Discoveries in Infectious Diseases Research and Reports

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ORIGINAL RESEARCH

# Why do people vaccinated with 4th dose of vaccines get COVID-19? Approach to the risk factors for COVID-19 infection in people with 4th dose of bivalent mRNA vaccines in general medicine from October 2022 to October 2023

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**Received** 11 Oct 2024
**Accepted** 1 Apr 2025
**Published** 12 Apr 2025

**Keywords:**
COVID-19; SARS-CoV-2; Vaccine Effectiveness; Breakthrough Infection; bivalent mRNA vaccines; Population Surveillance/methods; General Practice

## ABSTRACT

**Background** Risk factors for covid-19 infection in people vaccinated with the 4th dose of mRNA covid-19 vaccine remain the subject of debate and is not clearly known.
**Objective** To identify risk and protective factors of covid-19 in vaccinated people with 4th dose of bivalent mRNA vaccines.
**Methodology** A longitudinal and prospective study of cases and controls of adult patients with or without covid-19 infections in vaccinated people with 4th dose of bivalent mRNA vaccines, from October 1, 2022 to October 1, 2023.
**Results** 21 people with fourth dose and with covid-19 infections and 1133 people with fourth dose and without covid-19 infections from October 2022 to October 2023 were included. The following statistically significant risk factors were found for presenting covid-19 in 4th dose people. : 1) To be 65 years or older [RR= 3.07]; 2) To be socio-health care worker [RR= 7.03]; and 3) To have chronic diseases of the blood [RR= 3.76]. And it was found as a protective factor to have chronic diseases of musculo-skeletal group [RR= 0.39]
**Conclusion** In the general practice setting in Toledo, Spain, to be 65 years or older, being a socio-health care worker and having chronic diseases of the blood (variables presumably associated with immunosuppression and greater risk of exposure and transmission), were risk factors for covid-19 infection in people vaccinated with the 4th dose of bivalent mRNA vaccines. Prioritization of future booster doses for these groups is suggested.

## INTRODUCTION

Since the authorization of the use of vaccines against Covid-19 in December 2020[1] the question of vaccine effectiveness in real-world settings has been widely addressed[2]. Vaccination provides substantial protection against both symptomatic and severe covid-19. But, the continued emergence of new variants of covid-19, such as Omicron and its sub-variants, posing challenges for the public health response, including ensuring that vaccines continue to provide protection which has markedly reduced efficacy in vaccines based on Wuham variant; Thus, booster vaccination for the prevention of covid-19 is required to overcome this loss of protection[3-5]. Furthermore, this situation haminimizing severe disease[6]. There have been two main approaches to vaccine prioritization: directly vaccinating those who are most at risk of developing severe outcomes or vaccinating those who contribute most to transmission[7]. 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[8-12]. However, real-world effectiveness monitoring and continued surveillance are needed to determine when the antigenic composition of vaccines should be updated. Furthermore, there is controversy over whether bivalent boosts against the Omicron BA.4 and BA.5 sub variants of SARS-CoV-2,

as well as the ancestral strain, should or should not be deployed in the entire population[13-18]. With the emergence of Omicron, vaccine prioritization has been influenced more by the protection against severe outcomes than by the impact of vaccines on transmission. The roadmap of the World Health Organization's Strategic Advisory Group of Experts on Immunization advocates prioritizing booster doses for higher-risk groups[19] such as older adults and adults with comorbidities[20].

In a scenario of high level of population immunity, novel approaches are needed for sustained surveillance to evaluate the epidemiological consequences of new SARS-CoV-2 variants and sublineages and risk groups to guide rational vaccination decisions. Possible epidemiological approaches could include, among others, longitudinal[21] and small area level studies in primary health care[22]. Analysis of epidemiological data, such as risk factors, in small areas is suitable for investigating differences in clinical decision making, as well as differences in the organization of services [23].

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

## MATERIAL AND METHODS

A longitudinal study of cases and controls of adult patients with or without covid-19 infections in 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.

The current study shows 1-year results from the population cohort at risk From October 1, 2022 to October 1, 2023. The results of the same population, but with a shorter follow-up time of only 5 months (from October 1, 2022 to February 28, 2023) have already been published[24]. Likewise, descriptive data of the case series with covid-19 infections in vaccinated people with 4$^{th}$ dose of bivalent mRNA vaccines in this population have already been published[25-27]. Part of the methodology is repeated here to facilitate understanding of the study.

### Objective of the study

To Identify risk and protective factors of covid-19 in vaccinated 4$^{th}$ dose (vaccines bivalent mRNA against the original strain and BA.4/BA.5 variant) people in general practitioner consultation.

### Definition of cases and controls

Patients with acute infection of covid-19 and 4$^{th}$ dose of vaccine were considered “cases.” All cases seen in the consultation that was the subject of the study were included. People with fourth dose and without covid-19 infections were considered “controls.” The population vaccinated with the 4$^{th}$ dose was extrapolated from official data. The data of some "control patients" variables patients were taken from a sample in the same general medicine consultation object of the current study; In this case, the controls were chosen through random sampling among patients who consulted for a reason other than covid-19, had received the 4$^{th}$ 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, and their figures were extrapolated to the total population at risk (with 4$^{th}$ dose) in the consultation object of the study.

### 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 (4$^{th}$ dose) [28,29].

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 [30].

### Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [31] 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" [32] classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [33].
- If they were Socio-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) [34, 35].
- Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [36].

### Epidemiological analysis

Variables collected were compared by calculating the relative risk (RR) as the incidence of specific variables in people with 4$^{th}$ dose and with covid-19 infections / incidence of specific variables in people with fourth dose and without covid-19 infections. The RR was interpreted as follows: 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[37]. The incidence (new cases in a certain unit of time as the numerator, and the estimated population at the center of the period as the denominator) is a way of expressing the morbidity rate [38]. The classes that classify the age groups were made taking into account > and < 65 years [39]. The age of 65 years was used as the beginning of old age [40]. 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 correction or Fisher Exact Test when necessary, (according to the number the expected cell totals) for percentages, and the Student test for the mean.

### Ethical issues

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

### Result

21 people with 4$^{th}$ dose and with covid-19 infections and 1133 people with fourth dose and without covid-19 infections from October 2022 to October 2023 were included. The following risk factors were found for presenting covid-19 in fourth dose people: 1 ) To be 65 years or older [RR= 3.07 (95% CI: 2.985, 3.162). Strong risk; X2= 6.6449. p= .009944]; 2) To be socio-health care worker [RR= 7.03 (95% CI: 2.66, 18.55). Strong risk; Fisher exact test= 0.0014]; and 3) To have chronic diseases of the blood [RR= 3.76 (95% CI: 1, 14.14). Strong risk; Fisher exact test = 0.0401]. And it was found as a protective factor to have chronic diseases of musculo-skeletal group [RR= 0.39 (95% CI: 0.95, 0.16). Protection factor effectively; X2= 5.0356. p= .024832] (**Table 1, Table 2**).

## DISCUSSION

### Main findings

The main results of our study are that in the general practice setting in Toledo, Spain, to be 65 years or older, being a socio-health care worker and having chronic diseases of the blood, with mean variables presumably associated with immunosuppression and higher exposure risk and transmission, were statistically significant risk factors for covid-19 infection in people vaccinated with the 4$^{th}$ dose of bivalent mRNA vaccines.

These results are similar to those obtained in the same population cohort but in a shorter period, from October 2022 to February 2023[24].

Table 1 Risk factors in covid-19 infection with fourth dose of vaccines bivalent mRNA from October 2022 to October 2023

| Risk factors | People with fourth dose and with covid-19 infections from october 2022 to October 2023 n= 21 | People with fourth dose and without covid-19 infections from october 2022 to October 2023 n=1133 | Statistical significance | Relative risk (CI 95%) |
|---|---|---|---|---|
| >= 65 years | 14 (67) | 441 (39) | X2= 6.6449. p= .009944. Significant at p <.05. | RR= 3.07 (CI 95%: 2.985, 3.162). Strong risk |
| Women | 13 (62) | 556 (49) | X2= 1.3581. p= .243861. NS | RR= 1.66 (CI 95%: 0.58, 4.72). Weak risk |
| Socio-Health Care Workers | 5 (24) | 44 (4)* | Fisher exact test= 0.0014. The result is significant at p <.05. | RR= 7.03 (CI 95%: 2.66, 18.55). Strong risk |
| Complex family/ Problems in the family context | 2 (9) | 153 (13)* | Fisher exact test = 1. NS | RR= 0.68 (CI 95%: 24.87, 0.02). True benefits |
| Low income household | 0 | 22 (2)* | Fisher exact test = 1. NS | RR= 0 (CI 95%: Infinity, 0). Protection factor effectively |
| Ethnic minority | 0 | 22 (2)* | Fisher exact test = 1. NS | RR= 0 (CI 95%: Infinity, 0). Protection factor effectively |

*Taken from a sample through 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 [N=1133]; ( ): Denotes percentages; RR: Relative risk; NS: Not significant

It must be taken into account that in Spain, from November 21 to 27, 2022, the Omicron percentage stood at 100% [30]. 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 and pregnant women, social health personnel and severe cases[41]. The 4th dose began to be administered to older people and social health workers[10, 30]; these events may mean that not all patients with symptoms of viral infections in the community were tested (and cases would be missed), and that those who were tested were more likely older patients and health care workers.

**Comparison with other studies**

Why are there people vaccinated with 4th dose of bivalent mRNA vaccines who become infected with covid-19? Since the beginning of vaccination, serious cases of covid-19 have been significantly reduced. Even so, some of the people who have received the complete vaccination schedule and the 4th dose of bivalent mRNA vaccines become infected with covid-19. Likewise, vaccinated people who become infected can transmit covid-19; But viral loads are much lower and, therefore, transmission is also lower[42].

This does not mean that vaccines are not effective, in fact, current data shows that they have high efficacy and safety, also against new variants. Two Israeli studies have shown that a fourth dose is effective in people aged 60 years and older[43, 44]. A second booster dose with an mRNA vaccine (BNT162b2 or mRNA-1273) improves protection against symptomatic SARS-CoV-2 infection, covid-19 hospitalization, and intensive care-associated illness with oxygen therapy or outcome fatal, even in the elderly, compared to a single booster. This claim is supported by a large controlled trial from Singapore with participants over 79 years of age[45].

Many other reports indicate that the bivalent booster vaccine against covid-19 has greater efficacy than

Table 2. Chronic diseases risk factors in covid-19 infection 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 without covid-19 infections from October 2022 to October 2023 n=21 | People with fourth dose and without covid-19 infections from October 2022 to October 2023 n=1133 | Statistical significance | Relative risk (ci 95%) |
|---|---|---|---|---|
| -II Neoplasms | 2 (3) | 28 (5) | Fisher exact test= 0.7591. NS | RR= 0.64 (CI 95%: 7.27, 0.06). True benefits |
| -III Diseases of the blood | 3 (4) | 5 (1) | Fisher exact test= 0.0401. The result is significant at p <.05. | RR= 3.76 (CI 95%: 1, 14.14). Strong risk |
| -IV Endocrine | 14 (20) | 82 (13) | X2= 2.2269. p= .135625. NS | RR= 1.52 (CI 95%: 0.81, 2.84). Weak risk |
| -V Mental | 9 (13) | 53 (8) | X2= 1.3181. p= .250935. NS | RR= 1.47 (CI 95%: 0.65, 3.31). Weak risk |
| -VI-VIII Nervous and Senses | 5 (7) | 48 (8) | X2= 0.0456. p= .83098. NS | RR= 0.91 (CI 95%: 9396.91, 0). Not significant |
| -IX Circulatory system | 16 (22) | 118 (19) | X2= 0.4907. p= .483608. NS | RR= 1.21 (CI 95%: 0.61, 2.42). Weak risk |
| -X Respiratory system | 2 (3) | 36 (6) | X2 with Yates correction= 0.5999. p= .438608. NS | RR= 0.5 (CI 95%: 2.92, 0.09). Protection factor effectively |
| -XI Digestive system | 7 (10) | 79 (13) | X2= 0.4921. p= .482986. NS | RR= 0.77 (CI 95%: 2.1, 0.28). True benefits |
| -XII Diseases of the skin | 2 (3) | 12 (2) | Fisher exact test= 0.6468. NS | RR= 1.4 (CI 95%: 0, 748767.58). weak risk |
| -XIII Musculo-skeletal | 5 (7) | 108 (17) | X2= 5.0356. p= .024832. Significant at p <.05. | RR= 0.39 (CI 95%: 0.95, 0.16). Protection factor effectively |
| -XIV Genitourinary | 6 (8) | 50 (8) | X2= 0.0119. p= .913157. NS | RR= 1.04 (CI 95%: 0.55, 1.97). Not significant |
| TOTAL chronic diseases** | 71 (100) | 619 (100) | --- | --- |

*Patients could have more than one chronic disease; the percentages of chronic diseases are over the total of chronic diseases; **Taken from a sample through 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 [N=1133]; ( ): Denotes percentages; RR: Relative risk; NS: Not significant.

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 original vaccine [18, 29, 46-48].

The situation of vaccinated people presenting infections does not mean that the vaccines are not working. Covid-19 vaccines are not 100% effective. For this reason, it has been observed that a small proportion of people who are fully vaccinated become infected with covid-19. In addition, the appearance of variants of the SARS-CoV-2 virus has contributed to increasing infections among vaccinated people. Although there were already indications with other variants, the appearance of the omicron variant showed that vaccines based on the original SARS-CoV-2 strain (Wuhan) generate antibodies that do not effectively neutralize these new variants of the virus. In fact, it seems that the omicron subvariants BA.2.12.1, BA.4 and BA.5 escape the neutralizing antibodies induced by both vaccination and infection, being less neutralizing against the more recent subvariants. This suggests that there is a selective pressure that expands those subvariants that escape antibodies. This would explain why transmission of the virus continues in populations with high vaccination or infection rates[49].

Although immunocompromised people account for much of the decreased protection against severe disease [50,51], the bivalent vaccine appears to protect immunocompetent patients well, and the immunocompromised as well, providing greater protection against hospital admission for covid-19 [52-54]. We found that the presence of chronic diseases of the blood which can be interpreted as an indicator of immunocompromise, were significant risk factors for covid-19 in people with bivalent vaccines.

On the other hand, we found that being socio-health care workers was a strong risk to present covid-19 with the 4$^{th}$ dose of mRNA vaccine. Socio-healthcare workers can be considered at risk due to their increased exposure to SARS-CoV-2. Low vaccine efficacy against infections in healthcare workers has been reported, as well as relatively high viral loads suggesting that those infected were infectious, so a 4$^{th}$ dose in healthy young healthcare workers may have marginal benefits [10, 55, 56].

In addition to protecting people at highest risk of severe disease, vaccination is important to reduce the spread of the virus and prevent the emergence of new variants around the world. In this matter, the prevention of covid-19 in social health workers is an important element. As long as the SARS-CoV-2 virus continues to circulate, infections will continue to occur in people who have completed the vaccination schedule and new variants of the virus are more likely to appear.

### Study limitations and strengths

1. The small number of covid-19 cases may mask the statistical significance between variables.
2. Asymptomatic cases were missing because they did not attend in GP consultation, as no surveillance or systematic screening was done.
3. 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.
4. The great accessibility of patients to the GP, and the fact of the continuity of care that characterizes family medicine, have important epidemiological connotations, presenting a unique opportunity to study incidence rates of diseases in small geographical bases.

## CONCLUSION

In the general practice setting in Toledo, Spain, to be 65 years or older, being a socio-health care worker and having chronic diseases of the blood, which suppose variables presumably associated with immunosuppression and greater risk of exposure, were statistically significant risk factors for covid-19 infection in people vaccinated with the 4$^{th}$ dose of bivalent mRNA vaccines. Vaccinating people most at risk of severe outcomes remains the priority. Our results suggest prioritizing future booster doses for those at higher risk of developing severe outcomes, being more exposed to infections, and facilitating transmission; that is, older adults and adults with immunosuppression and health care workers.

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**To cite**: Jose Luis Turabian Why do people vaccinated with 4th dose of vaccines get covid-19? Approach to the risk factors for covid-19 infection in people with 4th dose of bivalent mRNA vaccines in general medicine from October 2022 to October 2023 *Discov. Infect. Dis. Res. Rep.* 2025; 1: 1-9.

**Conflict of interest:** The authors declare no competing interests.

**Funding sources: None**

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms

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