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Research Article

Reinfections of covid-19 with fourth dose of bivalent mrna vaccine. A case series study in a general medicine office in the period from october 2022 to october 2023

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Abstract

Background
Clinical-epidemiological data on SARS-CoV-2 reinfections in real-world settings are scarce.
target
To describe the clinical-epidemiological characteristics of cases of covid-19 re-infections in vaccinated people with 4th dose of bivalent mRNA vaccines.
Methodology
An observational, longitudinal and prospective case series study of adult patients with covid-19 re-infections in vaccinated people with 4th dose in general medicine from October 1, 2022 to October 1, 2023. The descriptive epidemiological analysis considered a set of selected demographic and clinical features.
Results
5 people with fourth dose and with covid-19 re-infections from October 2022 to October 2023 were included. The average age was 67.8 years. 3 (60%) were >= 65 years; 4 (80%) were women; 2 (40%) were social-health care workers; 1 (20%) presented problems in the family context; 1 (20%) presented moderate-severe severity of re-infection; The 5 cases (100%) had chronic diseases, which predominated in Endocrine group (25%). Regarding symptoms, the General (41%) and ENT (18%) groups predominated.
Conclusion
In our series from October 2022 October 2023, in the context of a general medicine consultation in Toledo (Spain), covid-19 re-infections in vaccinated people with 4th dose was rare but not insignificant (during Omicron variant prevalence), and they showed the following profile: milds, with general and NCD symptoms predominating, with few psychosocial risk factors, and they predominated in women, the elderly, and socio-health care workers, with chronic diseases, especially endocrine diseases.

Keywords: covid-19; sars-cov-2; reinfection; epidemiological characteristic; symptoms; case series

Introduction

There have been more than 772 million cases and 6.9 million deaths in the coronavirus disease 2019 (Covid-19) pandemic as of December 17, 2023, and the disease is now becoming an endemic respiratory infection [1]. Although reinfections due to coronavirus syndrome 2 (SARS-CoV-2) have occurred with increasing frequency over time, their clinical-epidemiological trends have not been characterized [2].

Reinfection with the virus that causes covid-19 occurs when you become infected, recover, and become infected again. A person can be reinfected several times. Reinfections are often mild, but there may be cases of severe disease. If you become reinfected, you can also spread the virus to other people. After having covid-19, the immune system responds in several ways. This immune response can protect you against reinfection for several months, but this protection wanes over time. People with weakened immune systems who get an infection may have a limited or no immune response [3].

As the virus evolves, new variants may emerge with the ability to evade a person's existing immunity. This could increase the risk of reinfection. For those who had a previous infection, vaccination often adds greater protection, especially against reinfections that lead to hospitalization (3). Thus, the number of reinfections is expected to increase as the cumulative incidence of first infections increases, immunity induced by infections and vaccines decreases, and new variants with greater transmissibility and immune escape characteristics emerge [4]. Furthermore, the risk of reinfection may also vary individually based on demographic characteristics,

vaccination history, and exposure risk, which are known to be interrelated [5-6].

Since September 2022, Moderna and Pfizer-BioNTech bivalent SARS-CoV-2 vaccines containing equal amounts of spiked mRNA from the ancestral and BA.4-BA.5 omicron subvariants replaced their monovalent counterparts as booster doses for people over 12 years old. It is strongly suggested that a bivalent booster may preserve the safety and serological efficacy of the original monovalent booster while broadening the spectrum of antibody response, helping to restore protection that might have diminished since the last previous dose [7-11]. But people can become infected with covid-19 for the second or third time despite having acquired natural antibodies after suffering from the disease for the first time and having received vaccines and boosters [12].

It can be thought that patients who are reinfected with covid-19 despite having received the fourth dose of the covid-19 vaccine constitute a population group with differential risk characteristics that make them more exposed to developing the infection. Therefore, describing these characteristics can be useful to learn to know your risk factors and use this data to better understand reinfections and be able to act on them, as well as extrapolate these measures to the entire community. However, data on the clinical-epidemiological factors of SARS-CoV-2 reinfections in real-world settings are scarce, and the effects of vaccine boosters on the risk of reinfection are unknown [13].

Furthermore, it must be taken into account that just as very detailed epidemiological surveillance was carried out during the pandemic period, now in the endemic phase many of the community surveillance studies that tract infection levels have ended [14-15].

In this context, we present an observational, longitudinal and prospective case series study of adult patients with covid-19 re-infections in general medicine from October 1, 2022 to October 1, 2023, with the objective of knowing their clinical-epidemiological characteristics.

Material And Methods

Design and emplacement

An observational, longitudinal and prospective study of **c**ovid-19 re-infections in vaccinated people with second vaccine booster (4th dose) was conducted 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). 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 [16].

Outcome of interest

To know and describe a set of selected clinical-epidemiological characteristics of cases of covid-19 re-infection in vaccinated people with 4th dose of bivalent mRNA vaccines, in the endemic period for one year (from October 1, 2022 to October 1, 2023) at primary health care level.

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [17] performed in health services or at home.

Definición de re-infection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection [18-19].

Booster dose for autumn-winter 2022-2023

On August 31, 2022, the Food and Drug Administration (FDA) authorized the bivalent covid-19 vaccines from Moderna and Pfizer-BioNTech, each with equal amounts of mRNA encoding the spike protein of the ancestral strain and the spike protein of BA.4 and BA.5 strains of the B.1.1.529 (omicron) variant, for emergency use as a single booster dose at least 2 months after the primary or booster vaccination. Since September 1, these two bivalent mRNA vaccines have replaced their monovalent counterparts as booster doses for people 12 years and older in the United States and other countries. In the patients included in the study, both were used as a booster dose (4th dose) [20- 21]. In Spain, this vaccination began on September 26, 2022. It was recommended for the population aged 60 and over, people in nursing homes and other disability centers and those with risk conditions and health care personnel. But, people under 60 years of age without risk factors requiring it could also be vaccinated [22].

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") [23] and symptoms, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [24]

-If they were Social-Health Care Workers

-Problems in the family context and low-income household based on the genogram and in the experience of the GP for their continuity of care and knowledge of the family (genogram is a schematic model of the structure and processes of a family, which included the family structure, life cycle and family relational patterns. It was understood that "complex" genograms present families with psychosocial problems) [25-26]

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [27]

-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.) [28]; to simplify comparison, moderate and severe cases were counted together;

-Date of covid-19 infection diagnosis

-Vaccination status with fourth dose (second booster) for fall-winter 2022 against covid-19 at the date of acute re-infection [29]

Epidemiological analysis

As much as possible, excessive fragmentation of the data was avoided to avoid low numbers of classes to be compared. The age of 65 years was used as the beginning of old age [30]. Figures with decimals were rounded to whole numbers to facilitate a more intuitive comparison.

Ethical issues

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

Results

5 people with fourth dose and with covid-19 re-infections from October 2022 to October 2023 were included. The age (mean and standard deviation) was 67.8 +-8.7 years. 3 (60%) were >= 65 years; 4 (80%) were women; 2 (40%) were social-health care workers; 1 (20%) had a complex family/problems in the family context; 1 (20%) presented moderate-severe severity of re-infection; The 5 cases (100%) had chronic diseases (TABLE 1),

VARIABLES	PEOPLE WITH FOURTH DOSE AND WITH COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023 N=5
Age (mean and standard deviation) (range)	67.8 +-8.7 years (57-77 years)
> = 65 years	3 (60)
= < 45 years	0
Women [ages of each case]	4 [77 years, 68 years, 59 years, 78 years] (80)
Socio-Health Care Workers [type of job]	2 [pharmaceutical, hospital administrative] (40)
Complex family/ Problems in the family context [type of problem]	1 [relationship problems] (20)
Low income household	0
Ethnic minority	0
Moderate-severe severity	1 [hypoxia] (20)
Chronic diseases	5 (100)

Table 1

Reinfections Of Covid-19 With Fourth Dose Of Bivalent Mrna Vaccines

( ): Denotes percentages which predominated in the Endocrine (25%), Genitourinary (19%), Neoplasms (13%) and Musculoskeletal (13%) groups (TABLE 2) .

CHRONIC DISEASES* (classified according to the ICD-10 Version: 2019)	PEOPLE WITH FOURTH DOSE AND WITH COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023 [type of chronic disease] N=5
-II Neoplasms	2 [glioma multiforme, bladder neoplasia] (13)
-III Diseases of the blood	0
-IV Endocrine	4 [altered basal glycemia, dyslipidemia, hypothyroidism] (25)
-V Mental	1 [anxiety] (6)
-VI-VIII Nervous and Senses	1 [migraine] (6)
-IX Circulatory system	1 [arterial hypertension] (6)
-X Respiratory system	0
-XI Digestive system	1 [ulcerative dyspepsia] (6)
-XII Diseases of the skin	1 [hyperhidrosis] (6)
-XIII Musculo-skeletal	2 [herniated disc, hallux valgus] (13)
-XIV Genitourinary	3 [microhematuria of glomerular origin, renal lithiasis, polypoid cystitis] (19)
TOTAL, chronic diseases**	16 (100)

Table 2

chronic diseases in re-infecciones with fourth dose of bivalent mrna vaccines ( ): Denotes percentages; *Patients could have more than one chronic disease; the percentages of chronic diseases are over the total of chronic diseases Regarding symptoms, the General (41%) and ENT (18%) groups predominated (TABLE 3).

SYMPTOMS COVID-19 RE-INFECTION* ACCORDING TO WHO, ICD-10 GROUPS	PEOPLE WITH FOURTH DOSE AND WITH COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023 [type of symptom] N=5
General	7 [discomfort, asthenia, myalgia, fever, arthralgia] (41)
Respiratory	5 [cough] (29)

ENT	3 [odinofagia, pharyngeal dryness-mucus] (18)
Digestive	0
Neurological	2 [dysarthria, disorientation] (12)
Psychiatric	0
Skin	0
Total, symptoms*	17 (100)

Table 3

Symptoms In Re-Infecciones with Fourth Dose of Bivalent Mrna Vaccines

(): Denotes percentages; * Patients could have more than one symptom; the percentages are over the total of symptoms

Discussion

1. Main findings

The main results of our case series study of re-infections from October 1, 2022 to October 1, 2023, were the following: there were few cases, but not a negligible number, most were mild with general symptoms and NCDs, and they occurred in older people , women, and with chronic diseases, mainly endocrine, and frequently in social-health workers. Therefore, although mild, as they occur in people at increased risk for serious individual outcomes or for transmission to patients, covid re-infections are not negligible.

The predominant variants in Spain during 2023 were those of the XBB family. The XBB.1.5 lineage became dominant globally in February 2023 and in March in Spain. The "Eris" variant (EG.5), a descendant of the omicron, also of the XBB family, had spread rapidly since the end of July 2023 throughout the United States, Europe (including Spain) and Asia [31-34].

On the other hand, 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 people, pregnant women, and social health personnel and severe cases (15), And 4th dose began to be administered in Spain to older people and social-health workers [35]. In Spain, 60% of the population over 80 years of age has received the vaccine adapted against the subvariants of Covid-19 in the October 2022 and October 2023 season, according to data from the Ministry of Health [36].

These facts may mean that:

1) Not all patients with symptoms of viral infections in the community were probably tested given the limitation of testing in health services (and cases would be missed; and consequently, the real number of re-infections will be higher); and those who were tested could be more likely older patients and health care workers (who will be overrepresented in the case series). Additionally, the number of reinfections is likely underestimated because not all people infected with SARS-CoV-2 become sick enough to undergo testing. Since reinfection usually results in somewhat milder symptoms, it is even more difficult to fully assess the true count [37].

2) Taking into account that the number of reinfections has been described as significantly more frequent when Omicron emerged and its more infectious subvariants became dominant (2), our results should not be directly compared with other time periods or from places where Omicron was not predominant during the covid-19 pandemic.

3) Social health workers and older people were the first in Spain to receive the fourth dose, starting on September 26, 2022 (9, 35), so at the end of data collection of our study (on October 1, 2023), were these people in whom the longest follow-up time was carried out, and in whom their immune levels presumably had the longest time to decrease.

For reinfection to occur, there are three key elements, according to the studies published to date: the time since the first infection occurred, the variant that was involved, and the time elapsed since the last dose of vaccine administered. Neutralizing antibodies (IgM and IgG) are a first line of defense against the virus; They prevent infection by blocking the tips of the coronavirus. They occur after vaccination or after an infection is overcome. But they are specific to each variant. It has been suggested that they persist after recovery from infection for perhaps three to seven months; but it depends on each person [32, 38].

2. Comparison with other studies

Repeat infections with viruses such as SARS-CoV-2, which infect mucosal surfaces without a viremic phase, should be anticipated, typically resulting in relatively short-lived antibody responses. Reinfection had been rare until late 2021 and there is evidence that reinfections have become more common with the arrival of the Omicron variant (13). Immunity, both the natural one that develops after the disease has passed and that from the vaccine, is limited in time, since viruses mutate frequently (36).

Although SARS-CoV-2 reinfections have occurred with increasing frequency, their epidemiological trends, associated outcomes, and clinical impact have not been fully characterized or understood (2, 13). In a meta-analysis that included nineteen studies involving a total of 34,375 cases of SARS-CoV-2 reinfection, 42% were asymptomatic, only 0.6% manifested as severe disease, and 0.04% manifested as critical disease (37). 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 were unaware that they had contracted the disease [39]; however, in some studies, reinfections were associated with serious outcomes, particularly among people who were hospitalized with a previous infection (2). Vaccination status, viral load, underlying medical conditions (such as cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and obesity, as well as immunosuppression and autoimmune diseases) influence in severity [40-41]. In our series, most cases were mild, but 100% had chronic diseases, predominantly from the Endocrine system. This is a high-risk population, and that makes us cautious about the future evolution of covid-19 re-infection symptoms.

The risk of reinfection may also vary individually in relation to the risk of exposure, which are known to be interrelated (5, 6). In this sense, it has been reported that SARS-CoV-2 reinfections were frequent during the period of Omicron transmission in healthcare workers [42]. We also found in our series a very high frequency (40%) of reinfections in social-health workers.

In summary, our results expand the evidence base that reinfection is rare but not insignificant in people with the fourth dose of vaccine received, and this reinfection is generally mild, but affects people with risk factors, exposure and transmission of virus (social health care workers); the combination of natural immunity from previous infection and vaccine-induced immunity does not eliminate the risk of reinfection. The totality of evidence suggests that strategies to prevent reinfection could benefit people regardless of prior infection history and vaccination status (38).

Limitations and strengths of the study

1. The case series was small, so some data may cause misinterpretation.

2. 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.

3. The cases treated by the GP may not be all existing cases, but given the situation of the GP as the gateway to the health system, the vast majority is likely to be present, and especially those with moderate-severe symptoms.

4. Asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done, may have been missed.

5. Case series studies are studies of "numerators" only. No control group or controlled assignments of patients is involved.

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

Conclusion

In our series from October 2022 October 2023, in the context of a general medicine consultation in Toledo (Spain), covid-19 re-infections in vaccinated people with 4th dose were rare, and showed the following profile: mild, with general symptoms and NCDs, with few psychosocial risk factors, and predominated in women, the elderly and socio-health care workers, with chronic diseases, especially endocrine diseases. Given the likelihood that SARS-CoV-2 will continue to mutate and may remain a threat for years, leading to the emergence of variants or subvariants that could be more immunoevasive, and given that reinfections contributes to a non-trivial health risk, it is reasonable to maintain covid-19 booster vaccination strategies to minimize these risks.

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