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Research Article

Covid-19 Reinfections Clinical-Epidemiological Characteristics Trend Between 2020-2022, 2023 And 2024 In A General Medicine Clinic in Toledo (Spain)

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Abstract

Background

Long-term clinical-epidemiological evolution data on SARS-CoV-2 reinfections cases in community settings are scarce.

Objective

To compare clinical-epidemiological characteristics in cases of covid-19 reinfections during 2020-2022 period, with 2023 and 2024 years in the same population in general medicine.

Methodology

Comparison of secondary data among covid-19 cases in 2020-2022, 2023 and 2024 years of previous studies, all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain.

Results

Reinfections are mild, infrequent in people over 65 years of age (although with a trend towards greater frequency in 2023 and 2024). There is a tendency to increase the frequency in women (predominant in 2020-2022 and 2024) [p= .002663] and chronic diseases presence (higher in 2020-2022 and especially in 2024) [p= .038334] which by groups tend to decrease in 2024 except Musculoskeletal, Nervous and Senses and Digestive system which increase strongly. The frequency of Health Care Workers with reinfections was high, with a peak in 2023 [p= .000978]. 67% of reinfections in 2024 had only 1 , 2 or 3 doses of vaccine. There were no differences between the frequencies of symptoms, but general symptoms always predominated, with a tendency to increase.

Conclusions

The trend of reinfections shows that they are mild, in women, in people under 65 years of age, with chronic diseases, and in healthcare workers. There are no differences between the symptoms, with general symptoms always predominating and tending to increase. Booster doses can be modestly reduce the risk of reinfection.

Keywords: covid-19; sars-cov-2; reinfection; covid-19 vaccines; boosters; epidemiological characteristic; secondary analysis; general practice

Introduction

Reinfections with severe acute respiratory syndrome coronavirus (SARS-CoV-2) were rare until late 2021 but became common with the arrival of omicron (1, 2). Reinfections with SARS-CoV-2 are an important aspect of coronavirus disease 2019 (covid-19) and its potential transition to endemicity (3-5). It is currently accepted that it may be normal to be infected by SARS-CoV-2 several times throughout life (6-10).

Furthermore, compared with the absence of reinfection, reinfection appears to contribute to additional risks of death, hospitalization, and sequelae, including pulmonary, cardiovascular, hematologic, diabetes, gastrointestinal, renal, mental health, musculoskeletal, and neurologic disorders. The risks appear to remain evident regardless of vaccination status (11). It has been estimated that after 4-6 months of a first episode of covid-19 or having been vaccinated (or both, (hybrid immunity), a new SARS-CoV-2 infection is expected to be associated with a higher risk of hospitalization and death in the most fragile population (12).

But for many people who get Covid-19 multiple times, subsequent infections will be as mild as the first or more, data show, likely due to partial immunity from previous infections, vaccination, and the fact that the latest circulating variants often cause less severe symptoms (13).

Given the current situation in many places, such as Spain, of not performing diagnostic tests in health services, except for those over 60 years of age and healthcare workers (14), many people with symptoms choose to test at home and the trend of reinfection rate over time is not clear (2). However, estimates of the burden of SARS-CoV-2 reinfections remain crucial to assess new

variants with immune escape potential (15) and to help guide public health measures and vaccination strategies (2, 16).

In this context, we present a comparative study based on previously published data, to evaluate the clinical-epidemiological characteristics of reinfections covid-19 cases in the period 2020-2022 (in 2020 without vaccination, in 2021 with 1 or 2 dose vaccination and in 2022 with first booster), in 2023 (with second booster), and 2024 (with third booster), from the same population attended in a general medicine consultation in these time periods.

Material And Methods

Design and emplacement

This study compares data from previous observational, longitudinal and prospective studies of covid-19 reinfections from March, 2020 to October, 2024, already published (17-21). All 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

To know and describe a set of selected clinical-epidemiological characteristics of cases of covid-19 reinfection from 2020-2022 period, in 2023 and 2024, at primary health care level.

Definition of reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection (22, 23).

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing (24) performed in health services or at home.

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 messenger RNA (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 (25-28).

Collected variables

The following variables were collected:

-Age and sex

-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" (29) and symptoms covid-19 infection, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (30)

-Social-occupancy class (according to the Registrar General's classification of occupations and social status code) (31, 32)

-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) (33-35)

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") (36)

-Disease severity (classified according to: 1. mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; 2. moderate cases: with symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests; and 3. 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.) (37); to simplify comparison, moderate and severe cases were counted together

-Vaccination status against covid-19 at the date of reinfection: vaccinated with 2 doses of vaccine (24), vaccinated with first booster for fall-winter 2021 (38), vaccinated with fourth dose (second booster) for fall-winter 2022 (39) and vaccinated with fifth dose (third booster) for fall-winter 2023 (40, 41)

Statistical analysis

The comparisons were performed using the Chi Square test (X2) or test of Kruskal-Wallis, when necessary, both with degrees freedom (df)= 2 [df= (número de filas-1) x (número de columnas-1)]

Ethical issues

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

Results

Reinfections are mild throughout the period (Not significant at $p < .05$ [NS]), relatively rare in those over 65 years of age (although with a tendency towards greater frequency in 2023 and 2024 versus the 2020-2022 period) [NS]. There is a tendency towards increasing frequency in women (predominant in 2020-2022 and 2024) [X2 (df = 2) = 11.8565. p = .002663. Significant at $p < .05$.] and chronic diseases presence (higher in 2020-2022 and especially in 2024) [X2 (df = 2) = 6.5228. p = .038334. Significant at $p < .05$.], with no statistically significant differences between the frequencies of chronic diseases according to WHO, ICD-10 groups, but all groups tend to decrease in 2024 except Musculo-skeletal, Nervous and Senses and Digestive system which increase strongly. The frequency of Health Care Workers with reinfections was non-negligible throughout the period with a peak in 2023 [X2(df=2)= 13.8594. p= .000978. Significant at $p < .05$.]. The frequency of Complex family in reinfections was higher in 2023 [NS]. 67% of reinfections in 2024 had only 1, 2 or 3 doses of vaccine (**Table 1, Table 2, Figure 1, Figure 2**). There were no statistically significant differences between the frequencies of symptoms according to WHO, ICD-10 groups, but general symptoms always predominated, with a tendency to increase; respiratory and ENT symptoms were in second place in frequency and with a tendency to decrease; the rest, Neurological, Digestive, Psychiatric, Skin, Genitourinary, with marginal figures throughout the period (**Table 3, Figure 3**).

Variables	Reinfections From March 1, 2020 To September 30, 2022 N=38	Reinfections From October 1, 2022 To September 30, 2023 N=12	Reinfections From October 1, 2023 To September 30, 2024 N=15	Statistical significance
> = 65 years	3 (8)	4 (33)	4 (27)	X2 (df=2) = 5.5146. p= .063464. NS
Women	30 (79)	3 (25)	10 (67)	X2 (df=2) = 11.8565. p= .002663. Significant at p < .05.
Health Care Workers	7 (18)	9 (75)	4 (27)	X2(df=2) = 13.8594. p= .000978. Significant at p < .05.
Moderate-severe severity of reinfection	0	3 (25)	0	Kruskal-Wallis (df=2): H=2.7. p = .259. NS
Chronic diseases	25 (66)	4 (33)	12 (80)	X2 (df=2) = 6.5228. p= .038334. Significant at p < .05.
Social-occupancy class of patients (people with some type of labor specialization)	16 (42)	1 (8)	4 (27)	X2 (df=2) =5.0399. P= .080462. NS
Complex family/ Problems in the family context	3 (8)	7 (58)	2 (13)	X2 (df=2) =15.7538. P= .000379. Significant at p < .05.
Ethnic minority	5 (13)	1 (8)	1 (7)	X2 (df=2) = 0.5625. p= .754858. NS
1, 2 ó 3 dose	38 (100)	7 (6)	10 (67)	NR
4 dose	NR	5 (42)	1 (7)	NR
5 dose	NR	NR	4 (27)	NR

Table: Comparison Of Selected Variables Of Covid-19 Reinfections In 2020-2022, 2023 And 2024

(): Denotes percentages; NS: Not significant at p< .05; df= Degrees freedom; NR: Not relevant

Chronic diseases*	Reinfections From March 1, 2020 To September 30, 2022 N=38	Reinfections From October 1, 2022 To September 30, 2023 N=12	Reinfections From October 1, 2023 To September 30, 2024 N=15	Statistical significance
-I Infectious	0	0	0	Kruskal-Wallis (df=2): H= 0.11. p = .949. NS
-II Neoplasms	1 (2)	2 (8)	2 (5)	X2 (df=2)= 2.4474. p= .294134. NS
-III Diseases of the blood	0	0	0	Kruskal-Wallis (df=2): H= 0.11. p = .949. NS
-IV Endocrine	11 (15)	5 (19)	5 (13)	X2 (df=2) = 0.4913. p= .782214. NS
-V Mental	5 (7)	3 (12)	4 (10)	X2 (df=2) = 0.6178. p= .734266. NS
-VI-VIII Nervous and Senses	6 (8)	1 (4)	7 (18)	X2 (df=2) = 3.9064. p= .141817. NS
-IX Circulatory system	7 (10)	3 (12)	3 (8)	X2 (df=2) = 0.2824. p= .8683. NS
-X Respiratory system	11 (16)	2 (8)	1 (3)	X2 (df=2) = 4.7922. p= .091071. NS
-XI Digestive system	6 (8)	1 (4)	4 (10)	X2 (df=2) = 0.8885. p= .641293. NS
-XII Diseases of the skin	3 (4)	3 (11)	0	Kruskal-Wallis (df=2): H= 0.51. p = .773. NS
-XIII Musculo-skeletal	9 (13)	3 (11)	9 (23)	X2 (df=2) = 2.4606. p= .292208.

-XIV Genitourinary	12 (17)	3 (11)	4 (10)	X2 (df=2) = 1.083. p= .581866.
TOTAL, chronic diseases*	71 (100)	26 (100)	39 (100)	---

Table 2: Comparison Of Chronic Diseases Of Covid-19 Reinfections In 2020-2022, 2023 And 2024

(): Denotes percentages; NS: Not significant; df= Degree's freedom; *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

Symptoms covid-19 reinfection* According to who, Icd-10 groups	**Reinfections from march 1, 2020 to september 1, 2022 N=38**	**Reinfections from october 1, 2022 to september 30, 2023 N=12**	**Reinfections from october 1, 2023 to september 30, 2024 N=15**	**Statistical Significance**
General (discomfort, asthenia, myalgia, fever, artralgias)	42 (40)	11 (31)	29 (54)	X2 (df=2) = 4.8005. p= .090696. NS
Respiratory (cough, dyspnea, chest pain)	29 (27)	10 (29)	13(24)	X2 (df=2) = 0.2964. p= .862259. NS
ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis)	25 (24)	10 (29)	8 (15)	X2 (df=2) = 2.6883. p= .260767. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	3 (3)	0	1 (2)	Kruskal-Wallis (df=2): H= 1.14. p = .565. NS
Neurological (headache, dizziness, mental confusion -brain fog)	7 (6)	4 (11)	3 (5)	X2 (df=2) = 1.1973. p= .549557. NS
Psychiatric (anxiety, insomnia)	0	0	0	Kruskal-Wallis (df=2): H=0.32. P = .851. NS
Skin (chilblains, flictenas, rash)	0	0	0	Kruskal-Wallis (df=2): H= 0.32. p = .851. NS
Genitourinary	0	0	0	Kruskal-Wallis (df=2): H= 0.32. p = .851. NS
Total, symptoms*	105 (100)	35 (100)	54 (100)	---

Table 3: Comparison Of Covid-19 Reinfection Symptoms In 2020-2022, 2023 And 2024

( ): Denotes percentages; NS: Not significant; df= Degree's freedom; * Patients could have more than one symptom. The percentages are over the total of symptoms

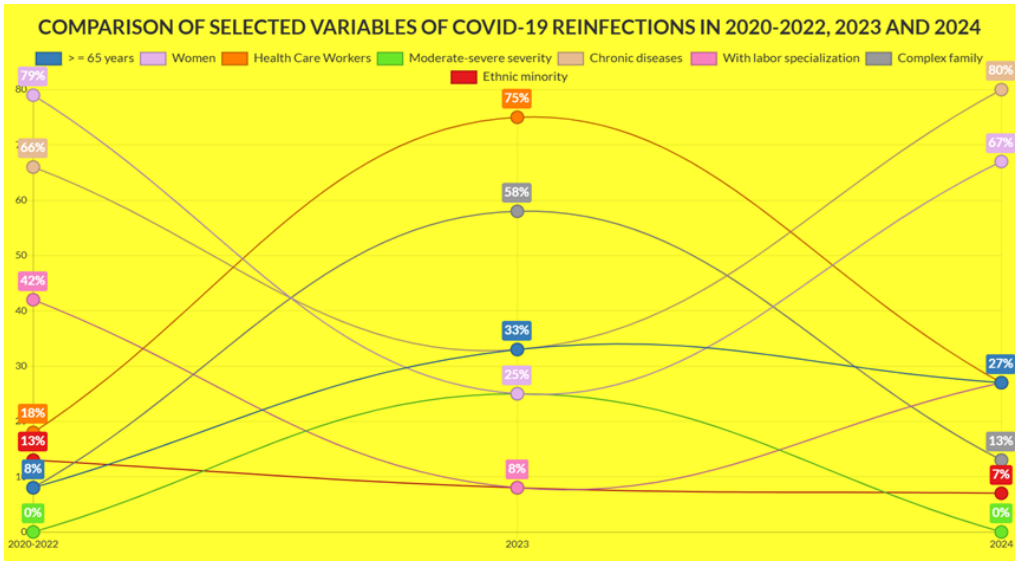

Figure 1: Comparison Of Selected Variables of Covid-19 Reinfections In 2020-2022, 2023 And 2024

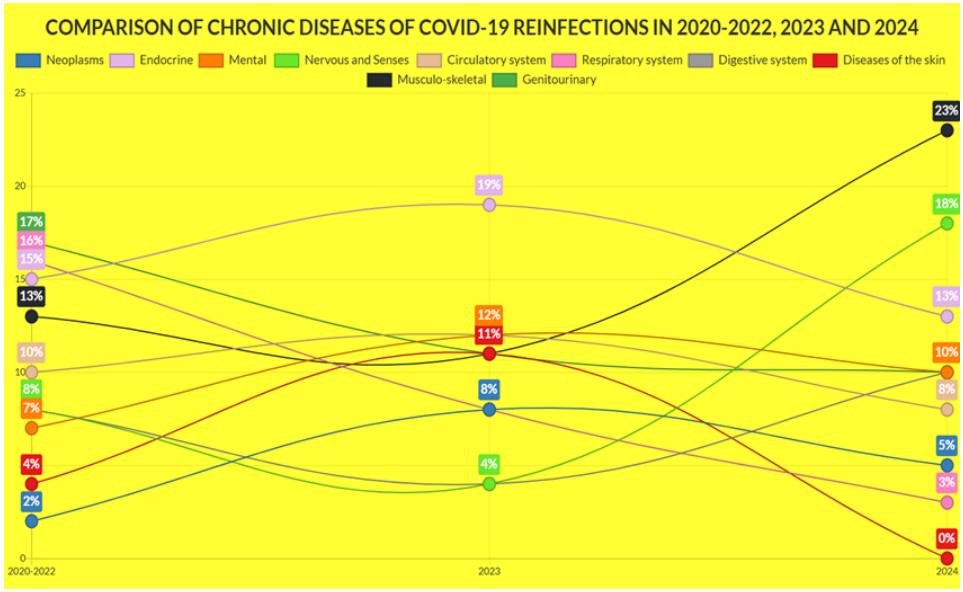

Figure 2: Comparison Of Chronic Diseases Of Covid-19 Reinfections In 2020-2022, 2023 And 2024

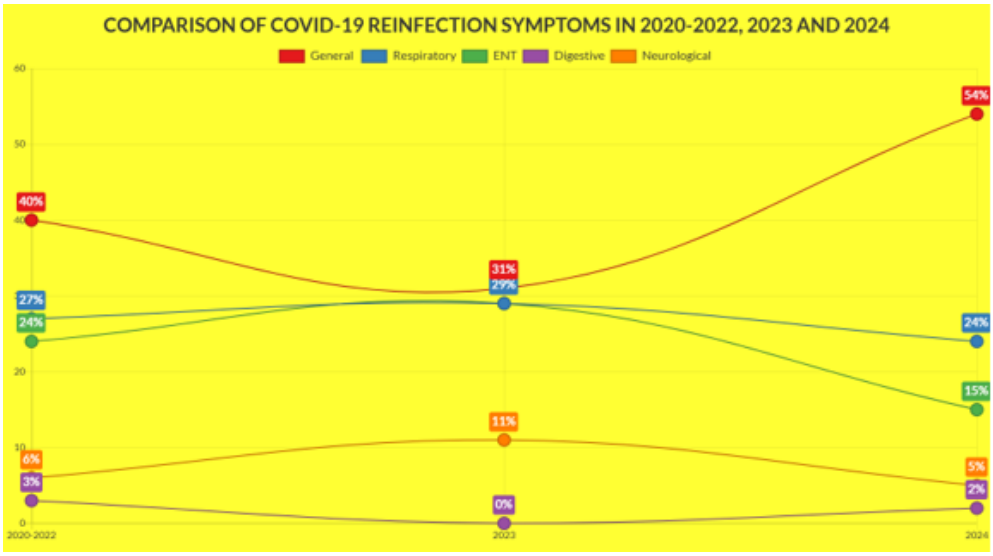

Figure 3: Comparison Of Covid-19 Reinfection Symptoms In 2020-2022, 2023 And 2024

Discussion

1. Main findings

Our main findings were:

1. Covid-19 reinfectons frequently had mild symptoms.

2. They were more frequent in women.

3. Most had chronic diseases, but not the classic comorbidities of the Circulatory system or Respiratory.

4. There is a considerable frequency of reinfections in social-health workers, possibly because they are more exposed and undergo diagnostic testing more frequently.

5. Booster doses can modestly reduce the risk of reinfection.

Three fundamental factors must be taken into account to correctly evaluate our data: the local evolution of SARS-CoV variants, local degree of vaccination, and degree of diagnostic testing when there are symptoms.

a) The predominant variants in Spain during 2023 were those of the XBB family (41-46). 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 (47). 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% (48, 49)

b) On the other hand, in Spain, 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 (50, 51). And 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 (52).

c) In any case, the results must be evaluated with caution. 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 (14). This means that positive cases have been counted with tests carried out in health services and with tests carried out at home and later reported to the GP. Thus, there is probably an underreporting. In addition, it is possible that many of the current infections are occurring with few symptoms or are confusing them with those of other mild conditions (43).

2. Comparison with other studies

Five years after the pandemic began, new SARS-CoV-2 infections continue to occur despite advances in vaccines (53). It has been reported that SARS-CoV-2 reinfections, commonly defined by a positive test ≥90 days after the previous episode, were rare until late 2021, but became common with the arrival of omicron; reinfections are mostly mild and hospitalizations are rare (1, 2, 13, 16). Our results are consistent with those findings, not including any severe or hospitalized cases. However, the frequency of cases with chronic diseases tends to increase in 2024, which is an indicator of risk. Moreover, at the population level, its transmissibility more than compensates for any reduction in disease severity or symptoms experienced by the individual (54).

The SARS-CoV-2 human host in 2023/2024 is different from those in 2020 in their vaccination status. Vaccines have been shown to be effective in reducing the severity of SARS-CoV-2 infection (55-57). While it is true that the efficacy of prior SARS-CoV-2 infection in preventing reinfection varies along the spectrum encompassing alpha, beta, delta, and omicron, it is also necessary to draw attention to the role of mutability in the SARS-CoV-2 variant subtypes responsible for prior infection (58). There is increasing scientific evidence that shows that the protection generated by vaccination decreases over time. In addition, the decrease in immunity as a result of the new variants must be taken into account. Although it is reestablished with the inoculation of booster doses (59, 60), the protection conferred by natural immunity, vaccination, and both against SARS-CoV-2 infection with the omicron variant is unclear (23, 61-62).

Unvaccinated and 1- or 2-dose vaccinated individuals have been reported to be slightly more likely to be reinfected compared with individuals who received a third (booster) vaccine dose, i.e., booster doses may modestly reduce the risk of reinfection (16). Likewise, regimens that included a booster dose, compared with no vaccination, offered protection against symptomatic omicron infection (63). These results are replicated in our study, with 67% of reinfections in 2024 having only 1, 2, or 3 vaccine doses.

A higher likelihood of reinfection has been reported for 2021 among younger adults, women, and HCWs; healthcare occupations are among the highest risk for covid-19 infection, possibly due to increased risk of exposure (64, 65). However, in our study, we cannot exclude the possibility that some of these population groups may also have been subjected to more intensive testing than others (16). Factors associated with the excess risk for reinfection in women need further investigation, but may be due to increased home testing (66-68).

In summary, we know that natural immunity is not sufficient against infection with omicron, and that vaccine immunity is also not sufficient to prevent reinfection, although it appears that booster doses may modestly reduce the risk of reinfection.

Limitations and strengths of the study

1. The samples were small, so some data may cause misinterpretation.

2.-Genetic sequencing was not performed.

3.-It must be taken into account that the results may not be applicable to other vaccination regimens different from those of the study

4. Asymptomatic cases were missing because they did not attend in GP consultation, as no surveillance or systematic screening was done. Thus, the number of reinfections has probably been underestimated

5. 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.

6. The study has the strength of its longitudinality, characteristic of work in general medicine.

Conclusion

In the context of general medicine in Toledo (Spain), from 2020 to 2024, the trend of reinfections shows that they are mild, relatively rare in people over 65 years of age, most frequent in women, with chronic diseases (with a tendency to increase the frequency of Musculoskeletal, Nervous and Senses and Digestive system), with a non-negligible frequency in social-health workers, and without statistically significant differences between symptoms, with general symptoms always predominating and tending to increase, while respiratory and ENT symptoms are in second place in frequency and tending to decrease. Booster doses can modestly reduce the risk of reinfection.

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