

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 of Toledo (Spain)

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Abstract

Background: *The effectiveness of administering booster or additional doses with vaccines adapted to new variants and subvariants is still a matter of debate.*

Objective: *To compare the cases of covid-19 in vaccinated 4th dose people with bivalent mRNA vaccines vs. cases of covid-19 in not vaccinated 4th dose people and assess the clinical-epidemiological differences and the relative effectiveness of this vaccine booster.*

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

Results: *21 covid-19 infections in vaccinated people with 4th dose and 55 without 4th dose were included. The cases of covid-19 in vaccinated people with 4th dose differed in a statistically significant way compared to the cases of covid-19 in people without 4th dose in that they were older (67% vs. 13% \geq 65 years); they had more chronic diseases (86% vs. 54%), being according to disease groups only significant in Genitourinary (8% vs. 21%); and presented fewer covid-19 symptoms of ENT (15% vs. 30%). The 4th dose vaccine effectiveness, calculated as: $1 - [\text{Covid-19 cases incidence with 4th vaccine dose} / \text{Covid-19 cases incidence without 4th vaccine dose}] \times 100$, was 60%.*

Conclusion: *In the context of general medicine in Toledo (Spain), there is a risk profile and a 4th dose vaccine effectiveness that together suggests that it is reasonable to maintain booster doses of the vaccine against covid-19 in the vulnerable population.*

Keywords: COVID-19; SARS-CoV-2; Vaccine Effectiveness; Breakthrough Infection; Hybrid Immunity; Epidemiology; General Practice.

Introduction

Four years after the start of the coronavirus disease 2019 (covid-19) pandemic, the nature and durability of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain unclear. Of course, the arrival of vaccines has dramatically changed the natural history of covid-19 infection. It is important to recognize that we are objectively in a better place regarding the virus than ever before; It is now recognized that Covid-19 is an endemic viral infection and will be with us for generations (Loewy, 2022, El-Sadr et al., 2023, Turabian, 2023). But, current mRNA Covid-19 vaccines have been shown to provide minimal protection against infection with XBB variants, although substantial protection against severe disease. However, that protection appears to decline rapidly (Lasrado & Barouch, 2023).

The emergence of immune escape variants of SARS-CoV-2 (Callaway, 2022) justifies the use of sequence-adapted vaccines to provide protection against covid-19. The new variants are more contagious, but remain in the upper respiratory tract and generally produce mild symptoms similar to the common cold, except in frail patients who are immunocompromised. In addition, there is a high level of population hybrid immunity (Lasrado & Barouch, 2023; Willyard, 2023, Bassetti & Mussini, 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. The FDA authorizations were based on nonclinical data for these two bivalent vaccines, safety and immunogenicity data for bivalent vaccines containing mRNA from the BA.1 lineage of the omicron variant, and safety and efficacy data for the COVID-19 vaccines of monovalent mRNA. 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 (Offit, 2023; Lin, 2023; Wang, 2023). However, some experts questioned the bivalent vaccine strategy given the apparent “immune imprinting,” where the immune system recognizes antigens from previous exposures more robustly than new antigens (Lasrado & Barouch, 2023). Thus, questions remain about the level of protection they confer when applied as reinforcement (Loewy, 2022) and their effectiveness will be resolved in real life (Wang, 2023; Loewy, 2022; Chalkias et al., 2022; Loewy, 2022; El Sahly et al., 2022; Winokur, 2023; Collier, 2023).

In this complex and changing scenario, epidemiological surveillance must be reinforced and new immunity studies must be promoted in the entire population to evaluate the impact on public health of the bivalent vaccine against covid-19 (Javierre Miranda et al., 2022; Hansen et al., 2023). It will be really interesting to see whether these specific vaccines make a big difference or not. All major vaccines currently in use target the spike, which is susceptible to frequent mutations (Looi & Mahase, 2022). Its in vitro performance is excellent; but its effectiveness in the real world awaits more data (Grewal et al., 2022; Glück, 2022; Jiménez, 2022; Ledford, 2022). Current covid-19 vaccines still prevent the most serious outcomes, but if the goal is to stop infections, updated vaccines may have little impact (Vogel, 2022).

But also, on the other hand, now it is not known how the virus is circulating because nasal swabs are not done. Since the disappearance of the health alarm in many countries, cases of covid-19 are not counted, and tests are carried out in health services only in certain situations, such as in people over 60 years of age, pregnant women, hospitalized patients, and health personnel, so people with symptoms in the community, who do not meet these criteria, frequently choose to take a private test at home. In this scenario, the official figures imply significant under-reporting and the incidence of covid-19 and its evolution over time in the community are truly unknown. However, frequently people with a positive test at home do communicate this circumstance to their general practitioner (GP) to seek treatment and/or sick leave. In this way, general medicine consultation can be an ideal place to monitor the real evolution of covid-19 cases (Turabian, 2022; Turabian, 2023; Turabian, 2023). Additionally, it has been postulated that hospitalization or death in patients with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (PCR) test may not be a sufficiently specific marker to monitor vaccine effectiveness (El Sahly et al., 2022).

In this context, we present a study to try to clarify the differences between cases of covid-19 in vaccinated 4th dose people with bivalent mRNA vaccines of the Comirnaty and Spikevax vaccines vs. cases of covid-19 in not vaccinated 4th dose people and assess their relative vaccine effectiveness, in a population of a general medicine outpatient clinic.

Material and Methods

An observational, longitudinal and prospective study of covid-19 infections 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, 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 methodology of the study and partial results for a shorter follow-up time in the same population cohort of the present study, have already been published (Turabian, 2023; Turabian, 2023; Turabian, 2023; Turabian, 2023). Some aspects of its methodology are repeated here to facilitate the understanding of the present study.

Objectives of the Study

1. To evaluate the 4th dose covid-19 vaccine effectiveness.
2. To compare the cases of covid-19 infections in vaccinated people with 4th dose de covid-19 vaccine vs. without 4th dose de covid-19 vaccine.

Booster dose for autumn-winter 2022

In the patients included in the study, bivalent Comirnaty, Original/Omicron BA.1 and bivalent Comirnaty, Original/Omicron BA.4-5 (Consejo interterritorial de salud, 2022), or bivalent Spikevax, Original/Omicron BA.1 and Spikevax bivalent, original/omicron BA.4-5 were used as a booster dose (4th dose) (Jiménez, 2022; Consejo interterritorial de salud, 2023). Throughout the months of September and October 2022, four vaccines adapted to the new circulating omicron variants were authorized in the European Union. These adapted vaccines are bivalent mRNA vaccines against the original strain and the BA.1 variant and against the original strain and the BA.4/BA.5 variant of the Comirnaty and Spikevax vaccines. The booster vaccination campaign for covid-19 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 hospitalized in nursing homes and other disability centers and those with risk conditions, as well as the staff of health centers, services and establishments. Vaccination was prioritized in nursing homes and other disability care centers and the population aged 80 and over (Consejo Interterritorial, 2022; ATLAS ESPAÑA, 2022; European Medicines Agency, 2022).

Diagnosis of Covid-19

The diagnosis was performed with PCR oropharyngeal swab tests or antigen testing (Ministerio de Sanidad, 2021) performed in health services or at home.

Calculation of vaccine effectiveness

We calculated the vaccine effectiveness as a percentage, as follows:

- $1 - [\text{Cases with cuarta dosis covid-19 vaccine} / \text{Cases without cuarta dosis covid-19 vaccine}] \times 100$ (Ministerio de Sanidad, 2021; Martínez-Baz, et al., 2021; Snijders et al., 2012; de Gier et al., 2021).

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” (Strauss, 1984) and symptoms covid-19 infection, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (World Health Organization (WHO), 2019)
- Social-occupancy class (according to the Registrar General’s classification of occupations and social status code) (Royal Collage of General Practitioners, 1986; Donaldson & Donaldson, 1983)
- 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) (Turabian, 2017; Russell, 2020; Watts & Shrader, 1988; McIlvain et al., 1998)
- Ethnic minority (defined as a “human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group”) (Diccionario panhispánico del español jurídico, 2022)
- 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.) (Mao et al., 2020); to simplify comparison, moderate and severe cases were counted together; date of covid-19 infection diagnosis; vaccination status against covid-19 at the date of acute infection; date of reinfection.

- Presence of reinfection (SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection) (Ayoub et al., 2022; Slezak et al., 2021; Altarawneh et al., 2022)
- Vaccination status against covid-19 at the date of acute infection: vaccinated with 4th dose (second booster) for fall-winter 2022 (Consejo Interterritorial, 2022)

Sample Size

All patients who met the criteria for covid-19 infection 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, and the Student test for the mean.

Results

From October 2022 to October 2023, 21 covid-19 infections in vaccinated people with 4th dose and 55 without 4th dose were included. The cases of covid-19 in vaccinated people with 4th dose differed in a statistically significant way with respect to the cases of covid-19 in people without 4th dose in that they were older (67% vs. 13% ≥ 65 years; $X^2 = 22.1119$, $p < 0.00001$; and 0% vs. 47% < 45 years; Fisher exact test = 0); they had more chronic diseases 86% vs. 54%; $X^2 = 6.3451$, $p = .011771$), being according to WHO, ICD-10 groups only significant in Genitourinary (8% v, 21%; $X^2 = 4.6772$, $p = .030565$); and presented fewer symptoms of ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistaxis, ear pain) (15% vs. 30%; $X^2 = 5.5514$, $p = .018466$) (TABLE 1, TABLE 2, TABLE 3). The 4th dose vaccine effectiveness, calculated as: $1 - [\text{Covid-19 cases incidence with 4th dose vaccine} / \text{Covid-19 cases incidence without 4th vaccine dose}] \times 100$, was 60% (TABLE 4).

VARIABLES	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4 TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 21	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4 TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 55	STATISTICAL SIGNIFICANCE
> = 65 years	14 (67)	7 (13)	X2= 22.1119. p= < 0.00001. Significant at p < .05.
= < 45 years	0	26 (47)	The Fisher exact test= 0. The result is significant at p < .05.
Women	13 (62)	35 (64)	X2= 0.0196. p= .888706. NS
Social-occupancy class of patients (people with some type of labor specialization)	7 (33)	24 (44)	X2= 0.668. p= .413763. NS
Socio-Health Care Workers	5 (24)	8 (14)	X2 with Yates correction= 0.3825. p= .536262. NS
Moderate-severe severity of primary infection	2 (9) (hipoxia, neumonía)	0	Fisher exact test= 0.0737. NS
Chronic diseases	18 (86)	30 (54)	X2= 6.3451. p= .011771. Significant at p < .05.
Complex family/ Problems in the family context	2 (9)	3 (5)	Fisher exact test= 0.6123. NS
Low income household	0	1 (2)	Fisher exact test = 1. NS
Ethnic minority	0	2 (4)	Fisher exact test = 1. NS
Reinfection	5 (24)	7 (13)	Fisher exact test= 0.1046. NS

Table 1: Comparison of Variables 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

SYMPTOMS COVID-19 INFECTION* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4 TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 21	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4 TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 55	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, artralgias)	30 (42)	65 (36)	X2= 0.6257. p= .428952. NS
Respiratory (cough, dyspnea, chest pain)	22 (31)	47 (26)	X2= 0.476. p= .49025. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistaxis, ear pain)	11 (15)	53 (30)	X2= 5.5514. p= .018466. Significant at p < .05.
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	1 (1)	5 (2)	Fisher exact test= 0.6767. NS
Neurological (headache, dizziness, mental confusion -brain fog, disartria, desorientación, photopsia, syncope and collapse)	7 (10) (síncope, cefalea, disartria, desorientación)	7 (4)	X2 with Yates correction= 2.2818. NS
Psychiatric (Anxiety, insomnia)	0	1 (1)	Fisher exact test = 1. NS

Skin (chilblains, flictenas, rash)	0	0	Fisher exact test = 1. NS
Urológico (disuria, polaquiuria)	1 (1)	1 (1)	Fisher exact test= 0.4946. NS
Total symptoms*	72 (100)	179 (100)	-

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

Table 2: Comparison Of Symptoms 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 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 21	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4TH DOSE FROM OCTOBER 2022 TO OCTOBER 2023 N= 55	S T A T I S T I C A L SIGNIFICANCE
-I Infectious	0	1 (1)	Fisher exact test= 1. NS
-II Neoplasms	2 (3)	2 (2)	Fisher exact test= 1. NS
-III Diseases of the blood	3 (4)	0	Fisher exact test= 0.0903.
-IV Endocrine	14 (20)	14 (16)	X2= 0.3139. p= .575278. NS
-V M/ental	9 (13)	6 (7)	X2= 1.4619. p= .226626. NS
-VI-VIII Nervous and Senses	5 (7)	8 (10)	X2= 0.2616. p= .609041. NS
-IX Circulatory system	16 (22)	14 (16)	X2= 0.9848. p= .321019. NS
-X Respiratory system	2 (3)	4 (5)	Fisher exact test= 0.6902. NS
-XI Digestive system	7 (10)	15 (18)	X2= 1.8559. p= .173102. NS
-XII Diseases of the skin	2 (3)	1 (1)	Fisher exact test= 0.5899. NS
-XIII Musculo-skeletal	5 (7)	3 (3)	X2 with Yates correction= 0.4138. p= .520059. NS
-XIV Genitourinary	6 (8)	18 (21)	X2= 4.6772. p= .030565. Significant at p < .05.
TOTAL chronic diseases*	71 (100)	86 (100)	-

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

(): 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

Cases with 4th dose vaccine covid-19	GROSS INCIDENCE RATE	Cases without 4 ^a dose vaccine covid-19	GROSS INCIDENCE RATE
21/76	30%	55/76	70%

4th vaccine covid-19 effectiveness = 1 - [Covid-19 cases incidence with 4^o dose vaccine / Covid-19 cases incidence without 4^a dose vaccine] × 100 = 60%

Table 4: 4th DOSIS VACCINE EFFECTIVENESS

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