, Spain, which has a list of 2,000 patients >14 years of age (in Spain, General Practitioner (GP) care for people >14 years of age, except for exceptions). The GPs in Spain work within the national health system, which is public in nature and are the gateway for all patients to the system and each person is assigned a GP. The methodology of all studies has been previously published and here only the main elements will be repeated for the current study.

Outcome of interest

Compare the clinical-epidemiological characteristics of cases of primary infection vs. COVID-19 reinfection.

Diagnosis of COVID-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing performed in health services or at home [13].

Definition of reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection [14-16].

COVID-19 vaccination

Patients could have received 1, 2 doses of vaccine, first booster for fall-winter 2021, fourth dose (second booster) for fall-winter 2022 and fifth dose (third booster) for fall-winter 2023. In our study, only Pfizer/BioNTech, Spikevax (mRNA-1273-Moderna), Vaxzevria, Oxford/AstraZeneca and Janssen (Johnson & Johnson) vaccines were used for the first and second doses. For the first booster, only mRNA was used. And only Moderna and Pfizer-BioNTech's bivalent COVID-19 vaccines were used for the second booster. The omicron-adapted vaccines XBB.1.5 Pfizer/BioNTech and Spikevax (Moderna) were used for the third booster in autumn-winter 2023-2024 [17-20].

Collected variables

- Age and sex.
- Symptoms of COVID-19 in reinfection and 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, requires special training of the patient for rehabilitation and/or can be expected to require a long period of control, observation or treatment both classified according to the International Statistical Classification of Diseases and Health-Related Problems, ICD-10 Version: 2019 [21,22].
- If they were health care workers.
- Problems in the family context based on the genogram. It



was understood that complex genograms present families with psychosocial problems [23,24].

- Ethnic minority, defined as a human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group [25].
- Severity of the disease primary infection and reinfection. Mild cases: Clinical symptoms are mild and no manifestation of pneumonia can be found on images. Moderate cases: With symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests and severe cases: respiratory distress, respiratory rate ≥ 30 breaths/min; pulse oxygen saturation $\leq 93\%$ with room air at rest; arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg) [26]. To simplify comparison, moderate and severe cases were counted together.
- Vaccination status against COVID-19: Vaccinated with 2 doses of vaccine, vaccinated with first booster for fall-winter 2021, vaccinated with fourth dose second booster for fall-winter 2022 and vaccinated with fifth dose (third booster) for fall-winter 2023 [13,27-30].

Epidemiological analysis

Descriptive epidemiological analysis considered a set of selected demographic and clinical features. Excessive fragmentation of the data was avoided to avoid showing a small number of cases. The age of 65 years was used as the beginning of old age [31]. Figures with decimals were rounded to facilitate a more intuitive comparison.

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X^2), X^2 with Yates correction or Fisher Exact Test.

Ethical Issues

No personal data of the patients were used, but only group results, which were taken from the clinical history.

Results

39 primary COVID-19 infections and 15 COVID-19 reinfections from October 2023 to October 2024 were included. Reinfections compared to primary infections were younger patients ($\geq 65.31\%$ vs. 27% years), more women (67% vs. 51%), less severe (moderate-severe severity 0% vs. 5%), in more complex families (13% vs. 8%), more ethnic minority (7% vs. 3%), more general symptoms (54% vs. 43%), less ENT (15% vs. 22%), more chronic diseases nervous and senses (16% vs. 11%) and musculoskeletal (23% vs. 13%) and less Neoplasms (5% vs. 8%). There was a high frequency of vaccination in both groups; the percentage of vaccinated with 4th and 5th doses was somewhat lower in

the reinfection group vs. primary infection (33% vs. 41%) and the vaccinated only 1, 2 or 3 dose slightly higher (67% vs. 54%). However, no statistically significant differences were found in any comparison of the sociodemographic variables, neither in symptoms nor in the presence of chronic diseases, except in the higher frequency of reinfections in socio-health care workers (5% in primary infections vs. 27% in reinfections; fisher exact test= 0.0439 . Significant at $p < 0.05$) (Tables 1, 2 and 3; Figures 1, 2 and 3).

Table 1: Selected variables of COVID-19 primary infections and reinfections from October 2023 to October 2024.

Variables	COVID-19 primary infections from October 2023 to October 2024 n=39	COVID-19 reinfections from October 2023 to October 2024 n=15	Statistical significance
≥ 65 years	12 (31)	4 (27)	X^2 with Yates correction =0.0014. $p=0.97051$ 3. NS
Women	20 (51)	10 (67)	$X^2=1.0385$. $p=0.30818$. NS
Socio-health care workers	2 (5)	4 (27)	Fet=0.043 9. Significant at $p < 0.05$.
Moderate-severe severity	2 (5)	0	Fet=1. NS
Chronic diseases	32 (82)	12 (80)	Fet=1. NS
Complex family/problems in the family context	3 (8)	2 (13)	Fet=0.609 9. NS
Ethnic minority	1 (3)	1 (7)	Fet=0.482 2. NS
Not vaccinated	2 (5)	0	Fet=1. NS
Vaccinated only 1, 2 or 3 dose	21 (54)	10 (67)	$X^2=0.7282$. $p=0.39345$ 6. NS
Vaccinated 4 dose	9 (23)	1 (7)	Fet=0.2515. NS
Vaccinated 5 dose	7 (18)	4 (27)	Fet=0.4751. NS
Vaccinated 4 or 5 dose	16 (41)	5 (33)	$X^2=0.2697$. $p=0.60351$ 3. NS

Note: (): Denotes percentages; X^2 : Chi square; Fet: Fisher exact test statistic.



Table 2: Symptoms of COVID-19 primary infections and reinfections from October 2023 to October 2024.

Symptoms COVID-19 infection* according to who, ICD-10 groups	COVID-19 primary infections from October 2023 to October 2024 n=39	COVID-19 reinfections from October 2023 to October 2024 n=15	Statistical significance
General (discomfort, asthenia, myalgia, fever, artralgiias)	50 (43)	29 (54)	$X^2=1.5434$, $p=0.2141$ 15. NS
Respiratory (cough, dyspnea, chest pain)	29 (25)	13(24)	$X^2=0.0257$, $p=0.8725$ 88. NS
ENT (anosmia/ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, pharyngeal dryness-mucus, facial pain)	25 (22)	8 (15)	$X^2=1.1212$, $p=0.2896$ 62. NS
Digestive (anorexia, nausea/vomiting, diarrhea, abdominal pain)	1 (1)	1 (2)	Fet=0.53 83. NS
Neurological (headache, dizziness, sleepiness)	8 (7)	3 (5)	Fet=1. NS
Psychiatric	0	0	Fet=1. NS
Skin	0	0	Fet=1. NS
Urological (pollakiuria-urinary incontinence)	1 (1)	0	Fet=1. NS
Ophthalmologic (conjunctivitis)	1 (1)	0	Fet=1. NS
Total symptoms*	115 (100)	54 (100)	-

Note: (): Denotes percentages; X^2 : Chi Square; Fet: Fisher exact test statistic; *Patients could have more than one symptom. The percentages are over the total of symptoms.

Table 3: Chronic diseases of COVID-19 primary infections and reinfections in the period from October 2023 to October 2024.

Chronic diseases* according to who, ICD-10 groups	COVID-19 primary infections from October 2023 to October 2024 n=39	COVID-19 reinfections from October 2023 to October 2024 n=15	Statistical significance
Infectious	2 (1)	0	Fet=1. NS
Neoplasms	12 (8)	2 (5)	Fet=0.7404. NS
Diseases of the blood	6 (4)	0	Fet=0.5862. NS
Endocrine	24 (15)	5 (13)	$X^2=0.1507$, $p=0.69786$ 1. NS
Mental	19 (12)	4 (10)	X^2 with Yates correction= 0.0018. $p=0.96606$ 4. NS
Nervous and senses	18 (11)	7 (18)	X^2 with Yates correction= 0.6694. $p=0.413254$. NS
Circulatory system	15 (10)	3 (8)	X^2 with Yates correction= 0.0026. $p=0.95966$ 6. NS
Respiratory system	8 (5)	1 (3)	Fet=0.6908. NS
Digestive system	17 (11)	4 (10)	X^2 with Yates correction= 0.0346. $p=0.85249$ 7. NS
Diseases of the skin	4 (2)	0	Fet=0.5862. NS
Musculo-skeletal	20 (13)	9 (23)	$X^2=2.6484$, $p=0.10365$ 4. NS
Genitourinary	12 (8)	4 (10)	Fet=0.5294. NS
Total chronic diseases*	157 (100)	39 (100)	-

Note: (): Denotes percentages; X^2 : Chi Square; Fet: Fisher exact test statistic; *Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases.

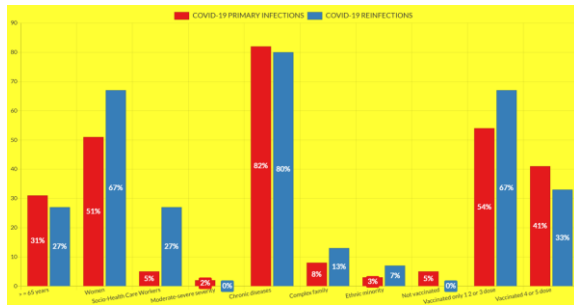


Figure 1: Selected variables of COVID-19 primary infections and reinfections from October 2023 to October 2024.

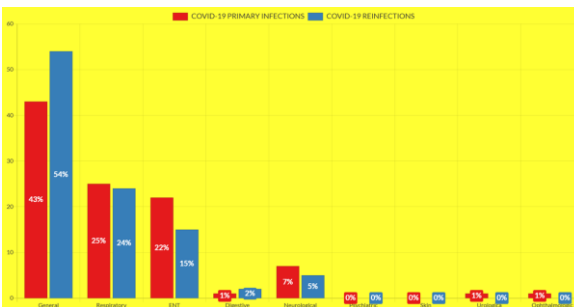


Figure 2: Symptoms of COVID-19 primary infections and reinfections from October 2023 to October 2024.

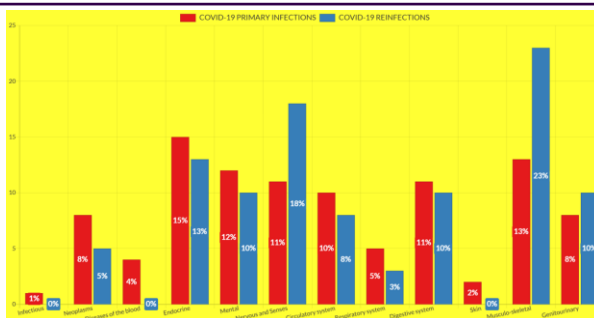


Figure 3: Chronic diseases of COVID-19 primary infections and reinfections from October 2023 to October 2024.

because in Spain, since April 28, 2022 there was a new surveillance and control strategy against COVID-19 that included the non-performance of diagnostic tests, which were focused only on those over 60 years of age, immunosuppressed and pregnant women, vulnerable areas (health and socio-health) and serious cases and the elimination of contact tracing [32]. It is therefore reasonable to think that in our study there was an excess of tests in socio-sanitary health workers, compared to the total. In addition, these restrictions lead people with symptoms to carry out the test at home; Although the majority of positive cases will be reported to the GP [33]. On the other hand, if infections are generally milder, it is likely that a greater proportion will not be diagnosed.

Third, it should be mentioned that in the study period, the omicron variant was the dominant one in Spain (in the week of November 21-27, 2022), the omicron percentage stood at 100% [20].

Comparison with other studies

The result of our study that there are probably no clinical-epidemiological differences between cases of reinfection and primary infection, is in agreement with what has been published by other authors. Thus, it has been reported that primary infections in vaccinated people (who have some immunity against COVID-19) are generally less severe than primary infections in unvaccinated people (who have no immunity). Therefore, it is reasonable to assume that, in general, reinfections should be less severe than primary infections, since the person who is reinfected will have some pre-existing immunity from their primary infection. In addition, many people will have been vaccinated between their infections, which will have raised their immunity levels even further. Although immunity against coronavirus infection wanes, protection against severe disease and death seems much longer lasting. So, reinfections definitely seem to be less severe. Thus, it has been reported that with an omicron reinfection, the rate of symptoms was almost the same in reinfection and primary infection and of similar severity [3,34].

Likewise, it has been reported that reinfections with BA.5 sub lineages had a significantly lower incidence and severity of fever, fatigue, sore throat and cough, compared to primary infections with BA.5 sub lineages. SARS-CoV-2 Omicron reinfections were less severe than primary Omicron infections during circulation of the same subvariant [35]. This has also been the case in the same population of the current study in a previous study from October 2022 to October 2023 [36].

Previous studies show that healthcare workers have an additional risk of exposure to SARS-CoV-2 compared to the general population, through contact with contagious patients [37-43]. Our study, although it may have an overrepresentation of this population, is in agreement with the accepted data. Likewise, there is an underreporting of reinfections, because some infections can be taken as primary and are in fact reinfections. A Canadian study estimated that 40% of people who had antibodies in their

Discussion

Main findings

The main results of our study were:

- Reinfections vs. primary infections were significantly more frequent in socio-health care workers.
- There are probably no clinical-epidemiological differences between cases of reinfection and primary infection, although reinfections seem to occur in younger people, women, complex families and ethnic minorities and patients with chronic nervous and senses and musculoskeletal diseases, with general symptoms, of mild severity and with a lower percentage of vaccinated with 4th and 5th doses.

However, these results should be interpreted with caution. Firstly, because of the few cases included. Second,



blood (proof that they had been infected by SARS-CoV-2) had not experienced any symptoms in the previous six months and were unaware that they had contracted the disease [44].

In our study, reinfections appear to occur in people fewer vaccinated with 4th and 5th dose and more with only 1, 2 or 3 doses. In the same population of the current study, it has been reported that the 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections was modest [45].

In short, our results indicate that reinfections vs. primary infections from October 2023 to October 2024 seem to occur (but without statistical significance) in younger people, women, complex families and ethnic minorities and patients with chronic nervous and senses and musculoskeletal diseases, with general symptoms, of mild severity and with a lower percentage of those vaccinated with 4th and 5th dose. But specially and significantly more frequent in socio-health care workers.

Study Limitations and Strengths

- The small number of COVID-19 cases may mask the statistical significance between variables.
- Asymptomatic cases were missing because they did not attend in GP consultation, as no surveillance or systematic screening was done.
- There may be an underreporting of infections to GP of patients with a positive test at home. But given the situation of the GP as the gateway to the health system, the vast majority of positive COVID-19 tests at home, is likely to be reported in GP office.
- The great accessibility of patients to the GP and the fact of the continuity of care that characterizes family medicine, have important epidemiological connotations, presenting a unique opportunity to study diseases in small geographical bases.

Conclusion

In the context of a general medicine consultation in Toledo (Spain) from October 2023 to October 2024 (omicron variant was dominant), reinfections vs. primary infections were significantly more frequent in socio-health care workers.

There are probably no clinical-epidemiological differences between cases of reinfection and primary infection, although reinfections seem to occur in younger people, women, complex families and ethnic minorities and patients with chronic nervous and senses and musculoskeletal diseases, with general symptoms, of mild severity and with a lower percentage of vaccinated with 4th and 5th dose. It is suggested that interventions and vaccines against COVID-19 should focus on socio-health workers. In any case, our results should be taken with caution due to the small number of COVID-19 cases included.

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