

Risk Factors for Re-Infection of Covid-19 with Fourth Dose versus without Fourth Dose of Bivalent mRNA Covid-19 Vaccines

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Abstract

Background

The possibility of SARS-CoV-2 reinfection in covid-19 survivors with the 4th dose of covid-19 vaccine given is known, but the associated risk remains unclear.

Objective

Determine the risk factors of covid-19 re-infections in patients with 4th dose of vaccine versus without 4th dose (no vaccine, with 1, 2 or 3 doses) in general practitioner consultation.

Methodology

An observational, longitudinal and prospective study of covid-19 re-infections was conducted from March 1, 2020 to July 1, 2023, in a general medicine office in Toledo, Spain.

Results

2 patients with covid-19 re-infection and 4th dose of vaccine versus 52 patients with covid-19 re-infection without 4th dose (no vaccination, 1, 2 or three doses of covid-19 vaccine) were included. The following were found as risk factors for presenting covid-19 reinfection despite having the 4th dose: ≥ 65 years, men, socio-Health Care Workers, mild severity of first infection, and presence of chronic diseases. Within chronic diseases: Neoplasms, Endocrine, Mental, Genitourinary, Circulatory system and Musculoskeletal. But only the last two were statistically significant.

Conclusion

In the general practice setting in Toledo, Spain, young men, social-health workers, with mild severity of first infection, and with chronic diseases, especially of the circulatory system and musculoskeletal, are at greater risk of presenting covid-19 reinfections despite having the 4th dose on. It is suggested that in these people, in addition to keeping up with the covid-19 vaccines, it may be necessary to implement certain additional prevention measures such as wearing masks and increasing interpersonal distance.

Keywords: COVID-19; SARS-CoV-2; Reinfections; COVID-19 Vaccine; Breakthrough Infection; Hybrid immunity; General Practice

Introduction

The coronavirus disease 2019 (covid-19) pandemic is at a tipping point, meaning that high levels of immunity to severe acute respiratory syndrome coronavirus (SARS-CoV-2) are beginning to limit its impact and scope. If covid-19

becomes endemic, it will be present at a certain level in a population at certain times of the year or throughout the year. A disease that is not eradicated is, by definition, endemic. This does not necessarily mean that you are circulating at low levels. Or that it is harmless (1).

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Large-scale efficacy trials showed that covid-19 vaccines reduced the risk of disease by more than 90% (2, 3). Similarly, the short-term efficacy of vaccines with respect to the severity of infection by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been demonstrated (4). But, on the other hand, there is growing scientific evidence showing that the protection generated through vaccination decreases over time, although it is restored with the inoculation of booster dose. In addition, the decrease in immunity as a consequence of the new variants must be taken into account (5). Thus, it is accepted that it can be normal to become infected by SARS-CoV-2 several times throughout life (6-9).

It has been reported that after several months, people with hybrid immunity were better protected against reinfection than uninfected people who had previously received two doses of the vaccine (10). But in any case, natural infection does not protect against contagion to new variants (11, 12). SARS-CoV-2 evolves very quickly and the new strains largely escape the old vaccines. To be well protected against new strains we need new vaccines. Thus, booster vaccination for the prevention of covid-19 is required to overcome this loss of protection (13-15).

Since September 2022, Moderna and Pfizer-BioNTech bivalent SARS-CoV-2 vaccines containing equal amounts of spiked mRNA from the ancestral BA.4-BA.5 and 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 (16-21). Despite vaccinations, boosters, and natural immunity, the highly infectious omicron variant appears able to evade any protection it may have gained against SARS-CoV-2 (22, 23).

At present, reinfection episodes and associated risk factors remain unclear (24, 25). Understanding reinfection risk factors

is crucial to assessing how infections might rise and whether health system will be able to cope. Ultimately, studying reinfections will help researchers understand what the transition from SARS-CoV-2 to an endemic virus will look like (26). Because many countries, such as Spain (27), no longer publish their covid-19 case counts, it is not clear how many people are infected, nor can the evolution of new waves be assessed; Of course, it is difficult to make estimates without precise data. But based on previous research, it is estimated that at least 30% of the population could be re-infected in successive waves. Scientists say that having a good surveillance system to monitor and track emerging virus variants is very important, since infection cycles will continue to occur (28).

In this context, we present an observational, longitudinal and prospective study with the aim of assessing the risk and protective factors to prevent covid-19 reinfections in those vaccinated with a fourth dose compared to those not vaccinated with fourth dose (no, vaccinated, with 1, 2 or three doses), and that was conducted from March 1, 2020 to July 1, 2023 in a general medicine office.

Material and Methods

Design and Emplacement

An observational, longitudinal and prospective study of Covid-19 reinfections was conducted from March 1, 2020 to July 1, 2023 in a general medicine office in the Santa Maria de Benquerencia Health Center, 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). Some previous data from this cohort have already been published (29-31).

Outcome of Interest

Assess the risk and protective factors to prevent covid-19 reinfections in people vaccinated with the fourth dose compared to those not vaccinated with the fourth dose (no vaccinated, with 1, 2 or three doses). In this sense, the variables collected were compared by calculating the relative risk (RR) as the Incidence of

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reinfections among the exposed population / Incidence of reinfections among the population not exposed. The RR was interpreted as follows (32): 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.

Diagnosis of Covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing (33).

Definition of Reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection, to avoid misclassification of prolonged PCR positivity as reinfection if a shorter time interval is used (24, 34, 35).

First and Second Dose

Vaccination campaign against covid-19 in Spain began on December 27, 2021, once the Pfizer / BioNTech vaccine was approved on December 21 by the European Medicines Agency. Little later the Spikevax (mRNA-1273 vaccine Moderna) vaccine was approved. The vaccination campaign was carried out in stages and prioritizing the groups of people most exposed to covid-19 (36).

Definition of 2 Doses of Vaccine

To have received 2 doses of vaccine separated by a minimum of 19 days if the first dose was BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech), 21 days in the case of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) or 25 days in the case of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), or a dose of Janssen vaccine (Johnson & Johnson vaccine) (33).

Definition of First Booster (Third Dose)

As of November 23, 2021 in Castilla La Mancha, the region where the study was carried out, first booster doses against covid-19 with messenger RNA (mRNA) vaccines began 6 months after completion the vaccination schedule and after 3 months

in case of having received a dose of the Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine). Recruitment was carried out actively by age cohorts in a descending manner, beginning with those over 80 years of age. The booster dose was administered with mRNA vaccines (0.3 ml of Comirnaty or 0.25 ml of Spikevax – half the usual dose in primary vaccination) (37-40).

Fourth Booster Dose for Fall-Winter 2022

Only Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccines were used. 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 (41).

Definition of Cases and Controls

Patients with covid-19 reinfection with fourth dose were considered cases. Control patients were considered patients with covid-19 reinfection in unvaccinated people, vaccinated with 2 or 3 doses (but without a fourth dose).

Collected Variables

-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" (42), classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (43).

-If they were Socio-Health Care Workers.

-Severity of primary infection and reinfection (mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; moderate cases: with symptoms such as fever and respiratory tract symptoms, and the manifestation of pneumonia can be seen on the imaging tests; and severe cases: respiratory distress, respiratory rate \geq 30 breaths / min; pulse oxygen saturation \leq

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93% with room air at rest; arterial partial pressure of oxygen / oxygen concentration \leq 300 mmHg) (44). To simplify comparison, moderate and severe cases were counted together.

-Doses of covid-19 vaccines received.

Statistic Analysis

The bivariate comparisons were performed using the Fisher Exact Test.

Results

2 patients with covid-19 reinfection and fourth dose of vaccine versus 52 patients with covid-19 reinfection without vaccination, with 1, 2 or 3 doses of covid-19 vaccine were included. The following risk factors were found to present covid-19 reinfection despite having the 4th dose: Being \geq 65 years [RR= 19.96 (95% CI: 0.28, 1446.25). Strong risk]; men [RR= 1.35 (CI 95% 0.43, 4.28). Weak risk]; Being a Socio-Health Care Worker [RR= 3.9 (CI 95%: 0, 25450237.59). Strong risk]; Having presented mild severity of first infection [RR= Infinity (95% CI: 0, Infinity). Strong

risk]; and presenting chronic diseases [RR= Infinity (95% CI: 0, Infinity). Strong risk]; and within them: Neoplasms [RR= 4.5 (95% CI: 0.03, 793.13). Strong risk], Endocrine [RR= 1.94 (95% CI: 0.23, 16.31). Moderate risk], Mental [RR= 8.01 (95% CI: 0.01, 4688.21). Strong risk], Circulatory system [RR= Infinity (95% CI: Infinity, Infinity). Strong risk. Fisher exact test= 0.0147. Significant at $p < .05$], Musculoskeletal [RR= Infinity (95% CI: Infinity, Infinity). Strong risk. Fisher exact test= 0.0384. Significant at $p < .05$], and Genitourinary [RR= 2.86 (95% CI: 0, 1.8718894541075744e+30). Strong risk]. The only statistical significances were in chronic diseases of the Circulatory system and Musculoskeletal. The following protective factors were found in covid-19 reinfection having the 4th dose: presence of chronic diseases of Nervous and Senses, Respiratory system, Digestive system, and Diseases of the skin; in all of them with a RR= 0 (95% CI: Infinity, 0). Protection factor effectively; But equally, in all of them without statistical significance (**TABLE 1**, **TABLE 2**).

Table 1: Comparison of Risk Factors of Reinfection Covid-19 in Non-Vaccinated Population, With First, Second Doses and First Booster Versus with Fourth Dose, Regarding the Vaccinated Population, from March 2020 to July 1, 2023

RISK FACTORS	COVID-19 REINFECTION WITHOUT FOURTH DOSE N=52	COVID-19 REINFECTIONS WITH FOURTH DOSE VACCINE (SECOND BOOSTER AND COMPLETE PREVIOUS VACCINATION SCHEDULE) N=2	STATISTICAL SIGNIFICANCE	RELATIVE RISK (RR)
\geq 65 years	2 (4)	1 (50)	Fisher exact test= 0.109. NS	RR= 19.96 (CI 95%: 0.28, 1446.25). Strong risk
Women	30 (58)	1 (50)	Fisher exact test= 1. NS	RR= 0.74 (CI 95%: 2.35, 0.23). True benefits
Men	22 (42)	1 (50)	Fisher exact test= 1. NS	RR= 1.35 (CI 95% 0.43, 4.28). Weak risk
Socio-Health Care Workers	10 (19)	1 (50)	Fisher exact test= 0.369. NS	RR= 3.9 (CI 95%: 0, 25450237.59). Strong risk
Moderate-severe severity of first infection	3 (pneumoniae) (6)	0	Fisher exact test= 1. NS	RR= 0 (CI 95%: 0, Infinity). Protection factor effectively
Mild severity of first infection	49	2	Fisher exact test= 1. NS	RR= Infinity (CI 95%: 0, Infinity). Strong risk
Presence of chronic diseases	29 (56)	2(100)	Fisher exact test= 0.5017. NS	RR= Infinity (CI 95%: 0, Infinity). Strong risk

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Vaccinated 1 dose	9 (17)	NR	NR	NR
Vaccinated 2 doses	14 (27)	NR	NR	NR
Vaccinated with booster (3 doses)	19 (37)	NR	NR	NR
not vaccinated	10 (19)	NR	NR	NR

(): Denotes percentages; RR: Relative risk; NS: Not significant; NR: Not relevant

Table 2: Comparison of Chronic Diseases as Risk Factors of Covid-19 Reinfection in the Non-Vaccinated Population, with First, Second Doses and First Booster Versus with Fourth Dose, Regarding the Vaccinated Population, from March 2020 To July 1, 2023

CHRONIC DISEASES*	COVID-19 REINFECTION WITHOUT FOURTH DOSE N=52	COVID-19 REINFECTIONS WITH FOURTH DOSE VACCINE (SECOND BOOSTER AND COMPLETE PREVIOUS VACCINATION SCHEDULE) N=2	STATISTICAL SIGNIFICANCE	RELATIVE RISK (RR)
-I Infectious	0	0	Fisher exact test= 1. NS	RR= NaN
-II Neoplasms	1 (1)	1(10)	Fisher exact test= 0.2277. NS	RR= 4.5 (CI 95%: 0.03, 793.13). Strong risk
-III Diseases of the blood	0	0	Fisher exact test= 1. NS	RR= NaN
-IV Endocrine	12 (16)	3 (30)	Fisher exact test= 0.377. NS	RR= 1.94 (CI 95%: 0.23, 16.31). Moderate risk
-V Mental	5 (7)	1 (10)	Fisher exact test= 0.2117. NS	RR= 8.01 (CI 95%: 0.01, 4688.21). Strong risk
-VI-VIII Nervous and Senses	6 (8)	0	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-IX Circulatory system	5 (7)	2 (20)	Fisher exact test= 0.0147. Significant at p <.05.	RR= Infinity (CI 95%: Infinity, Infinity). Strong risk
-X Respiratory system	12 (16)	0	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XI Digestive system	4 (6)	0	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XII Diseases of the skin	6 (8)	0	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XIII Musculo-skeletal	9 (12)	2 (20)	Fisher exact test= 0.0384. Significant at p <.05.	RR= Infinity (CI 95%: Infinity, Infinity). Strong risk
-XIV Genitourinary	13 (19)	1 (10)	Fisher exact test= 0.4549. NS	RR= 2.86 (CI 95%: 0, 1.8718894541075744e+30). Strong risk
TOTAL chronic diseases**	73 (100)	10 (100)		---

(): Denotes percentages; RR: Relative risk; NS: Not significant; NaN (Not a Number): Result impossible to calculate; *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 finding is that the profile of the person at risk of covid-19 reinfection despite being vaccinated with a fourth dose is a young male, a social and health worker, who presented mild severity of first infection, and who has chronic diseases, especially of the circulatory system and musculoskeletal.

It is important to note that the small number of reinfections in people with a fourth dose may be false, and represent a "visible minimum" number, especially in young people. In Spain, since April, 2022 there is a new "Surveillance and Control Strategy Against Covid-19" that include the non-performance of diagnostic tests, which are focused only on those over 60 years of age (27). And on the other hand, the fourth dose began to be given to older people (41). Thus, these results should be interpreted with caution given that the number of tests carried out in the community is low, which suggests an indeterminate covid-19 situation, and data should also be sought from other sources (45).

On the other hand, it should be mentioned that in the period from March to April, 2020, in Spain, the A lineage of the coronavirus predominated, especially the SEC7 and SEC8, and from summer to December, 2020, the 20E (EU1) variant (46, 47). In the period from January 2021 the alpha variant predominated, and from the summer-autumn of 2021 the delta variant. In December 2021 there was a rapid expansion of omicron nationwide. In January 2022, omicron was predominant in Spain together with a very significant increase in covid-19 incidence. Since March 2022 there was an expansion of the BA.2 lineage; on those dates the prevalence of the alpha variant was declining (48, 49). The omicron variant was the dominant one in Spain in November, 2022, with an omicron percentage stood at 100% (41, 50, 51).

Comparison with Other Studies

Research is ongoing to find out if certain people are at increased risk of reinfection (52). The current situation is that despite the high level of vaccination of

the population, which in many countries reaches 90%, large waves of reinfections due to the highly infectious subvariants of Omicron continue to be seen, which can reach 85% of the population, coinciding with the fact that many governments have eliminated control and surveillance measures (28). So far, emerging data suggests that people vaccinated against SARS-CoV-2 and who have had covid-19 are better protected against reinfection than people with vaccine-derived immunity. Experts suspect that hybrid immunity (infection and vaccination) generates a broader spectrum of antibody response and immunity (53-55). But in practice reinfections have become more common in recent months, and experts say the trend is expected to continue. It is predicted that all people will be infected with covid-19 several times in their lives (53).

Immunity is waning and new subvariants can evade protection from vaccines and previous infections. Although current vaccines can provide good protection against serious disease and death, they are not very good at providing long-lasting protection against infection. Repeated infections, even with a mild virus like the latest Omicron variants, can still lead to health problems like prolonged covid-19, and vulnerable people, such as older adults, are still at risk of severe illness (28).

Bivalent boosters provide substantial additional protection against severe omicron infection in previously vaccinated or boosted persons, although efficacy decline over time. A fourth dose improves the efficacy of the vaccine, and current findings support recommendations for the widespread use of the fourth booster dose (56-59). However, at this time, what we know about messenger RNA vaccines is that compared to the second dose, the third increases the immune response for a longer time; However, the fourth dose does not exceed the maximum levels obtained with the third and its effect wears off about three months after vaccination. For this reason, the time to be vaccinated should coincide with situations in which community transmission is high and the risk of contagion is very high (60).

Similarly, given that the immune response of the population with a history of infection is heterogeneous, and the immune response after vaccination is more reliable, consistent and predictable than that produced by infection, the fourth dose does have value for vulnerable or fragile populations. This includes older adults; people who are immunocompromised, and those who have underlying illnesses that may complicate a coronavirus infection, even if they have had covid-19 before. Primary vaccination decreases the risk of future infections in people with a history of SARS-CoV-2 infection, and immunological studies show that subsequent vaccination strengthens the immune response and reduces the risk of reinfection, including new virus variants (50, 61).

In our study, the results indicate that being ≥ 65 years old, the presence of chronic diseases and a socio-health work context are the variables that characterize the people who have a higher risk of reinfection despite having received the fourth dose of covid-19 bivalent mRNA vaccine. It is suggested that in these people, in addition to keeping up-to-date with covid-19 vaccines, it may be necessary to implement certain additional prevention measures such as wearing masks and increasing interpersonal space and distance.

Study limitations

1. Infections were not genetically sequenced
2. The small number of covid-19 cases may mask the statistical significance between variables
3. Follow-up was short-term after the booster vaccination
5. In our study, only Pizfer / BioNTech, Spikevax (mRNA-1273-Moderna), Vaxzevria, Oxford / AstraZeneca and Janssen (Johnson & Johnson) vaccines were used for the first and second doses. For the first booster, only messenger RNA (mRNA) was used. And only Moderna and Pfizer-BioNTech's bivalent covid-19 vaccines were used for the second booster. Thus our results may not directly apply to other covid-19 vaccine platforms.

Conclusion

In the general practice setting in Toledo, Spain, young men, social-health workers, with mild severity of first infection, and with chronic diseases, especially of the circulatory system and Musculoskeletal, are at greater risk of presenting covid-19 reinfections despite having the 4th dose on. In these people, in addition to keeping up-to-date with covid-19 vaccines, it may be necessary to implement certain additional prevention measures such as wearing masks and increasing interpersonal space and distance.

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