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Clinical-Epidemiological Characteristics of COVID-19 Reinfection from October 1, 2023 to October 1, 2024 According to Time Elapsed Since Primary Infection in a General Medicine Office in Toledo, Spain

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Abstract

Background: Protection against SARS-CoV-2 reinfection based on time since primary infection is not clearly known.

Objective: To interpret the duration of protective immunity after a COVID-19 infection, based on the time elapsed until reinfection.

Methods: An observational, longitudinal and prospective study of adult patients with COVID-19 reinfections in general medicine from October 1, 2023 to October 1, 2024. Reinfections with a time elapsed since primary infection of < and >15 months were compared.

Results: 15 COVID-19 reinfections were included, of which 13% had a time elapsed from COVID-19 primary infections to reinfections <15 months and 87% >15 months. Reinfections with a time <15 months *vs.* >15 months were older, male, socio-health care workers, with less Chronic diseases, less Complex family, less ethnic minority and more vaccinated with 4th or 5th dose, but none of these variables showed statistically significant differences; ENT symptoms were significantly more frequent (36% *vs.* 8%; fisher exact test=0.0214).

Conclusion: In the context of a general medicine consultation in Toledo (Spain) reinfections by omicron variants (occurred from October 2023 to October 2024) with primary infections by omicron occurred from July 2023 onwards had a short-term immunity (<15 months). These reinfections *vs.* those > 15 months since primary infection differ in presenting more ENT symptoms. 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; General practice

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Introduction

The problem of reinfections became significantly more frequent when omicron emerged and its more infectious subvariants became dominant in December 2022 [1,2]. How long do antibodies against coronavirus disease 2019 (COVID-19) last? It is not known exactly and in part, this is because the new variants are a bit different from the previous variants that existed. The data are imperfect and also, the variants are to some extent ahead of clinical data [3].

Studies have documented the efficacy of past infection in preventing reinfection and subsequent symptomatic disease and severe disease (hospitalization or death), including the

extent to which immunity wanes over time. However, to date, none have comprehensively assessed how the risk of reinfection varies by time since infection [4].

The magnitude of the antibody response against severe acute respiratory syndrome coronavirus (SARS-CoV-2) is highly heterogeneous between individuals. This heterogeneity means that long-term longitudinal studies will be required to precisely define the kinetics of antibodies against SARS-CoV-2. Thus, immune responses at short time points after resolution of infection are not highly predictive of long-term memory [5-7]. Therefore, assessing responses over an interval of 6 months or more is generally required to determine the durability of immune memory [8]. A basic understanding of immune memory after COVID-19 is thought to require simultaneous measurement of circulating antibodies, memory B cells, CD8+ T cells and SARS-CoV-2-specific CD4+ T cells, in a group of subjects with a wide range of diseases and distributed from short time points after infection to at least 8 months later [8].

Understanding the characteristics of the protection offered by a previous SARS-CoV-2 infection against a subsequent reinfection is essential to predict the potential future disease burden and to design preventive policies including decisions on when to receive vaccine doses [4].

In this context, we present a longitudinal and prospective study of cases of reinfection of adult people in general medicine from October 1, 2023, to October 1, 2024, classifying them into more or less than 15 months of time elapsed since primary infection, with the aim of Reasonably interpreting the duration of protective immunity after COVID-19 infection, based on the time elapsed until reinfection.

Materials and Methods

Design and emplacement

An observational, longitudinal and prospective study of adult patients with COVID-19 infections from October 1, 2023 to October 1, 2024 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 current study compares some data from previous study of COVID-19 reinfections from October, 2023 to October, 2024 [9].

The following were compared:

- Reinfections with a time since primary infection of <15 months (primary infections from July 2023; in 2023-2024 the omicron subvariants were dominant; the fifth dose (third booster dose) was administered in autumn-winter 2023-2024).
- With reinfections with time from primary COVID-19 infections to reinfections >15 months (primary infections before July 2023; in this period during 2020-2022 the SARS-CoV-2 variants were successively alpha, delta and omicron and the population had received only 1, 2 or 3 doses (first booster of the vaccine in autumn-winter 2021-2022); The fourth dose (second booster dose) was inoculated in autumn-winter 2022-2023. In 2023, omicron was dominant).

This 15-month period was chosen as a cut-off point based on data that recommend longitudinal studies lasting more than 8 months [8]. The descriptive epidemiological analysis considered a set of selected demographic and clinical characteristics.

Outcome of interest

Compare the clinical-epidemiological characteristics of cases of COVID-19 reinfection from October 1, 2023 to October 1, 2024, according to the time elapsed since primary infection, classified into two groups: < and >15 months of time elapsed since primary infection and reasonably interpret the duration of protective immunity after a COVID-19 infection, based on these data.

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 [9].

Definition of reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection [10-12].

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 Pizfer/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 Pizfer/BioNTech and Spikevax (Moderna) were used for the third booster in autumn-winter 2023-2024 [13-16].

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 [17,18].

- 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 [19,20].
- Ethnic minority, defined as a human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group [21].
- 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 ≤ 93% with room air at rest; arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg [22]. 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 [9,23-26].

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 [27]. 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

15 COVID-19 reinfections from October 2023 to October 2024 were included, of which 13% had a time elapsed from COVID-19 primary infections to reinfections <15 months and 87% >15 months of the 15 reinfections, the first primary infection in time was in August 2020 and the last in August 2023. The distribution by year of the primary infections of the 15 reinfection cases was as follows: In 2020, 2 primary infections occurred; in 2021, 1; in 2022, 10; and in 2023, 2. All reinfections were mild. Reinfections with a time elapsed since primary infection <15 months (primary infections from July 2023) *vs.* >5 months (primary infections before July 2023) were older, male, socio-health care workers, with less chronic diseases, less complex family, less Ethnic minority and more vaccinated with 4th or 5th dose, but none of these variables showed statistically significant differences; ENT symptoms were significantly more frequent in reinfections with a time elapsed since primary infection <15 months (36% *vs.* 8%; Fisher exact test=0.0214) **(Tables 1, 2, 3 and 4; Figures 1, 2, 3 and 4)**.

Table 1: Time elapsed from COVID-19 primary infections to reinfections that occurred from October 2023 to October 2024.

Time elapsed from COVID-19 primary infections to reinfections	COVID-19 reinfections from October 2023 to October 2024 N=15
Time elapsed from COVID-19 primary infections to reinfections <15 months (primary infections from July 2023 onwards; In 2023-2024 omicron subvariants were dominant; Fifth dose (third booster) was administered in fall-winter 2023-2024)	2 (13)
Time elapsed from COVID-19 primary infections to reinfections >15 months (primoinfections before July 2023; in this period during 2020-2022 SARS-CoV-2 variants were successively alpha, delta and omicron and the population had received only 1, 2 or 3 doses -first booster for fall-winter 2021 vaccine; Fourth dose (second booster) was inoculated in fall-winter 2022-2023. In 2023 omicron was dominant)	13 (87)
Note: ( ): Denotes percentages.	

Table 2: Comparison of selected variables between COVID-19 reinfections with a time elapsed since primary infection of less and greater than 15 months.

Time in months	COVID-19 reinfections with an elapsed time since primary infection <15 months (primary infections from July 2023 onwards) N=2	COVID-19 reinfections with an elapsed time since primary infection >15 months (primary infections before July 2023) N=13	Statistical significance
>=65 years	2 (100)	2 (15)	Fet=0.0571. NS
Women	1 (50)	9 (69)	Fet=1. NS
Socio-health care workers	1 (50)	3 (23)	Fet=0.4762. NS
Moderate-severe severity	0	0	Fet=1. NS

Chronic diseases	1 (50)	11 (85)	Fet=0.3714. NS
Complex family/Problems in the family context	0	2 (15)	Fet=1. NS
Ethnic minority	0	1 (8)	Fet=1. NS
Not vaccinated	0	0	Fet=1. NS
Vaccinated only 1, 2 or 3 dose	0	10 (77)	Fet=0.0952. NS
Vaccinated 4 or 5 dose	2 (100)	3 (23)	Fet=0.0952. NS

Note: ( ): Denotes percentages; Fet: Fisher exact test statistic.

Table 3: COVID-19 reinfection symptoms with a time elapsed since primary infection of minor and greater than 15 months.

Symptoms COVID-19 infection* according to WHO, ICD-10 groups	COVID-19 reinfections with an elapsed time since primary infection <15 months (primary infections from July 2023 onwards) N=2	COVID-19 reinfections with an elapsed time since primary infection >15 months (primary infections before July 2023) N=13	Statistical significance
General (discomfort, asthenia, myalgia, fever, artralgias)	8 (57)	21 (52)	X^2=0.0899. p=0.76429. NS
Respiratory (cough, dyspnea, chest pain)	1 (7)	12 (30)	X^2 with Yates correction =1.8455. p=0.17430 4. NS
ENT (anosmia/ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, pharyngeal dryness-mucus, facial pain)	5 (36)	3 (8)	Fet=0.0214. Significant at p <0.05.
Digestive (anorexia, nausea/vomiting, diarrhea, abdominal pain)	0	1 (2)	Fet=1. NS
Neurological (headache, dizziness, sleepiness)	0	3 (8)	Fet=0.5597. NS
Psychiatric	0	0	Fet=1. NS
Skin		0	Fet=1. NS
Urological	0	0	Fet=1. NS
Ophthalmologic	0	0	Fet=1. NS
Total symptoms*	14 (100)	40 (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 4: COVID-19 reinfection chronic diseases with a time elapsed since primary infection of minor and greater than 15 months.

Chronic diseases* according to WHO, ICD-10 groups	COVID-19 reinfections with an elapsed time since primary infection <15 months (primary infections from July 2023 onwards) N=2	COVID-19 reinfections with an elapsed time since primary infection >15 months (primary infections before July 2023) N=13	Statistical significance
Infectious	0	0	Fet=1. NS
Neoplasms	0	2 (6)	Fet=1. NS
Diseases of the blood	0	0	Fet=1. NS
Endocrine	2 (32)	3 (9)	Fet=0.1614. NS
Mental	0	4 (12)	Fet=1. NS
Nervous and Senses	0	7 (21)	Fet=0.5679. NS
Circulatory system	1 (17)	2 (6)	Fet=0.403. NS
Respiratory system	0	1 (3)	Fet=1. NS
Digestive system	1 (17)	3 (9)	Fet=0.5025. NS
Diseases of the skin	0	0	Fet=1. NS
Musculo-skeletal	1 (17)	8 (25)	Fet=1. NS
Genitourinary	1 (17)	3 (9)	Fet=0.5025. NS
Total chronic diseases*	6 (100)	33 (100)	-

Note: ( ): Denotes percentages; 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

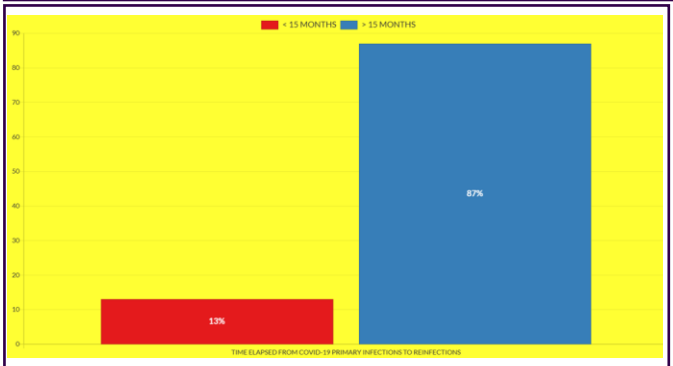

Figure 1: Time elapsed since COVID-19 primary infections to reinfections that occurred from October 2023 to October 2024.

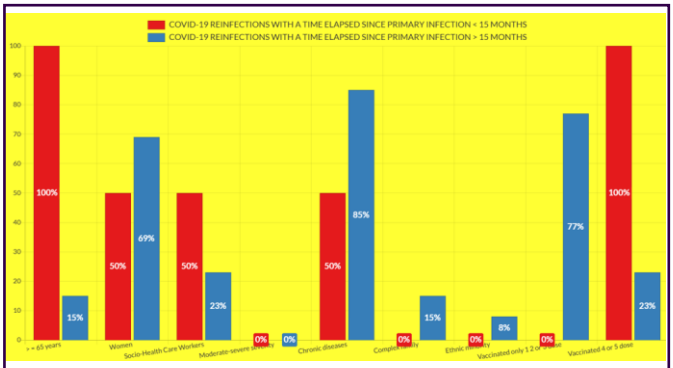

Figure 2: COVID-19 reinfections with a time elapsed since primary infection of less and greater than 15 months.

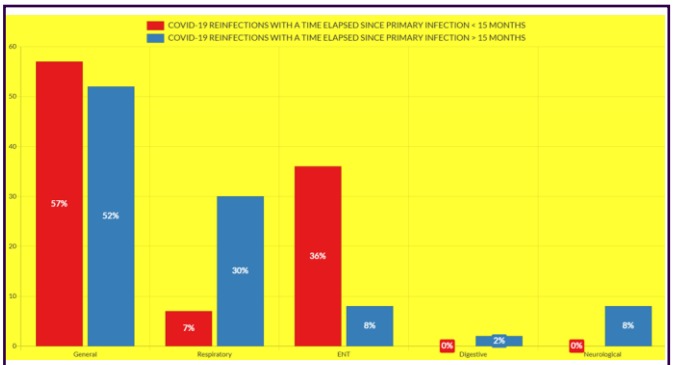

Figure 3: COVID-19 reinfection symptoms with a time elapsed since primary infection of minor and greater than 15 months.

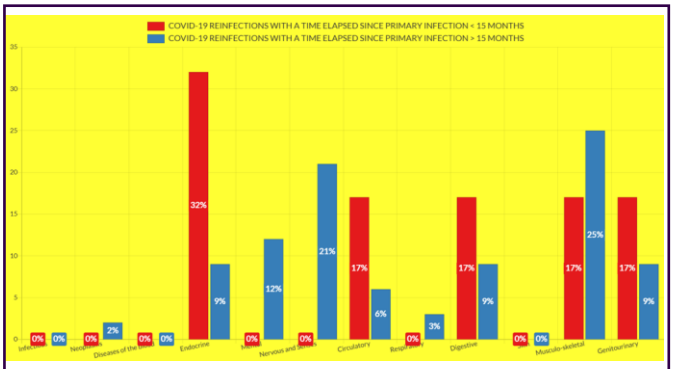

Figure 4: COVID-19 reinfection chronic diseases with a time elapsed since primary infection of minor and greater than 15 months.

Discussion

Main findings

The main results of our study were:

- ENT symptoms were significantly more frequent in reinfections with a time since primary infection <15 months *vs.* >15 months (36% *vs.* 8%; Fisher exact test=0.0214).

- Reinfections with a time since primary infection <15 months *vs.* >15 months were older, male, Socio-Health Care Workers, with less Chronic diseases, less Complex family, less Ethnic minority and were more vaccinated with 4th or 5th dose, but none of these variables showed statistically significant differences.

These findings suggest that reinfections with a time since primary infection <15 months (primary infections from July 2023 onwards), which are reasonably due to omicron (prevalent variant at that time) have a short duration of natural immunity (<15 months).

However, these results should be interpreted with caution:

Firstly, because of the few cases included and important confounding variables could not be controlled.

Second, 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 [28]. 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 [29]. 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 period 2020-2022 SARS-CoV-2 variants were successively alpha, delta and omicron and the population had received only 1, 2 or 3 doses of vaccine [30].

In May 2022, the Omicron variant was the dominant one in Spain after having displaced the Delta variant [31]. The omicron variant was the dominant one in Spain November, 2022 (in the week of November 21 to 27, 2022), the omicron percentage stood at 100%) [16]. The XBB.1.5 lineage became the dominant in March de 2023 in Spain [32]. The predominant variants in Spain during 2023 were those of the XBB family [26,32-36]. In January 2024 in Spain, XBB.1.5-like+F456L accounted for 42% and BA.2.86 for 44% of positive cases [23]. In July and August 2024, the KP.3 lineage was detected in 84% of cases [37]. In September 2024, the incidence of the XEC variant of the coronavirus, a new Omicron subvariant was increasing markedly in Spain. At that time, it was the second most common strain in cases recorded in September, although still far behind the main

KP.3.3, with an incidence of 13% [38,39].

Fourth, vaccination rates in our population were very high. In this sense, our results on the duration of natural immunity post infection could be considered to correspond to a population with almost 100% vaccine immunity. In Spain, in April 2022, the population vaccinated with the complete regimen (2 or 3 doses) was 85.27% [40]. In November 2022, more than 60% of people over 80 years of age and 37% of people over 60 years of age, already had the second booster dose of the COVID-19 vaccine [41,42]. By June 2023, the number of people with the 1st booster dose was 56% of the population [43]. In 2024 the population received 5th booster doses of vaccine. 60% of the population over 80 years of age has already received the vaccine adapted against the COVID-19 subvariants of the 2023/2024 campaign [44].

Comparison with other studies

B cell memory to some other infections has been observed to be long-lived, including more than 60 years after smallpox vaccination or more than 90 years after influenza infection. A median time of 123 days has also been observed for memory CD8+ T cells after yellow fever immunization. These data suggest that T cell memory might reach a more stable plateau or slower decay phase, beyond the first 8 months after infection. Although immunological memory is the source of long-term protective immunity, direct conclusions about protective immunity cannot be drawn based on quantification of circulating SARS-CoV-2 antibodies, memory B cells, CD8+ T cells and CD4+ T cells, because the mechanisms of protective immunity against SARS-CoV-2 or COVID-19 are not defined in humans. However, reasonable interpretations can be made [8].

In four large-scale studies in the UK, the US and Denmark, infection with the original SARS-CoV-2 virus from Wuhan was estimated to confer 80%-90% protection against reinfection at 7 months and 94% against symptomatic disease. In people aged over 65 years, effectiveness was estimated to be around 50% for reinfection [45]. One year after SARSCoV-2 infection, the vast majority of people maintain anti-spike antibodies regardless of symptom severity, according to a cohort study of 173 primary care healthcare workers in Barcelona, Spain, recruited during the first peak of the pandemic (March–April 2020) [46]. A 2020 study of 2800 people found no symptomatic reinfections during a ~118-day window and a study of 1246 people observed no symptomatic reinfections over 6 months [8,47,48].

One study found that people's immune systems remember COVID-19 for months after recovery. The number and type of antibodies varied between people. But levels generally remained stable over time. They declined slightly six to eight months after infection [8]. Researchers also found that having COVID-19 reduced the risk of someone being hospitalized and dying from reinfection by 88% for at least 10 months. Protection against reinfection with pre-omicron variants was very high and remained high even after 40 weeks. Protection was substantially lower for the BA.1 omicron variant and declined more rapidly over time than protection against earlier variants. Protection against severe disease was high for all variants. While protection against hospitalization and death remained high over the study period, protection against symptoms of the virus faded faster. Having had COVID-19 before the omicron variants emerged did not seem to help much. People who had a previous infection with a different variant had a 74% chance of being protected from reinfection after one month, but that percentage dropped to 36% after 10 months [4]. According to data from Biobank, infection with the Omicron variant generates immunity for a period of 6 months in 88% of cases and 3 months in 99% of cases. Infection with Omicron induces a limited humoral immune response [49,50].

In short, our results indicate that in the context of a general medicine consultation in Toledo (Spain) we can reasonably infer that reinfections by Omicron variants with primary infections by Omicron have a short-lived immunity. This conclusion, in line with the existing literature, is based on the fact that reinfections that occurred from October 2023 to October 2024 in our study (when omicron subvariants were dominant and fifth dose (third booster) was administered in fall-winter 2023-2024)) had primary infections from July 2023 onwards (time elapsed since primary infection <15 months (short time) and with omicron as the prevalent variant at those dates. On the other hand, these omicron reinfections from omicron primary infections (duration of their natural immunity is <15 months) differ in a statistically significant way only in presenting more ENT symptoms compared to omicron reinfections from primary infections from 2020 to June 2023. Although our results should be taken with caution due to the small number of COVID-19 cases included. The short-term immunity conferred by infection due to the previous omicron variant must be weighed against the protection of vaccination when assessing the future burden of COVID-19 disease and vaccination policies in the community.

Study Limitations and Strengths

- The small number of COVID-19 cases may mask the statistical significance between variables. The study was not powered to control for variables simultaneously.
- 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 viruses responsible for the cases were not genetically characterized and only the variant is assigned based on the prevalence in the periods studied.
- 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, reinfections with a time since primary infection <15 months (primary infections from July 2023 onwards; In 2023-2024 Omicron subvariants were dominant; Fifth dose (third booster) was administered in fall-winter 2023-2024), are reasonably due to omicron and the duration of their natural immunity is <15 months. These reinfections differ in a statistically significant way only in presenting more ENT symptoms. Although our results should be taken with caution due to the small number of COVID-19 cases included. The brief immunity conferred by infection due to the previous omicron variant must be weighed together with the protection of vaccination when assessing the future burden of COVID-19 disease and vaccination policies in the community.

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