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Incidence Rates and Risk Factors of Covid-19 Reinfections from March 1, 2020 to July 1, 2022 in A General Medicine office in Toledo, Spain

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Abstract

Background: The possibility of SARS-CoV-2 reinfection in covid-19 survivors is known, but the rate and associated risk and protective factors remain unclear.

Objectives: 1. Determine incidence rate of covid-19 re-infections in GP consultation; 2. Assess the risk and protective factors to present covid-19 re-infections.

Methodology: An observational, longitudinal and prospective study of Covid-19 re-infections was conducted from March 1, 2020 to July 1, 2022, in a general medicine office in Toledo, Spain.

Results: 43 patients were included. The raw rate of re-infections over the total number of first infections was 10% x 28 months. The only variables with statistical significance as a risk or protective factor for reinfection were: Chronic respiratory disease (RR= 2.11, Moderate risk), and age >= 65 years (RR= 0.28, Protection factor effectively).

Conclusion: In the general practice setting in Toledo, Spain, we found a moderately high rate of reinfection, a higher risk in patients with chronic respiratory diseases, and a lower risk in people >= 65 years. These data are probably influenced by the decrease in natural and vaccine immunity over time, by the appearance of new variants, and by the level of compliance with preventive measures. These findings underscore: 1) the importance of booster vaccination for protection against emerging variants; and 2) reinfection is not only a matter of the immune system, but also of relationships with our environment.

Introduction

It is currently accepted that severe acute respiratory syndrome corona virus (SARS-CoV-2) is a pathogen whose behaviour increasingly resembles that of the rest of the corona viruses that coexist with humans, which cause colds. Most experts believe that it will be normal to be infected several times throughout life, if SARS-CoV-2 does not suffer mutations that change its behaviour [1-4]. It is now evident that covid-19 reinfections increased during the omicron attack [5]. On the other hand, infection with any variant of SARS-CoV-2 is very effective in combating severe covid-19 in reinfection; consequently, substantial evidence for the capabilities of natural immunity is admitted [6].

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However, people infected with the omicron variant show increased poor immunity against future covid-19 infections. This may explain why recurrent infections have been a common feature of the omicron wave of the pandemic, even among people who have received the triple vaccine [7, 8]. As large numbers of people continue to be infected, the efficacy and duration of natural immunity in terms of protection against SARS-CoV-2 reinfections and severe disease is of crucial significance for the future [9]. Data from vaccination studies show vaccination-derived immunity declines over time, although they have demonstrated the short-term efficacy of vaccines with respect to the severity of SARS-CoV-2 infection [10].

At present, the rate, severity of reinfection episodes, and associated risk factors, as well as the presence or extent of decreased natural and vaccine immunity, remain unclear [11,12]. Understanding reinfection rates is crucial to assessing how infections might rise and whether hospitals will be able to cope. Ultimately, studying reinfections will help researchers understand what the transition from SARS-CoV-2 to an endemic virus will look like [5].

In this scenario, this study aims to determine Incidence Rate (IR) of corona virus disease 2019 (covid-19) re-infections in GP consultation, and assess the risk and protective factors to present covid-19 re-infections over time, in the 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

Design and emplacement

An observational, longitudinal and prospective study of Covid-19 re-infections was conducted from March 1, 2020 to July 1, 2022 in a general medicine office in the Santa Maria de Benquerencia Health Center, Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, the general practitioners [GPs] care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP); the dependent neighbourhood of the Health Center has a population of 20,000 inhabitants. 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 [13]. The descriptive results of the case series have already been published [14].

Outcomes of interest

1. Determine incidence rate of covid-19 re-infections in GP consultation. IR was calculated by dividing the number of re-infection events by the primoinfections follow-up time [15]. Likewise, the data on the incidence of covid-19 reinfections were extrapolated to the entire population attended in the consultation and to the community that depended on the health center where the study was carried out [16].

2. Assess the risk and protective factors to present covid-19 re-infections. In this sense, the variables collected were compared by calculating the Relative Risk (RR) as the Incidence among the exposed population / Incidence among the population not exposed to possible risk factors. The RR was interpreted as follows [17]: From 0 to 0.5: Protection factor effectively; from 0.6 to 0.8: true benefits; from 0.9 to 1.1: not significant; from 1.2 to 1.6: weak risk; From 1.7 to 2.5: moderate risk; More than 2.5: Strong risk.

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase Polymerase Chain Reaction (PCR) oropharyngeal swab tests or antigen testing. A symptomatic confirmed case with active infection was considered to be any person with a clinical picture of sudden onset acute respiratory infection of any severity that occurs, among others, with fever, cough or feeling of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain or headache, among others, were also considered symptoms of suspected SARS-CoV-2 infection according to clinical criteria; and a positive PCR or rapid antigen test positive [18]. The onset date of a confirmed case was defined as the date of the first appearance of self-reported clinical symptoms [19]. The onset date for an asymptomatic carrier was defined as the date a positive covid-19 PCR test was obtained [20].

Definition of reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection, to avoid misclassification of prolonged PCR positivity as reinfection if a shorter time interval is used [11,21,22].

Definition of 2 doses of vaccine (fully vaccinated)

That they received 2 doses of vaccine separated by a minimum of 19 days if the first dose was BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech), 21 days in the case of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) or 25 days in the case of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), and that a minimum period of 7 days has elapsed since the last dose if it was with BNT162b2 mRNA vaccine (Comirnaty), or 14 days with ChAdOx1 nCoV-19 vaccine (Vaxzevria) or mRNA-1273 vaccine (Spikevax). People who received a dose of Janssen vaccine (Johnson & Johnson vaccine) more than 14 days ago were also considered fully vaccinated [18].

Definition of booster

As of November 23, 2021 in Castilla La Mancha, the region where the study was carried out, booster doses against covid-19 with messenger RNA (mRNA) vaccines began 6 months after completion the vaccination schedule and after 3 months in case of having received a dose of the Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine). Recruitment was carried out actively by age cohorts in a descending manner, beginning with those over 80 years of age The booster dose was administered with mRNA vaccines (0.3 ml of Comirnaty or 0.25 ml of Spikevax-half the usual dose in primary vaccination) [19].

Definition of cases and controls

Patients with COVID-19 reinfection were considered cases. Control patients were considered unvaccinated people, vaccinated with 2 or 3 doses for COVID-19, from the GP's list of patients, who did not seek medical attention or were diagnosed at another level of the health system with COVID reinfection. -19. Control data were obtained from previous studies in the same consultation, with the same population attended, and carried out by the same researcher [23-26]. In the period from March to April, in Spain, the A lineage of the corona virus predominated, especially the SEC7 and SEC8, and from summer to December, 2020, the 20E (EU1) variant [27,28]. In the period from January

2021 the alpha variant predominated, and from the summer-autumn of 2021 the delta variant [29,30]. In December 2021 there was a rapid expansion of omicron nationwide. In January 2022, omicron was predominant in Spain together with a very significant increase in covid-19 incidence. Since March 2022 there was an expansion of the BA.2 lineage; on those dates the prevalence of the alpha variant was declining [31,32].

Collected variables

Data on the index case and close contacts were extracted from the medical records of the general medicine practice under study. 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" [33], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [34].

-If they were Health Care Workers

-Severity of 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) (20). To simplify comparison, moderate and severe cases were counted together.

Statistic analysis

The bivariate comparisons were performed using the Chi Square test (X2), X2 with Yates correction or Fisher Exact Test when necessary (according to the number the expected cell totals) for percentages, and the Student test for the mean.

Results

From March 1, 2020 to July 1, 2022, 43 patients were included; 2 patients had 2 reinfections (2 women, 17 and 19 years old, with 2 and 1 dose of vaccine, respectively). Non-repeated individuals (N= 43) were used for comparisons in this study. The raw rate of reinfections over the total number of primary infections was: 45/450 covid-19 cases in the consultation during the study period=10.2% x 28 months (from March 2020 to June 30, 2022). For the total population attended in the consultation object of the study, the raw rate of reinfections was: 45/2000=2.25% x 2,000 people x 28 months.

The 43 cases of reinfection were compared with 188 primary covid-19 infections (in non-vaccinated, 1, dose, 2 doses and booster) without reinfection.

The following risk factors for reinfection were found:

Present chronic respiratory disease (RR= 2.11, Moderate risk; $p < .05$); Present severity in primary infection (RR= 1.5: Weak risk; not statistically significant); and present chronic genitourinary diseases (RR= 1.58. Weak risk; not significant statistically).

The following protective factors for reinfection were found:

Age >= 65 years (RR= 0.28, Protection factor effectively; $p < .05$); presence of chronic circulatory diseases (RR= 0.58. Protection factor effectively); chronic diseases of the digestive system (RR= 0.48; Protection factor effectively); neoplasms (RR= 0.59, Protection factor effectively); diseases of the blood (RR= 0, Protection factor effectively), diseases of the nervous and senses (RR= 0.75; True benefits); and muscle-skeletal diseases (RR= 0.87, True benefits), but in all of them without statistical significance **(Table 1, Table2)**.

Table 1: Risk Factors of Covid-19 Reinfection.

Risk Factors	Covid-19 Reinfection N=43	Primary Covid-19 Infections (In Non-Vaccinated, 1, Dose, 2 Doses And Booster) Without Reinfection N=188	Statistical Significance	Relative Risk (RR)
> = 65 years	2 (5)	32 (17)	X2= 4.2662. p= .038878. Significant at p < .05.	RR= 0.28 (CI 95%: 1.09, 0.07). Protection factor effectively
Women	24 (56)	101 (54)	X2= 0.0616. p= .803993. NS	RR= 1.07 (CI 95%: 0.2, 5.61). Not significant
Health Care Workers	7 (2)	31 (16)	X2= 0.0011. p= .973231. NS	RR= 0.99 (CI 95%: 1.1, 0.89). Not significant
Moderate-severe severity of primary infection	3 (pneumoniae) (7)	8 (pneumoniae) (4)	Fisher exact test = 0.4337. NS	RR= 1.5 (CI 95%: 0.16, 13.64). Weak risk
Chronic diseases presence	26 (60)	108 (57)	X2= 0.1309. p= .717517. NS	RR= 1.11 (CI 95%: 0.38, 3.26). Not significant
Vaccinated 1 dose	8 (19)	12 (6)	NR	NR
Vaccinated 2 doses	12 (28)	30 (16)	NR	NR
Vaccinated with booster (3 doses)	15 (35)	46 (25)	NR	NR
not vaccinated	8 (19)	100 (53)	NR	NR

( ): Denotes percentages; NS: Not significant; RL: Not relevant

Table 2: Chronic diseases risk factors in covid-19 reinfection.

Chronic Diseases	Covid-19 Reinfection N=43	Primary Covid-19 Infections (In Non-Vaccinated, 1, Dose, 2 Doses And Booster) Without Reinfection N=188	Statistical Significance	Relative Risk (RR)
-I Infectious	0	0	Fisher exact test= 1. NS	NaN
-II Neoplasms	1 (2)	9 (3)	Fisher exact test= 1. NS	RR= 0.59 (CI 95%: 582.17, 0). Protection factor effectively
-III Diseases of the blood	0	5 (1)	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-IV Endocrine	12 (17)	65 (19)	X2= 0.0857. p= .769699. NS	RR= 0.92 (CI 95%: 3.59, v). Not significant
-V Mental	5 (7)	24 (7)	X2 with Yates correction= 0.0317. p= .858626. NS	RR= 1.03 (CI 95%: 0.75, 1.42). Not significant
-VI-VIII Nervous and Senses	5 (7)	34 (10)	X2= 0.4675. p= .494153. NS	RR= 0.75 (CI 95%: 2.56, 0.22). True benefits
-IX Circulatory system	5 (7)	44 (13)	X2= 1.6895. p= .193668. NS	RR= 0.58 (CI 95%: 1.53, 0.22). Protection factor effectively
-X Respiratory system	11 (16)	23 (7)	X2= 6.5176. p= .010681. Significant at p < .05.	RR= 2.11 (CI 95%: 1.12, 3.98). Moderate risk
-XI Digestive system	4 (6)	43 (12)	X2= 2.5604. p= .109572. NS	RR= 0.48 (CI 95%: 1.35, 0.17). Protection factor effectively
-XII Diseases of the skin	5 (7)	11 (3)	Fisher exact test= 0.1606. NS	RR= 1.94 (CI 95%: 0.69, 5.48). Not significant
-XIII Musculo-skeletal	8 (12)	46 (13)	X2= 0.1598. p= .689306. NS	RR= 0.87 (CI 95%: 3.41, 0.22). True benefits
-XIV Genitourinary	13 (19)	40 (12)	X2= 2.6728. p= .102074. NS	RR= 1.58 (CI 95%: 0.85, 2.94). Weak risk
TOTAL chronic diseases**	69 (100)	344 (100)		---

( ): Denotes percentages; NS: Not significant; NaN: Not a Number (result impossible to calculate)
*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.

Discussion

1. Severity of reinfection

It is unclear whether reinfection increases the risk incurred after the first infection [35]. In general, most studies suggest that the second SARS-CoV-2 infection is milder than the first. In fact, that is what should be expected from an immunological point of view [36-40]. On the other hand, it has been suggested that each new infection can have consequences and that, for example, a second infection is associated with twice the risk of dying from any cause or having heart or lung problems [35,41]. In any case, it must be remembered that although omicron may be somewhat less serious than delta, and people have greater immunity through vaccination [43]. In our study, presenting severity in primary infection was a risk factor for reinfection.

2. Incidence rate of covid-19 reinfections

Our study finds a raw rate of reinfections over the total number of primary infections of 10.2% x 28 months. This figure is within the published values, although there are clear differences before and after 2021, with the appearance of new variants, and this is a fact that also occurs in our context [14]. Until 2021, there was biological, epidemiological and clinical evidence that a previous infection with COVID-19 reduced the risk of reinfection; worldwide, as of January 2021, there had been 31 confirmed cases of covid-19 reinfection [39]. Thus, in the initial periods of the pandemic, data on reinfection rates ranging from 0.02% to 17% have been reported [18, 38,44-54].

On those dates, if among those recovered from covid-19 the risk of reinfection is very rare, in those vaccinated with two doses it is estimated that the probability of becoming infected was 1.5% [55]. Being unvaccinated was associated with a 2.34-fold increased odds of reinfection compared with being fully vaccinated [56]. In this sense, the time factor must be taken into account, both due to the decrease in immunity and due to the new variants. Thus, it has been published that the risk of reinfection by covid-19 is approximately 5% at three months, which increases to 50% after 17 months [57]. If anything, the occurrences of reinfection correlated more positively with the overall regional increase in cases [44]. In other words, reinfection is not only a matter of the immune system, but also of luck in relationships with our environment.

3. Risk and protective factors against reinfection by SARS-CoV-2

We found a statistically significant factor of protection for reinfection: being >= 65 years old, which may be related to better compliance with preventive measures and/or a higher rate of booster vaccination. Older adults are especially vulnerable to covid-19 [11,12,58] and may have a higher perception of susceptibility and severity of covid-19 [59]. The perceived benefit was the most frequently significant predictor of COVID-19-related behaviour [60]. Age has also been reported to significantly influence COVID-19 preventive behaviours [61]. It was showed that the likelihood of severe illness was higher among people with co morbidity and among people aged 40-59 years and 60 years and older, compared with individuals aged 19-24 years [62]. We

found chronic respiratory disease to be a significant risk factor for reinfection. Patients who have underlying lung disease may worsen these conditions by being exposed to covid-19 and are more predisposed to contracting it [63,64].

Natural and vaccine immunity and risk of reinfection

Previous studies showed greater protection in previously infected persons with or without an additional dose of vaccine than in previously uninfected persons who had received two doses of mRNA vaccines [2,65]. While the amount of antibodies decreases over time in both recovered covid-19 patients and vaccinated individuals, the quality of antibody yield increases after infection but not after vaccination. However, these also decreased more steeply in the vaccinated group [66]. It has been reported that after several months, people with hybrid immunity were better protected against reinfection than uninfected people who had previously received two doses of the vaccine [2, 21, 67], but natural infection does not protect against contagion to new variants [68, 69].

In this sense, in our study it seems that not being vaccinated is a protective factor for reinfection. This is an artifact, since reinfections predominate in 2021 and especially 2022, when almost 100% of the population is already vaccinated, while it is compared with primary infections that occur in a period of time with a population that was not yet vaccinated. In other words, as time progresses and the vaccinated population rate approaches 100% (and in Spain as of July 2022 there were 85% vaccinated with 2 doses, 67% with one dose, and 54% with booster, predominantly older people), almost all infections, logically, occur in vaccinated [70].

Limitations and strengths of the study

1. The lineages of the infections were not sequenced. Therefore, it cannot be completely ruled out that the recurrence of a case corresponds to a reactivation of the strain involved in its first episode.
2. The number of cases was relatively small.
3. It may have missed asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done.
4. Preventive behaviours associated with transmission were not analyzed and could have been different during the study periods.
5. The use of databases collected for specific purposes in the primary analysis, other than the secondary analysis, limits the analysis and interpretation of results.
6. All the studies were carried out in the same general medicine practice and carried out by the same researcher, which gives coherence to the results.

Conclusion

The rate of reinfection after a primary infection is moderately high (probably influenced by the decline in natural and vaccine immunity over time, and by the appearance of new variants). There is a higher risk in patients with chronic respiratory diseases, and a lower risk in people >= 65 years, possibly due to better compliance with preventive measures and more booster vaccination. These findings underscore: 1) the importance of booster vaccination for protection against emerging variants; and 2) reinfection is not only a matter of the immune system, but also of luck in relationships with our environment.

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