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Research Article

Effectiveness of 4th doses of bivalent mRNA vaccine in reinfections from October 2022 to October 2023 in a general medicine office in Toledo (Spain)

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Abstract

Background: The effectiveness of the COVID-19 vaccine in preventing reinfections is uncertain and there is little community-level research published at this time.

Objective: To compare the cases of COVID-19 reinfections in vaccinated versus not vaccinated 4th dose people with bivalent mRNA vaccines and assess the effectiveness of this vaccine booster.

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. The 4th dose vaccine COVID-19 effectiveness was calculated as 1 - [COVID-19 cases incidence of reinfection with 4th dose vaccine / COVID-19 cases incidence of reinfection without 4th vaccine dose] × 100.

Results: 12 COVID-19 reinfections were included. Of them, 5 were in people with a fourth vaccine dose of bivalent mRNA and 7 were in people without a fourth vaccine dose of bivalent mRNA. The population vaccinated with the 4th dose was estimated at 1,133 people. The population without a 4th dose was estimated at 867 people. The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on the total number of cases of reinfections in vaccinated and unvaccinated was 30%. The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on population denominators of the total number of people vaccinated or not, was 46%.

Conclusion: In the context of general medicine in Toledo (Spain), the 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections was modest. However, these results should be interpreted with caution because of the few cases included and possible underreporting.

Introduction

Vaccine effectiveness is a measure of how well vaccination protects people against health outcomes such as infection, symptomatic illness, hospitalization, and death. Vaccine effectiveness is generally measured by comparing the frequency of health outcomes in vaccinated and unvaccinated people [1]. Coronavirus disease 2019 (COVID-19) vaccines have been shown to be safe, effective and life-saving. Although like other vaccines, COVID-19 vaccines do not completely immunize all vaccinated people, the effectiveness studies of the second booster or fourth dose of COVID-19 vaccines in real life leave no doubt in selected vulnerable patients (the elderly, people with multimorbidity, immunosuppressed, and socio-health care workers) of your usefulness [2-4].

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

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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 [5-14]. A fourth dose improves vaccine efficacy, and current findings support recommendations for widespread use of booster doses [2,14-16].

However, its effectiveness in preventing reinfection is lower. 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. After having COVID-19, the immune response provides protection against reinfection for several months, but this protection decreases over time [17]. The number of reinfections is expected to increase as the cumulative incidence of first infections increases, infection- and vaccine-induced immunity declines, and new variants with increased transmissibility and immune escape characteristics emerge [18,19].

Monitoring vaccine effectiveness against infection provides useful information about actual effectiveness against new variants or maybe an early signal of waning vaccine effect [1]. No vaccine is approved if its theoretical efficacy rate is not greater than 50% [4]. Subsequently, surveillance is maintained to verify that they remain safe and effective in practice. The actual effectiveness of vaccines is a measure of the degree to which they work in practice [4]. In the case of COVID-19, studies monitoring the effectiveness of the SARS-CoV-2 vaccine may be subject to bias due to changes in testing practices, including increased use of at-home tests, or different testing practices between vaccinated and unvaccinated people [1].

Furthermore, to date, data on the rate and severity of SARS-CoV-2 reinfections in real-world settings are scarce, and the effects of vaccine boosters on the risk of reinfection are unknown [20]. Furthermore, due to differences in the definition of reinfection, epidemic period, follow-up time, and other factors used in different studies, there is still great uncertainty about SARS-CoV-2 reinfection. However, accurate assessment of SARS-CoV-2 reinfection cases is essential for the rational allocation of medical resources and optimization of vaccination strategies [21].

In this context, we present a longitudinal and prospective study of cases of reinfection in adult people with and without a fourth dose of bivalent mRNA vaccines, in general medicine from October 1, 2022, to October 1, 2023, with the objective of evaluating the 4th dose COVID-19 vaccine effectiveness to prevent reinfections.

Materials and methods

Study design, location and duration

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 is 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.

Methodology

Objective of the study: To evaluate the 4th dose of COVID-19 vaccine effectiveness to prevent reinfections.

Fourth booster dose for fall-winter 2022: In the patients included in the study, 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, to people admitted to nursing homes and other centers with disabilities, and to those with risk conditions, including social-health personnel [24].

Diagnosis of COVID-19: The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [25] performed in health services or at home by the patient himself.

Definition of reinfection: SARS-CoV-2 reinfection was defined as a documented infection occurring at least 90 days after a previous infection [26-28].

Calculation of 4th dose COVID-19 vaccine effectiveness

We calculated the vaccine effectiveness as a percentage, as follows [29-31]:

1-[Cases with cuarta dosis COVID-19 vaccine / Cases without cuarta dosis COVID-19 vaccine] × 100

Vaccine effectiveness was calculated in two modalities: 1. Vaccine effectiveness was calculated on the total number of cases of reinfections in vaccinated and unvaccinated; AND 2. Vaccine effectiveness is calculated on population denominators of the total number of people vaccinated or not. In the latter case, the population denominators were taken from a previously published estimate [32].

Sample population and calculation and selection criteria

All patients who met the criteria for COVID-19 infection during the time of the study and who were treated in the general medicine consultation object of the study were included.

Ethical issues

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

Statistical analysis

Given the number of cases included, no software was used, but rather a "pencil and paper" calculation.

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Epidemiological analysis

The incidence of new cases of reinfection was evaluated. This is a measure of the frequency of occurrence of new cases of a disease within a defined population during a specific period of time. Given the number of cases included, only crude incidence data are presented. The aim is to avoid excessive fragmentation of the data, which would be unrepresentative and may lead to confusion.

Results

12 COVID-19 reinfections were included in the period from October 2022 to October 2023. Of them, 5 were in people with a fourth vaccine dose of bivalent mRNA, and 7 were in people without a fourth vaccine dose of bivalent mRNA. The population vaccinated with the 4th dose was estimated at 1,133 people. The population without a 4th dose was estimated at 867 people. The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on the total number of cases of reinfections in vaccinated and unvaccinated was 30% (Table 1). The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on population denominators of the total number of people vaccinated or not, was 46% (Table 2).

Discussion

Main findings

Our main results were:

1. Reinfections were rare.

2. The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on the total number of cases of reinfections in vaccinated and unvaccinated was low (30%). The 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections calculated on population denominators of the total number of people vaccinated or not, was moderate (46%).

Table 1: Calculation of the fourth dose of vaccine covid-19 bivalent effectiveness (without population denominators).

Cases of reinfection with 4th dose of vaccine COVID-19	Gross Incidence Rate (Total number of reinfection cases: N=12)	Cases of reinfection without the 4th dose of vaccine COVID-19	Gross Incidence Rate (Total number of reinfection cases: N=12)
5	41%	7	58%
The fourth dose of vaccine COVID-19 effectiveness = 1 - [COVID-19 cases incidence of reinfection with 4th dose vaccine / COVID-19 cases incidence of reinfection without 4th vaccine dose] × 100 = 1-(0.41/0.58)x100= 30%			

Table 2: Calculation of the fourth dose of vaccine COVID-19 bivalent effectiveness (with population denominators).

Cases of reinfection with 4th dose of vaccine COVID-19	Gross Incidence Rate (Population with 4th dose: N=1133)	Cases of reinfection without the 4th dose of vaccine COVID-19	Gross Incidence Rate (Population without 4th dose: N = 867)
5	0.44%	7	0.81%
The fourth dose of vaccine COVID-19 effectiveness = 1 - [COVID-19 cases incidence of reinfection with 4th dose vaccine / Covid-19 cases incidence of reinfection without 4th vaccine dose] × 100= 1-(0.0044/0.0081)x100= 46%			

One fact to keep in mind is that in the current phase, many of the community surveillance studies that track infection levels have been completed [33]. 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 the elimination of contact tracing [34]. 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. Official statistics, which already tend to underestimate the number of cases, may become even less sensitive to the true dimensions of viral transmission, and thus alter the calculation of vaccine effectiveness [35].

However, because in some countries, such as Spain, general practitioners (GP) are the gateway for all patients to the system, and each person is assigned a GP, based on a geographical population [36], the data of COVID-19 cases in the GP consultation level (with tests done at home or in health services) would be an acceptable indicator [37,38]. In any case, probably a certain number of cases of symptoms of viral infections in the community did not have diagnostic tests performed, and those that were performed were more likely in at-risk and/or vulnerable patients. Therefore, it can be thought that the number of reinfections was possibly underestimated.

Another element to take into account in our study is that cases of reinfection and not serious cases or hospitalizations were used as the final result. So we talk about vaccine effectiveness in preventing cases of reinfection and not preventing serious cases of reinfection. The difference is important.

Comparison with other studies

The additional efficacy of a booster dose (third, fourth, or fifth dose) has been estimated at 69% in the first two months after the injection, which then decreases to 55% between the second and fourth month, 30% between the fourth and sixth and only 22% at the sixth month. Protection increases with bivalent vaccines, but of course, also declines over time [39].

To date, there are few studies evaluating the effectiveness of vaccination to prevent reinfections. Often, studies of COVID-19 reinfections do not evaluate the effectiveness of the vaccine [40]. Among the available data, one study reported that vaccination, particularly a booster dose, modestly decreased the probability of reinfection in a case-control analysis [20]. In another study, a meta-analysis of 91 published studies, showed that vaccination decreased the risk of reinfection, although the vaccines were less effective in preventing reinfections against the Omicron variants [41].

However, the number of reinfections is likely underestimated because not all people infected with SARS-CoV-2 become sick enough to be tested. Since reinfection usually results in somewhat milder symptoms, it is even more difficult to fully assess the true count [21]. For those who had a previous infection, vaccination often adds greater protection against reinfections that lead to hospitalizations [17].

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Study limitations and strengths

1. Temporal information between vaccination and COVID-19 infection events is missing. To calculate the 4th dose vaccine effectiveness, a formal survival analysis model was not carried out with a measurement of the time from vaccination with the fourth dose until the result. Relative risk was used, but this measure does not take into account the duration of vaccination until the outcome under study occurs.

2. The number of cases was small and this may lead to an imprecise determination of vaccine effectiveness.

3. Non-randomized design is a limitation for the generalization of the results, although by including all cases that were consulted with the GP and taking into account the structure of the health system, the vast majority of cases were probably included.

4. May have been overlooked asymptomatic cases that did not attend GP consultation, as no surveillance or systematic screening was done.

5. 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 vaccine effectiveness in small geographical bases.

Conclusion

In the context of general medicine in Toledo (Spain), from October 1, 2022, to October 1, 2023, a period where the omicron variant was the dominant one in Spain, 4th dose of bivalent mRNA vaccine effectiveness to prevent reinfections were moderate-low, both calculated on the total number of cases of reinfections in vaccinated and unvaccinated (30%) and calculated on population denominators of the total number of vaccinated or unvaccinated people (46%). However, these modest results should be interpreted with caution. Firstly, because of the few cases included; and secondly, the possible underreporting of cases, which may lead to an imprecise determination of vaccine effectiveness. It should be noted that our study did not assess hospitalization outcomes, and consequently, at the current time, it is reasonable to maintain booster doses of the COVID-19 vaccine in the vulnerable population.

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