

What are the risk factors of covid-19 reinfection in people with 4th dose of bivalent mrna vaccines? A study in general medicine from october 2022 to october 2023

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Abstract

Background

Risk factors of covid-19 reinfection in people vaccinated with the 4th dose of mRNA covid-19 vaccine remain the subject of debate.

Objective

To identify risk and protective factors of covid-19 reinfection in vaccinated people with 4th dose of bivalent mRNA vaccines.

Location

A general practitioner office in Toledo (Spain).

Methodology

A longitudinal and prospective study of cases and controls of adult patients with or without covid-19 reinfections in vaccinated people with 4th dose of bivalent mRNA vaccines, from October 1, 2022 to October 1, 2023.

Results

5 people with fourth dose and covid-19 re-infections and 1133 people with fourth dose without covid-19 re-infections were included. The following were risk factors: Women, > = 65 years, Social Health Care Worker, Complex family, and Chronic diseases of Neoplasms, Skin, Genitourinary and Endocrine. And protective factors: Low-income household, Ethnic minority, Chronic Diseases of the blood, Circulatory, Respiratory, Digestive, Mental, Nervous and Senses, and Musculoskeletal. The only statistically significant factor was to be Social Health Care Workers.

Conclusion

Covid-19 reinfections in people with fourth dose were uncommon. The risk factors, in part, are those acknowledged for covid-19 infection, for suggesting immunosuppression, and greater risk of exposure: social-health care workers, women, > = 65 years of age. But psychosocial factors and chronic diseases showed mixed patterns. However, number of reinfections was possibly underestimated and some population groups were evaluated more intensively. It is suggested that these differences in risk and protection in these variables should be studied in greater depth

Keywords: COVID-19; SARS-CoV-2; Reinfection; Risk factors; Vaccine Effectiveness; Breakthrough Infection; bivalent mRNA vaccines; General Practice

Introduction

Reinfection due to coronavirus syndrome 2 (SARS-CoV-2) that causes coronavirus disease 2019 (Covid-19) 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. When a person is reinfected, they can also transmit the virus to other people. As the virus evolves, new variants may emerge with the ability to

evade a person's existing immunity (1). Reports of possible covid-19 reinfections after initial recovery have increased over time (2, 3), especially during the Ómicron waves BA.1, BA.2, BA.4 /BA.5 and BQ.1/BQ.1.1 (4).

The immune system responds quickly to infectious processes, and SARS-CoV-2 infection is no exception. Studies from early 2021 initially suggested that natural immunity could protect against reinfection for at least 8 to 12

months (5, 6). However, real-world cases have contradicted this, reporting that reinfection occurs within 3 to 6 months (7, 8). Furthermore, the understanding of sustainable and long-lasting protective immunity after covid-19 infection remains uncertain and the underlying mechanisms are not yet fully understood (2, 9, 10).

Vaccination against SARS-CoV-2 has shown promise in reducing infection rates, but there is still ambiguity regarding cases of reinfection among fully vaccinated people. The mRNA-based vaccines developed by Pfizer-BioNTech and Moderna have demonstrated remarkable effectiveness, particularly in countering the challenges posed by emerging variants. But several studies propose a gradual weakening of protective measures over time, which generated dialogue about the need for booster doses (2).

Early risk stratification in covid-19 remains a challenge (10). Estimates suggest that more than half a billion people around the globe have been infected with SARS-CoV-2 at least once (11). For the large and growing number of people who encountered a first infection, the question to answer would be: Who is at greatest risk of reinfection? To improve our understanding of the risk factors associated with SARS-CoV-2 reinfection, there is a clear need for further studies employing an observational analytical design, including cases and controls. Therefore, understanding Covid-19 reinfection becomes a fundamental element that guides government and public health policies (2, 9, 12)

In this context, we present a longitudinal and prospective study of cases and controls of adult patients with or without covid-19 infections in vaccinated people with a fourth dose of bivalent mRNA vaccines, in general medicine from October 1, 2022, to October 1, 2023, whose objective was to identify risk factors of covid-19 of this booster (vaccines bivalent mRNA against the original strain and BA.4/BA.5 variant).

Material And Methods

A longitudinal study of cases and controls of adult patients with or without covid-19 reinfections in vaccinated people with fourth dose of vaccines bivalent mRNA, from October 1, 2022 to February 28, 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. Descriptive data of the case series with covid-19 reinfections in vaccinated people with fourth dose of bivalent mRNA vaccines in this population have already been published (13).

Objective of the study

Identify risk and protective factors of covid-19 reinfection in vaccinated 4th dose (vaccines bivalent mRNA) people in general practitioner consultation.

Definition of reinfection

SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection (14, 15).

Definition of cases and controls

Patients with reinfection of covid-19 and 4th dose de vaccine were considered "cases." "Control" were people who had received the 4th dose of vaccine, and had not presented covid-19. They were taken from a random sampling among patients who consulted for a reason other than covid-19, had received the 4th dose of vaccine, and had not presented covid-19 since that booster until April 15, 2023 in the same general medicine consultation object of the current study [n=52] and extrapolated to the total population at risk [people with 4th dose and without covid-19 reinfections from October 2022 to October 2023; n=1128].

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 (16-19).

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing (20) performed in health services or at home.

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" (21) classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (22)

-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) (23, 24)

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") (25)

-Date of covid-19 reinfection diagnosis

-Vaccination status with 4th dose (second booster) for fall-winter 2022 against covid-19 at the date of acute re-infection (26)

Sample size

All patients with 4th dose 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.

Epidemiological analysis

The variables collected were compared by calculating the relative risk (RR) as the incidence of selected variables in people with 4th dose and with covid-19 reinfections / incidence of selected variables in people with fourth dose and without covid-19 reinfections. the RR was interpreted as follows (27): 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. The classes that classify the age groups were made taking into account > and < 65 years. The age of 65 years was used as the beginning of old age (29). Figures with decimals were rounded to whole numbers to facilitate a more intuitive comparison.

Statistical analysis

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

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 4th dose and covid-19 re-infections and 1128 people with fourth dose without covid-19 re-infections from October 2022 to October 2023 were included.

The following risk factors were found: 1) Strong risk [Women (RR= 4.24), Social-Health Care Workers (RR= 15.21), Complex family/ Problems in the

family context (RR= 23.14), Chronic diseases of neoplasms group (RR= 2.59), Skin (RR= 3.18), and Genitourinary (RR= 2.58); and 2) Moderate risk [\geq 65 years (RR= 2.34) and Chronic diseases of Endocrine (RR = 2.17).

The following protective factors were found: 1) Protection factor effectively [Low-income household (RR= 0), Ethnic minority (RR= 0), Chronic Diseases of the blood (RR= 0), Circulatory system (RR= 0.29), Respiratory (RR= 0), and Digestive (RR= 0.45)], and 2) True benefits [Chronic diseases of Mental group (RR= 0.78), Nervous and Senses (RR= 0.76) and Musculoskeletal (RR= 0.7)]. But due to the few cases of reinfection, the only statistically significant factor was to be Social-Health Care Workers (RR= 15.21; Fisher exact test= 0.0156) (TABLE 1, TABLE 2).

RISK FACTORS	PEOPLE WITH FOURTH DOSE AND WITH COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023 N=5	PEOPLE WITH FOURTH DOSE AND WITHOUT COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023 N=1128	STATISTICAL SIGNIFICANCE	RELATIVE RISK (CI 95%)
\geq 65 years	3 (60)	440 (39)	Fisher exact test= 0.385. NS	RR= 2.34 (CI 95%: 0.08, 65.55). Moderate risk
Women	4 (80)	553 (49)	Fisher exact test= 0.2103. NS	RR= 4.24 (CI 95%: 0.2, 89.03). Strong risk
Socio-Health Care Workers	2 (40)	45 (4)*	Fisher exact test= 0.0156. Significant at $p < .05$.	RR= 15.21 (CI 95%: 2.43, 95.13). Strong risk
Complex family/ Problems in the family context	1 (20)	11 (1)*	Fisher exact test= 0.0519. NS	RR= 23.14 (CI 95%: 1, 535.46). Strong risk
Low income household	0	23 (2)*	Fisher exact test = 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
Ethnic minority	0	23 (2)*	Fisher exact test = 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively

Table 1: Risk Factors in Covid-19 Reinfection with Fourth Dose of Vaccines Bivalent Mrna from October 2022 to October 2023

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 N=5	PEOPLE WITH FOURTH DOSE AND WITHOUT COVID-19 RE-INFECTIONS FROM OCTOBER 2022 TO OCTOBER 2023** N=1128	STATISTICAL SIGNIFICANCE	RELATIVE RISK (CI 95%)
-II Neoplasms	2 (40)	31 (5)	Fisher exact test= 0.2012. NS	RR= 2.59 (CI 95%: 0.22, 30.14). Strong risk
-III Diseases of the blood	0	6 (1)	Fisher exact test = 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-IV Endocrine	4 (25)	80 (13)	X ² with Yates correction is 1.0495. $p = .305615$. NS	RR = 2.17 (CI 95%: 0.49, 9.62). Moderate risk
-V Mental	1 (6)	49 (8)	Fisher exact test = 1. NS	RR= 0.78 (CI 95%: 7.14, 0.09). True benefits
-VI-VIII Nervous and Senses	1 (6)	50 (8)	Fisher exact test = 1. NS	RR= 0.76 (CI 95%: 12.89, 0.04). True benefits
-IX Circulatory system	1 (6)	117 (19)	X ² with Yates correction= 0.9342. $p = .333781$. NS	RR= 0.29 (CI 95%= 3.54, 0.02). Protection factor effectively

-X Respiratory system	0	37 (6)	Fisher exact test= 0.6159. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XI Digestive system	1 (6)	80 (13)	Fisher exact test= 0.7074. NS	RR= 0.45 (CI 95%: 18.69, 0.01). Protection factor effectively
-XII Diseases of the skin	1 (6)	12 (2)	Fisher exact test= .2858. NS	RR= 3.18 (CI 95%: 0, 6094.68). Strong risk
-XIII Musculoskeletal	2 (12)	105 (17)	Fisher exact test = 1. NS	RR= 0.7 (CI 95%: 103.21, 0). True benefits
-XIV Genitourinary	3 (19)	49 (8)	Fisher exact test= 0.1372. NS	RR= 2.58 (CI 95%: 0.47, 14.18). Strong risk
TOTAL, chronic diseases**	16 (100)	616 (100)	---	--

Table 2: Chronic Diseases Risk Factors in Covid-19 Reinfection with Fourth Dose of Vaccines Bivalent Mrna from October, 2022 to October, 2023

*Patients could have more than one chronic disease; the percentages of chronic diseases are over the total of chronic diseases; **Taken from random sampling among patients who consulted for a reason other than covid-19, had received the 4th dose of vaccine, and had not presented covid-19 since that booster until April 15, 2023 in the same general medicine consultation object of the current study [N=52] and extrapolated to the total population at risk; (): Denotes percentages; RR: Relative risk; NS: Not significant

*Taken from random sampling among patients who consulted for a reason other than covid-19, had received the 4th dose of vaccine, and had not presented covid-19 since that booster until April 15, 2023 in the same general medicine consultation object of the current study [N=52] and extrapolated to the total population at risk; (): Denotes percentages; RR: Relative risk; NS: Not significant

Discussion

Main findings

The main results of our study in the general practice setting in Toledo, Spain were:

1. Covid-19 reinfections in people with fourth dose were uncommon.
2. Risk factors were to be: Social-Health Care Workers, women, ≥ 65 years of age.
3. Psychosocial factors showed mixed results, with Complex family/Problems in the family context being a risk factor, but Low-income household and Ethnic minority were protection factors.
4. Likewise, Chronic diseases showed a mixed pattern, being risk factors neoplasms, skin, Genitourinary and Endocrine; but Chronic Diseases of the blood, Circulatory, Respiratory, Digestive, Mental, Nervous and Senses, and Musculoskeletal were protective factors.

These results are similar to those obtained in the same population cohort but in a shorter period, from October 2022 to February 2023 (30). But, to correctly assess these results, it must be taken into account that the study was carried out during a high prevalence of the Omicron variant [in Spain, from November 21 to 27, 2022, the Omicron percentage stood at 100% (19)]. And 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, pregnant women, social health personnel and severe cases (31). Additionally, not all people infected with SARS-CoV-2 become sick enough to undergo testing (32). This situation, plus the fact that in Spain the fourth dose began to be administered to older people and social health workers (19, 33), possibly meant that the number of reinfections was underestimated (cases were lost) and that those who were evaluated were more probably older patients and health care workers.

Comparison with other studies

What are the predisposing factors of covid-19 reinfection? Risk factors for covid-19 appear to include: Close contact with someone who has covid-19, especially someone with symptoms; Being coughed or sneezed on by an infected person; and being near an infected person when in an indoor space with poor airflow (34). Numerous reports indicate that the bivalent booster

vaccine against covid-19 has greater efficacy than monovalent boosters, reduces the risk of symptomatic infection, provides substantial additional protection against severe omicron infections, and elicits higher neutralizing responses suggesting that it is more immunogenic than vaccine original (35-39).

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, antibody levels, mainly in the elderly and the comorbid, but also in the immunosuppressed, 6 months after vaccination, there are no detectable antibody levels or they are only low (40). But the durability of immunity is complex (41, 42). The risk of reinfection may vary individually based on demographic, temporal characteristics, disease history, vaccination history, and exposure risk, which are known to be interrelated (43, 44). 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 modifies the natural history of the disease (45).

A systematic review of the evidence on the risk factors associated with reinfection by covid-19, until August 2022, found that the probability of reinfection is higher for women, people with pre-existing chronic diseases, people over 60 years of age and those who have previously experienced severe symptoms of the disease or are immunocompromised; Furthermore, the cases linked to the Delta and Omicron variants were directly related to the factors analyzed (2, 11). In a cohort study of healthcare workers (N = 8205), a highly vaccinated population, followed from the start of the pandemic (March 1, 2020) until January 31, 2023, in the provinces of Trieste and Gorizia (northeast from Italy), SARS-CoV-2 reinfections were frequent during the Omicron transmission period; The lowest risk of reinfection occurred in men and for healthcare workers over 60 years of age (46). In another study, being ≥ 70 years of age, having ≥ 1 comorbidity, and a severe or critical primary infection were significantly associated with severe reinfections (47). But, other authors observed higher percentages of reinfections among covid-19 cases among younger adults compared to older adults, particularly in late 2022 (3).

Higher rates of SARS-CoV-2 reinfections have also been observed among healthcare workers (in New Delhi, India) during the Omicron wave (48). In a retrospective cohort study of SARS-CoV-2-positive healthcare workers in 2020, reinfections were rare and more likely in women, adults,

immunocompromised, and previously hospitalized for covid-19 (14). The estimated higher probability of reinfection among younger adults and groups employed as healthcare workers supports the hypothesis that the risk of reinfection is a function of exposure risk. However, the possibility that some of these population groups have been evaluated more intensively than others cannot be excluded (47).

Do all comorbidities and psychosocial factors represent the same risk for covid-19 reinfection? This question currently has no definitive answer. 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 (49). 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 (although they have risk factors for the severity).

Furthermore, while certain infectious diseases have been linked to socioeconomic disadvantage, mental health problems and lower cognitive function, the relationships with covid-19 are uncertain or unproven. A number of specific and non-specific mechanisms have been postulated that may link psychosocial variables to covid-19 risk: basically, worse health knowledge and behaviors, but it could also be the case that people who experience higher levels of psychological distress have lower resistance to infection (50).

In summary, our results are in line with the aforementioned studies, showing as risk factors for covid-19 reinfections in people with fourth dose were, those with variables suggesting immunosuppression, and greater risk of exposure: Social health care workers, women, and ≥ 65 years of age. But, on the other hand, psychosocial factors and chronic diseases showed mixed patterns, suggesting the need for further future research.

Limitations and strengths of the study

1. Infections were not genetically sequenced
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 small number of covid-19 cases may mask the statistical significance between variables.
4. 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.
5. Asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done, may have been missed.
6. The study has the strength of its longitudinality, characteristic of work in general medicine.

Conclusion

In the general practice setting in Toledo, Spain, the risk factors for covid-19 reinfections in people with fourth dose were, in part, those known for covid-19 infection, for suggesting immunosuppression, and greater risk of exposure: Social Health Care Workers, women, and ≥ 65 years of age. But psychosocial factors and Chronic diseases showed mixed patterns: Complex family/ Problems in the family context were risk factors, but Low-income household and Ethnic minority protective factors; Neoplasms, Chronic diseases of skin, Genitourinary and Endocrine were risk factors; but Chronic Diseases of the blood, Circulatory, Respiratory, Digestive, Mental, Nervous and Senses, and Musculoskeletal, were protective factors.

It is suggested that not all psychosocial factors nor all chronic diseases are a risk factor for covid-19 reinfections in people with fourth dose, and the causes of these differences in risk and protection in these variables should be studied in greater depth. Our results also suggest prioritizing future booster doses for those at higher risk of developing reinfection and being more

exposed to infections and facilitating transmission; that is, older adults and women and social health workers.

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