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Reinfections of COVID-19 with and Without Fourth Dose of Bivalent mRNA Vaccine in the Period from October 2022 to October 2023 in a General Medicine Office in Toledo (Spain)

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ABSTRACT

Background: Clinical-epidemiological differences between cases of covid-19 reinfections in people vaccinated with the 4th dose of bivalent mRNA versus cases of covid-19 reinfections in people not vaccinated with the 4th dose of bivalent mRNA are unknown.

Objective: Compare the cases of covid-19 reinfections in people vaccinated with the 4th dose with bivalent mRNA vaccines versus cases of covid-19 reinfection in people not vaccinated with the 4th dose.

Methodology: An observational, longitudinal and prospective case series study of adult patients with covid-19 reinfections in general medicine from October 1, 2022 to October 1, 2023.

Results: 12 covid-19 reinfections were included in the period from October 2022 to October 2023. Of them, 5 were in people with fourth vaccine dose of bivalent mRNA and 7 in people without fourth vaccine dose of bivalent mRNA. There were no statistically significant differences by sex, age, psychosocial factors, severity of infection, symptoms, or in the comparison of chronic diseases by groups. A statistically significant difference was only found in the total presence of chronic diseases: 100% in covid-19 reinfections with fourth vaccine dose of bivalent mRNA versus 29% in covid-19 reinfections without fourth vaccine dose of bivalent mRNA.

Conclusion: In the context of general medicine in Toledo (Spain), reinfections are rare, but the presence of chronic diseases represents a significant risk factor for covid-19 reinfections even if these people have fourth vaccine dose of bivalent mRNA. However, number of reinfections was possibly underestimated. The results should be taken with caution due to the small number of covid-19 cases included.

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Introduction

More than four years after the start of the coronavirus disease 2019 (covid-19) pandemic, it is important to recognize that the arrival of vaccines has dramatically changed the natural course of covid-19 infection. However, the nature and durability of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain unclear [1,2]. Covid-19 is now an endemic viral infection that will remain with us throughout generations, and there is also a high level of population hybrid immunity [3-5].

Reinfection due to SARS-CoV-2 occurs when a person becomes infected, recovers, and becomes infected again. A person can be reinfected several times. Reinfections are often mild, but there may be cases of severe disease. Reports of possible covid-19

reinfections after initial recovery have increased over time, especially during the Ómicron waves [6-8].

The emergence of immune escape variants of SARS-CoV-2 justifies the use of sequence-adapted vaccines to provide protection against covid-19 [9]. Given the ability to use mRNA technology to rapidly respond to variant strains, bivalent vaccines were created to counter this new threat. In January and February 2022, Pfizer-BioNTech produced a bivalent vaccine containing 15 µg of mRNA directed against the ancestral strain of SARS-CoV-2 and 15 µg directed against BA.1. Moderna used 25 µg of mRNA directed against each of the same two strains. They were later adapted against BA.4 and BA.5 [10].

As of September 1, 2022, these two bivalent mRNA vaccines replaced their monovalent counterparts as booster doses for people 12 years and older in the United States and other countries [11,12].

But questions remain about the level of protection they confer when applied as reinforcement and their effectiveness will be resolved in real life [12,13,14-19].

In this scenario, epidemiological surveillance must be reinforced and new immunity studies promoted in the entire population to evaluate the impact of the bivalent vaccine against Covid-19 on public health [20,21]. We present a study to try to clarify the differences between cases of covid-19 reinfection in vaccinated 4th dose with bivalent mRNA vaccines of the Comirnaty and Spikevax vaccines versus cases of covid-19 reinfection in not vaccinated 4th dose in a general medicine outpatient clinic.

Material and Methods

An observational, longitudinal and prospective study of covid-19 reinfections in vaccinated people with 4th dose vaccine 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. The study methodology has already been published [22,23]. Some aspects of its methodology are repeated here to facilitate the understanding of the present study.

Objectives of The Study

To compare the cases of covid-19 reinfections in vaccinated people with 4th dose de covid-19 vaccine versus without 4th dose de covid-19 vaccine.

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).

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 [24-27].

Definition of Reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection [28-30].

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 [31].

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” and symptoms covid-19 infection, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [32,33].
- Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [34,35].
- If they were 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) [36-39].
- Ethnic minority (defined as a “human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group”) [40].
- 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 $\leq 93\%$ with room air at rest, arterial partial pressure of oxygen / oxygen concentration ≤ 300 mmHg.); to simplify comparison, moderate and severe cases were counted together [41].

Sample Size

All patients who met the criteria for covid-19 reinfection from October 1, 2022 to October 1, 2023 and who were treated in the general medicine consultation object of the study, were included.

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.

Results

12 covid-19 reinfections were included in the period from October 2022 to October 2023. Of them, 5 were in people with fourth vaccine dose of bivalent mRNA and 7 in people without fourth vaccine dose of bivalent mRNA. There were no statistically significant differences between cases of covid-19 reinfections between people with and without fourth vaccine dose of bivalent mRNA by sex, age, psychosocial factors, severity of infection, or symptoms, nor in the comparison of chronic diseases by groups. A statistically significant difference was only found in the total presence of chronic diseases: 100% in covid-19 reinfections with fourth vaccine dose of bivalent mRNA versus 29% in covid-19 reinfections without fourth vaccine dose of bivalent mRNA (Table 1, Table 2, Table 3).

Table 1: Comparison of Variables Between Covid-19 Reinfections in Vaccinated People With 4th Dose and COVID-19 Reinfections in People Without 4th Dose in The Period from October 2022 To October 2023

VARIABLES	COVID-19 REINFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 REINFECTIONS IN PEOPLE WITHOUT 4TH DOSE N= 7	STATISTICAL SIGNIFICANCE
> = 65 years	3 (60)	1 (14)	Fisher exact test= 0.2222. NS
= < 45 years	0	3 (43)	Fisher exact test= 0.2045. NS
Women	4 (80)	5 (71)	Fisher exact test= 1. NS
Social-occupancy class of patients (people with some type of labor specialization)	0	3 (43)	Fisher exact test= 0.2045. NS
Socio-Health Care Workers	2 (40)	2 (29)	Fisher exact test= 1. NS
Moderate-severe severity of infection	1 (20)	0	Fisher exact test= 0.4167. NS
Chronic diseases	5 (100)	2 (29)	Fisher exact test= 0.0278. Significant at p < .05.
Complex family/ Problems in the family context	1 (20)	0	Fisher exact test= 0.4167. NS
Low income household	0	0	Fisher exact test= 1. NS
Ethnic minority	0	0	Fisher exact test= 1. NS

(): Denotes percentages; NS: Not significant

Table 2: Comparison of Symptoms Between Covid-19 Re-Infections in Vaccinated People with 4th Dose and COVID-19 Re-Infections in People without 4th Dose in the Period from October 2022 To October 2023

SYMPTOMS COVID-19 INFECTION* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 REINFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 RE-INFECTIONS IN PEOPLE WITHOUT 4TH DOSE N= 7	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, artralgiás)	7 (41)	5 (28)	X2=0.6966. P= .403917. NS
Respiratory (cough, dyspnea, chest pain)	5 (29)	5 (28)	X2 with Yates correction= 0.0715. p= .789184. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis, ear pain)	3 (18)	7 (39)	X2 with Yates correction is 1.0323. p= .309626. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	0	0	Fisher exact test= 1. NS
Neurological (headache, disartria, desorientación)	2 (12)	1 (5)	X2 with Yates correction= .0323. p= .309626. NS
Psychiatric (Anxiety, insomnia)	0	0	Fisher exact test= 1. NS
Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Urológico (disuria, polaquiuria)	0	0	Fisher exact test= 1. NS
Total symptoms*	17 (100)	18 (100)	---

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

Table 3: Comparison of Chronic Diseases Between COVID-19 Infections in Vaccinated People With 4th Dose and COVID-19 Infections in People Without 4th Dose in The Period from October 2022 To October 2023

CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 REINFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4TH DOSE N= 7	STATISTICAL SIGNIFICANCE
-II Neoplasms	2 (13)	0	Fisher exact test= 0.5077. NS
-III Diseases of the blood	0	0	Fisher exact test= 1. NS
-IV Endocrine	4 (25)	1 (10)	Fisher exact test statistic= 0.6169. NS
-V Mental	1 (6)	2 (20)	Fisher exact test= 0.5385. NS
-VI-VIII Nervous and Senses	1(6)	0	Fisher exact test= 1. NS
-IX Circulatory system	1 (6)	2 (20)	Fisher exact test= 0.5385. NS
-X Respiratory system	0	2 (20)	Fisher exact test= 0.4839. NS
-XI Digestive system	1 (6)	0	Fisher exact test= 1. NS
-XII Diseases of the skin	1 (6)	2 (20)	Fisher exact test= 0.5385. NS
-XIII Musculo-skeletal	2 (13)	1 (10)	Fisher exact test= 1. NS
-XIV Genitourinary	3 (19)	0	Fisher exact test= 0.2615. NS
TOTAL chronic diseases*	16 (100)	10 (100)	---

(): Denotes percentages; NS: Not significant; *Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases

Discussion

Main Findings

Our main results were:

1. Reinfections are rare.
2. The cases of covid-19 reinfections in vaccinated people with 4th dose vs. without 4th dose they had more chronic diseases. And there were no statistically significant differences by sex, age, psychosocial factors, severity of infection, or symptoms, or in the comparison of chronic diseases by groups.

The predominance of chronic diseases in cases of covid-19 reinfections in vaccinated people with 4th dose is logical when prioritizing vaccination in this population [42]. One fact to keep in mind is that in the current phase many of the community surveillance studies tracking infection levels have been completed [43]. 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, health workers and serious cases, as well as elimination of contact tracing [44]. In this situation, covid-19 testing has increasingly shifted towards a home model. With so few home testing results reported, it is difficult to estimate the true magnitude of the current situation. However, because in some countries, such as Spain, GP are the gateway for all patients to the system, and each person is assigned a GP, based on a geographical population, the data of covid-19 cases at the GP consultation level (with tests done at home or in health services) would be an acceptable indicator [45-47]. However, it must be taken into account that despite what has been said, in practice probably a certain number of cases of symptoms of viral infections in the community did not perform diagnostic tests, and that those that were performed were more likely in patients at risk. Another fact to take into account to contextualize our results is that since January 2022 omicron was the variant predominated in Spain. In November 2022 the percentage of omicron was of 100% [48-51].

Comparison with Other Studies

In many Western countries almost 100% of the population has had contact with SARS-CoV-2. However, with time since the last vaccination or since the last infection, the immune response decreases. Thus, in the comorbid and the immunosuppressed patients, 6 months after vaccination, there are no detectable antibody levels or they are only low [52]. Durability of immunity is complex, and risk of reinfection may vary individually based on demographic, temporal characteristics, disease history, vaccination history, and exposure risk, which are known to be interrelated [53-56]. That is, the risk for infection and reinfection by covid-19 involves intrinsic factors such as the susceptibility of the host and the virulence of the causal agent, as well as extrinsic factors including immunizations and treatments which modify the natural history of the disease [57].

Various studies found that the probability of reinfection is higher for people with pre-existing chronic diseases [6,58,59]. Those people diagnosed with high blood pressure, diabetes, cardiovascular diseases, chronic lung diseases (Asthma, COPD...) and cancer, as well as those over 60 years of age, are considered vulnerable groups [60]. But it is not clear if these comorbidities are risk factors for acquiring infection or reinfection, or even if their effect is through other intermediate mechanisms. People who are vulnerable groups for severe covid-19, less frequently than other groups could express the infection asymptotically, and thus be overrepresented with respect to their risk factors for the infection.

In summary, our results are in line with the aforementioned studies, showing as risk factor for covid-19 reinfections in people with fourth dose the presence chronic diseases.

Study Limitations and Strengths

1. The number of cases was small and did not get adequate power; so the statistical significance of some variables could be hidden.
2. Non-randomized design is a limitation for the generalization of the results, although by including all cases that were consulted with the GP, the vast majority of cases were probably included.

3. May have been overlooked asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done.
4. Our prospective study based on continued GP care allowed a long follow-up time.

Conclusion

In the context of general medicine in Toledo (Spain), reinfections are rare, but the presence of chronic diseases represents a significant risk factor for covid-19 reinfections even if these people have fourth vaccine dose of bivalent mRNA. This means that patients with chronic diseases are a vulnerable group for covid-19 reinfections. However, number of reinfections was possibly underestimated. Furthermore, our results should be taken with caution due to the small number of covid-19 cases included.

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