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What is the Frequency with which Sars-COV-2 Reinfection Occurs in People with Fourth Dose of Vaccines Bivalent mRNA? Incidence Rate of Covid-19 Re-Infection from October 2022 to October 2023 in A General Medicine Office in Toledo (Spain)

Jose Luis Turabian

Specialist in Family and Community Medicine Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain

***Corresponding Author:** Jose Luis Turabian, Specialist in Family and Community Medicine Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain.

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Abstract

Background: *A better understanding of reinfection incidence rate and the immune response to SARS-CoV-2 is needed to inform vaccine planning efforts.*

Objective: *Estimate the incidence rate of covid-19 reinfection in vaccinated 4th dose people in general practitioner care*

Methodology: *A longitudinal study of cases of covid-19 reinfection in people with 4th dose of bivalent mRNA vaccines, from October, 2022 to October, 2023*

Results: *5 cases of covid-19 reinfection in vaccinated people with fourth dose were included. Incidence rate of covid-19 reinfection in total vaccinated people with fourth dose from October 2022 to October 2023 was 0.4%; It was greater in > = 65 vs. < 65 years (0.7% vs. 0.3%) and in women vs. men (0.7% vs. 0.2%). Regarding the incidence rate in general population of the office was 0.2%; being again greater at > = 65 vs. < 65 years (0.6% vs. 0.1%), and in women vs. men (0.4% vs. 0.1%). For vaccinated people with fourth dose, covid-19 reinfection incidence rates were 5 times lower for all people, four times lower for > = 65 years, 3 times lower for < 65 years and for women and 5 times lower for men that primoinfection incidence rate.*

Conclusion: *The incidence rate of reinfections vaccinated people with fourth dose is low (0.4%), but not insignificant in older people and women (0.7%). Reinfection could present challenges to controlling viral transmission within specific vulnerable populations.*

Keywords: COVID-19; SARS-CoV-2; Vaccine Effectiveness; Breakthrough Infection; Population Surveillance/methods; Public Health Practice; General Practice

Introduction

As successive variants of the coronavirus syndrome 2 (SARS-CoV-2) have appeared from the original virus with greater infective capacity, transmissibility, or with the ability to avoid the recognition of antibodies that should protect against infection, has been increasing the risk of reinfection [1]. The Omicron variant is by far the most dangerous strain, with greater transmissibility and immune escape than previous variants that cause the coronavirus disease 2019 (Covid-19), such as Alpha, Beta, Gamma and Delta [2]. These mutations result in a lower protective effect of existing vaccines. Thus, a booster vaccination for the prevention of covid-19 is required to overcome this loss of protection [3-5]. For those who had a previous infection, vaccination often adds greater protection, especially against reinfections that lead to hospitalization [1].

Anecdotal cases of numerous reinfections in the same person have been reported [6]. Although a previous SARS-CoV-2 infection can protect against reinfection for an average of seven months, immunity wanes afterward. Repeated outbreaks of covid-19 are harmful (even if the episodes are mild) because the long-term consequences accumulate with each additional infection [6].

Since September 2022, the bivalent SARS-CoV-2 vaccines from Moderna and Pfizer-BioNTech containing equal amounts of enriched mRNA from the ancestral subvariants BA.4-BA.5 and omicrons replaced their monovalent counterparts as booster doses for people over 12 years old [7-12]. These bivalent mRNA vaccines against Covid-19 trigger a stronger immune response than a fourth dose of the original monovalent vaccine, quadrupling the antibody titer against the BA.4 and BA.5 omicron sub-

variants in people over 55 years of age [13]. But there is a lack of data on how these events translate into significant clinical outcomes at the population level in the sense of preventing any infection [7,13, 14].

It must be added that since the disappearance of the health alarm in many countries, cases of covid-19 are not counted and tests are carried out in health services only in certain situations, such as in people over 60 years, pregnant women, hospitalized patients and health personnel; In this way, people with symptoms in the community, who do not meet these criteria, frequently choose to perform specific tests at home [15-17].

The possibility of reinfection could present challenges to controlling viral transmission within communities or within specific vulnerable populations. A better understanding of reinfection and the immune response to SARS-CoV-2 is also needed to inform vaccine planning efforts [18]. Despite SARS-CoV-2 reinfections have occurred with increasing frequency, and is expected to increase further (as the cumulative incidence of first infections increases, infection- and vaccine-induced immunity declines, and new variants with increased transmissibility), epidemiological trends in reinfections have not been characterized [19-21].

In this scenario, data on the rate of SARS-CoV-2 reinfections in real-world settings are scarce, and the effects of vaccine boosters on the risk of reinfection are unknown [22]. Findings on the likelihood of reinfection will be used to guide future public health surveillance and prevention guidance for covid-19. Additionally, confirmed or suspected SARS-CoV-2 reinfection case detection can inform future research into SARS-CoV-2 host immunity and vaccine development [18]. An accurate estimate of the frequency of SARS-CoV-2 reinfections would be essential to optimize restriction and vaccination policies for the hundreds of millions of previously infected subjects [21, 23].

In this context, we present a longitudinal and prospective study of adult patients with covid-19 reinfection in vaccinated people with fourth dose of bivalent mRNA vaccines, in general medicine from October 1, 2022 to October 1, 2023, to identify covid-19 reinfection incidence rate.

Material and Methods

A longitudinal and prospective study of cases and controls of adult patients with covid-19 reinfections in vaccinated people with fourth dose of vaccines bivalent mRNA, from October 1, 2022 to October 1, 2023, in a general medicine office in 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) was carried out. 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 descriptive data of the case series with covid-19 reinfections in vaccinated people with fourth dose of bivalent mRNA vaccines have already been published [24].

Objective of the Study

Determine the frequency (incidence rate) at which SARS-CoV-2 infection occurs among persons who appear to have recovered clinically from COVID-19 in vaccinated people with fourth dose of vaccines bivalent mRNA in a GP consultation.

Definición De Reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after previous infection [25,26].

Calculation of Incidence Rates

Cumulative incidence rates were calculated at the GP's office by dividing the number of reinfection events during the study period divided by the individuals that could developed the event at start of the study (population at risk) [27]. That is, for people with fourth dose, the incidence rate was calculated by dividing the number of cases of covid-19 reinfections in vaccinated people with fourth dose by the vaccinated people with fourth dose in the follow-up time (from October 1, 2022 to October 1, 2023) [28]. Similarly, the data on the incidence were extrapolated to the entire population attended in the consultation (N=2,000 people) [29].

Calculation of Rate Denominators

The denominators (number of people vaccinated with the 4th dose in the clinic object of the study) were obtained by extrapolating vaccination data at the national level to the population of the clinic and the neighborhood served by the health center [30-24]. 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 [35, 36].

Fourth Booster Dose for Fall-Winter 2022

In the patients included in the study Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccines were used [37, 38]. The vaccination campaign began in Spain on September 26, 2022. The administration of a booster dose against covid-19 was recommended to the population aged 60 and over, to people admitted to nursing homes and other centers with disabilities and those with risk conditions, including social-health personnel [31].

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 [39].

Epidemiological analysis

The calculation of the incidence rates as explained above (subsection “Calculation of incidence rates”) was made by dividing the number of infection events by the person follow-up time (from October, 2022 to October, 2023) (27, 28). Data on the incidence were extrapolated to the entire population attended in the consultation (N=2,000 people) [29]. The classes that classify the age groups were made taking into account > and < de 65 años [40]. The age of 65 years was used as the beginning of old age [41]. Figures with decimals were rounded to facilitate a more intuitive comparison.

Results

5 cases of covid-19 reinfection in vaccinated people with fourth dose were included. Incidence rate of covid-19 reinfection in total vaccinated people with fourth dose from October 2022 to October 2023 was 0.4%; was greater in > = 65 vs. < 65 years (0.7% vs. 0.3%), and in women vs. men (0.7% vs. 0.2%). Regarding the incidence rate in general population of the office was 0.2%; being again greater at > = 65 vs. < 65 years (0.6% vs. 0.1%), and in women vs. men (0.4% vs. 0.1%) (TABLE 1). The comparison of the incidence rates between covid-19 infection and reinfection in revaccinated people with fourth dose showed that the crude rate of reinfection was 5 times lower, four times lower for > = 65 years, 3 times lower for < 65 years, 3 times lower for women, and 5 times lower for men (TABLE 2).

Table 1: Incidence Rates of Covid-19 Re-Infection with 4ª Dose Bivalent Mrna Vaccines in General Medicine (Toledo, Spain) from October 2022 to October 2023.

Variables	Population of the General Medicine Office N=2.000	Population Vaccinated with Fourth Dose at the General Medicine office N=1133	Covid-19 Re-Infections in Vaccinated People With 4th Dose N= 5	Incidence Rates of Covid-19 Re-Infection in Vaccinated People with Fourth Dose	Incidence Rates of Covid-19 R-Infection in Vaccinated People with Fourth Dose in General Population of the Office
= > 14 years	2.000	1.133 (100)	5 (100)	0.4%	0.2%
> = 65 years	480 (24)	455 (95)	3 (60)	0.7%	0.6%
< 65 years	1520 (76)	678 (45)	2 (40)	0.3%	0.1%
Women	1020 (51)	580 (57)	4 (80)	0.7%	0.4%
Men	980 (49)	555 (57)	1 (20)	0.2%	0.1%

(): Denotes Percentages.

Table 2: Incidence Rates of Covid-19 Infection* and Re-Infection With 4ª Dose Vaccines Bivalent Mrna in General Medicine (TOLEDO, SPAIN) from October 2022 TO October 2023

Variables	Incidence Rates of Covid-19 Infection in Vaccinated People with Fourth Dose*	Incidence Rates of Covid-19 Re-Infection in Vaccinated People with Fourth Dose	Incidence Rates of Covid-19 Infection in Vaccinated People with Fourth Dose in General Population of the Office*	Incidence Rates of Covid-19 Re-Infection in Vaccinated People with Fourth Dose in General Population of the Office
TOTAL = > 14 years	2%	0.4%	1%	0.2%
> = 65 years	3%	0.7%	3%	0.6%
< 65 years	1%	0.3%	0.5%	0.1%
Women	2%	0.7%	1%	0.4%
Men	1%	0.2%	1%	0.1%

(): Denotes Percentages; *Taken from Reference 43.

Discussion

1. Main Findings

The main results of our study were:

1. The incidence rate of reinfections vaccinated people with fourth dose is low (0.4%), but not insignificant, and is higher in > = 65 years (0.7%) and women (0.7%).

2. In vaccinated people with fourth dose, the crude rate of reinfections was 5 times lower than primary infections, four times lower for > = 65 years, 3 times lower for < 65 years and women, and 5 times lower for men.

However, these results should be interpreted with caution. It must be taken into account that 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 [16]. And on the other hand, the fourth doses began to be given to older people [31]. This meant in practice that in many cases of symptoms of viral infections in the community no diagnostic tests were carried out, and that those that were carried out were more likely in older patients. Therefore, it can be thought that 1) there were more covid-19 reinfection cases; 2) the cases of covid-19 reinfection in older people are probably closer to reality than the cases in younger people. Furthermore, it should be mentioned that in the study period, the omicron variant was the dominant one in Spain (in the week of November 21 to 27, 2022), the omicron percentage stood at 100%) [31].

2. Comparison with other Studies

Previous exposure to the virus can hypothetically be expected to reduce the risk of reinfection and its severity; However, SARS-

CoV-2 is mutating rapidly and every few months new variants and subvariants replace older ones. Evidence suggests that the risk of reinfection is especially higher with the Omicron variant. Furthermore, any protection against prior infection also decreases with time since the last immunity-conferring event [6].

Although reported rates of reinfection have been consistently low, due to differences in the definition of reinfection, epidemic period, follow-up time, economic, political, cultural and geographic differences, epidemic status, surveillance and level of covid-19 tests and other factors used in different studies, there is great uncertainty about the frequency of reinfection by SARS-CoV-2 [42].

Reinfection is known to occur with other human coronaviruses. A study in Kenya found that between 4% and 21% of people infected with endemic coronaviruses had two or more episodes of infection with the same virus species over a six-month period [18]. In the United States, about 2.7% of all covid-19 cases reported during the Delta variant surge in late 2021 were reinfections. But the problem worsened significantly when Omicron emerged, and its more infectious subvariants became dominant [19].

A Centers for Disease Control and Prevention analysis of laboratory-confirmed adult Covid-19 cases between September 2021 and December 2022 found that reinfection rates increased to 10.3% during the Omicron BA.1 surge; to 12.5% when BA.2 was dominant; to 20.6% during BA.4/BA.5; and 28.8% during BQ.1/BQ.1.1 [21].

The results of a meta-analysis showed that the reinfection rate of SARS-CoV-2 was approximately 0.97%, and the risk of reinfection increased substantially over time, even reaching 3.31% in the first three months during the Omicron wave [21]. Various studies carried out in different countries suggest that reinfection rates can range between 5% and 15% [22]. In a study in Shanghai, China, which included covid-19 patients who were first infected with BA.2 (March 1, 2022 to May 23, 2022) and who were followed for reinfection since June 1, 2022 through January 31, 2023, of 897 primary infections, 148 (16.5%) experienced reinfection. The incidence rate of reinfection was 0.66 cases per 1,000 person-days. Female sex was a risk factor for reinfection. Protection offered by both vaccination and previous infection was poor against SARS-CoV-2 reinfection [43].

But the number of reinfections is likely underestimated because not all people infected with SARS-CoV-2 become sick enough to be tested. Nineteen studies involving a total of 34,375 cases of SARS-CoV-2 reinfection and 5,264,720 cases of primary SARS-CoV-2 infection were included in a meta-analysis. Among cases of SARS-CoV-2 reinfection, 41.77% were asymptomatic [40]. In this sense, a Canadian study estimated that 40% of people who had antibodies in their blood (proof that they had been infected by SARS-CoV-2) had not experienced any symptoms in the previous six months and did not know that had contracted the disease [44].

In our study, the incidence rate of reinfections vaccinated people with fourth dose was low (0.4%), but it was higher in > = 65 years (0.7%) and women (0.7%). Finally, regarding the comparison with primary infections in vaccinated people with fourth dose in the same population treated in that general medicine consultation and during the same time (45), our results indicate that the raw rate of reinfections was 5 times lower than primary infections, four times lower for > = 65 years, 3 times lower for < 65 years and women, and 5 times lower for men.

Study limitations and Strengths

- The sample was small, so some data may cause misinterpretation.
- It was not analyzed the time since the first infection occurred or the time elapsed from the last dose of vaccine administered until re-infection.
- 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, are important epidemiological opportunities to study incidence rates of diseases in small geographical bases.
- Moderna and Pfizer-BioNTech bivalent Covid-19 vaccines were only used, so it may not be appropriate to extrapolate the results to other types of vaccines against Covid-19.

Conclusion

Crude incidence rate of reinfections in vaccinated people with fourth dose is low (0.4%), but not insignificant, and is higher in > = 65 years (0.7%) and women (0.7%). Reinfection could present challenges to controlling viral transmission within communities or within specific vulnerable populations. However, given that the number of tests carried out in the community was low, these results should be interpreted with caution.

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