Effectiveness of the Fourth Dose: Clinical-Epidemiological Comparison between Covid-19 Infections in Vaccinated People with and without 4th Dose of Vaccines Bivalent mRNA in the Period from October 2022 to February 2023

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ABSTRACT

Background: The effectiveness of the 4th dose of mRNA covid-19 vaccine is not clearly known.

Objective: To compare the cases of covid-19 in vaccinated 4th dose people with bivalent mRNA vaccines from Comirnaty and Spikevax vaccines vs. cases of covid-19 in not vaccinated 4th dose people and assess their relative effectiveness.

Methodology: An observational, longitudinal, and prospective case series study of adult patients with covid-19 infections in general medicine from October 1, 2022, to February 28, 2023

Results: Five cases of covid-19 infections in vaccinated people with 4th dose (3 from COMIRNATY BIVALENTE and 2 from SPIKEVAX BIVALENTE) and 31 cases of covid-19 infections in vaccinated people without 4th dose were included. The cases with the 4th dose had a higher mean age (65.6 +- 22.42 vs. 48.41 +- 14.29; t-value= 2.30361), more Endocrine chronic diseases (32% vs. 8%; Fisher exact test= 0.0276) and less Digestive (4% vs. 24%; X2= 3.9082. p= .048052). In both groups General symptoms prevailed followed by ENT. There were no statistically significant differences between those vaccinated and not vaccinated with the 4th dose for the rest of the variables, but the cases with the 4th dose had more chronic diseases (80% vs. 45%), more Circulatory system chronic diseases (32% vs. 14 %) and diseases of the blood (9% vs 0%), and less Respiratory system chronic diseases (0% vs. 8%), and Genitourinary (4% vs. 16%). 4th dose vaccine covid-19 effectiveness (calculated as 1 - [Covid-19 cases with 4th vaccine dose / Covid-19 cases without 4th vaccine dose] × 100) was 84%.

Conclusion: In the general practice setting in Toledo, Spain, from October 1, 2022, to February 28, 2023, the effectiveness of the 4th dose of mRNA bivalent vaccine against covid-19 was high.

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

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Introduction

The current moment in the coronavirus disease 2019 (covid-19) pandemic is fundamental. At present covid-19 is an endemic viral infection and it is urgent to face a future in which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will remain with us throughout the generations.[1,2] The emergence of a collection of immune escape variants of SARS-CoV-2[3] justifies the use of sequence-adapted vaccines to provide protection against covid-19. Thus, it is convenient to update the vaccine against the latest variants. In the fall of 2022, the infection in the world was caused by the omicron variant of which there are several subtypes: BA1; BA1,1; BA2; BA3; BA4, and BA5.[4,5]

Given the ability to use messenger ribonucleic acid (mRNA) technology to rapidly respond to variant strains, bivalent vaccines have been created to counter this new threat. In January and February 2022, Pfizer-BioNTech produced a bivalent vaccine containing 15 µg of mRNA directed against the ancestral strain of SARS-CoV-2 and 15 µg directed against BA.1. Moderna used 25 µg of mRNA directed against each of the same two strains. They were subsequently adapted against BA.4 and BA.5.[6] On August 31, 2022, the Food and Drug Administration (FDA) authorized Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccines. As of September 1, 2022, 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.[7,8] Therefore, omicron-adapted mRNA vaccines are the protagonists of this new booster campaign, which promise a greater immunogenic response, although their additive serological and clinical value remains to be demonstrated.[8-10]

In this scenario, it is accepted that the effectiveness of the vaccine against infection decreases rapidly, while against severe disease it lasts longer.[11] On the other hand, the most vulnerable groups (immunosenescent, immunosuppressed) who have limited protection over time, whether derived from vaccination or natural infection, are the ones that have benefited the most from vaccination and those who should receive new booster doses. For the rest of the population, studies are lacking, especially with regard to cellular immunity and the duration of immunity.[12]

Thus, therefore, in such a changing situation, questions remain about the level of protection conferred by bivalent vaccines when applied as a booster. Consequently, epidemiological surveillance should be strengthened and immunity studies promoted in the entire population, to find out its effectiveness in real life, and how serological data translate into clinical results, both with respect to the prevention of the most serious outcomes, as well as in elderly and other high-risk groups, and regard to infections in general.[13-24] In addition, it must be taken into account that 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 specific enough marker to monitor vaccine effectiveness.[11]

In this context, we present a study to try to clarify the clinical-epidemiological differences between cases of covid-19 in vaccinated with 4th dose people with bivalent mRNA vaccines from Comirnaty and Spikevax 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 breakthrough infections in vaccinated people with the 4th dose vaccine was conducted 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). 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.

Objective of the study

A. To evaluate the 4th dose of Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccine effectiveness (4VE).

B. To compare the clinical-epidemiological data of cases of covid-19 infections in vaccinated people with 4th dose of Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccines vs. without 4th dose of covid-19 vaccine.

Booster dose for fall-winter 2022

In the patients included in the study, bivalent Comirnaty, Original/Omicron BA.1 and bivalent Comirnaty, Original/Omicron BA.4-5 (25) or bivalent Spikevax, Original/Omicron BA. 1 and bivalent Spikevax, original/omicron BA.4-5, were used as a booster dose (4th dose).[21,26]

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 were bivalent mRNA vaccines against the parent strain and BA.1 variant and against the parent strain and BA.4/BA.5 variant of the Comirnaty and Spikevax vaccines. The covid-19 booster 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 hospitalized in residences for the elderly and other centers for disabilities and those with risk conditions, as well as the personnel of the centers, services, and health establishments. Priority was given to vaccination in nursing homes and other care centers for the disabled and the population aged 80 and over.[21,27-29]

Diagnosis of Covid-19

The diagnosis was performed with PCR) oropharyngeal swab tests or antigen testing. Asymptomatic confirmed case with active infection was considered to be any person with a clinical picture of sudden onset acute respiratory infection of any severity that occurs, among others, with fever, cough, or feeling of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain, or headache, among others, were also considered symptoms of suspected SARS-CoV-2 infection according to clinical criteria; and a positive PCR or rapid antigen test positive.[30] Previous SARS-CoV-2 infection was defined as a positive result in the PCR assay or antigen test at least 90 days before a new positive result.[31]

Calculation of vaccine effectiveness

We calculated the 4VE, which was estimated as a percentage, as follows:[32-34] 1 - [Covid-19 cases with 4th vaccine dose / Covid-19 cases without 4th vaccine dose] × 100)

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"[35] and symptoms covid-19 infection, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019.[36]
- Social-occupancy class (according to the Registrar General's classification of occupations and social status code).[37]
- If they were Health Care Workers.
- Problems in the family context and low income household based on the genogram. It was understood that "complex" genograms present families with psychosocial problems).
- Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group").[40]
- 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 ≤ 93% with room air at rest, arterial partial pressure of oxygen / oxygen concentration ≤ 300 mmHg.) (41); 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 or reinfection.

Sample size

All patients who met the criteria for covid-19 infection from October 1, 2022, to February 28, 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 of the expected cell totals) for percentages, and the Student test for the mean.

Results

From October 1, 2022, to February 28, 2023, 5 cases of covid-19 infections in vaccinated people with 4th dose were included (3 from COMIRNATY BIVALENTE and 2 from SPIKEVAX BIVALENTE) and 31 cases of covid-19 infections in vaccinated people without 4th dose. The cases with the 4th dose had a higher mean age (65.6 +- 22.42 vs. 48.41 +- 14.29; t-value= 2.30361. p= .013743), more Endocrine chronic diseases (32% vs. 8%; Fisher exact test= 0.0276) and less Digestive chronic diseases (4% vs. 24%; X2= 3.9082. p= .048052).

In both groups, General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) prevailed, followed by ENT (Anosmia/ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistasis, ear pain).

There were no statistically significant differences between those vaccinated and not vaccinated with the 4th dose for the rest of the variables, but the cases with the 4th dose had more chronic diseases (80% vs. 45%), more Circulatory system chronic diseases (32% vs. 14 %) and diseases of the Blood (9% vs 0%), and less of Respiratory system (0% vs. 8%) and of Genitourinary chronic diseases (4% vs. 16%).

In the group without the 4th dose of mRNA covid-19 vaccine, the doses received were: 1 (3%) with a single dose, 4 (13%) with 2 doses, and 26 (84%) with 3 doses. 59% of covid-19 infections occurred in 2022 (**Table 1, Table 2, Table 3**).

The 4VE (calculated as 1 - [Covid-19 cases with 4th dose vaccine / Covid-19 cases without 4th dose vaccine] × 100) was 84%.

VARIABLES	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4TH DOSE N=31	STATISTICAL SIGNIFICANCE
Mean age (Arithmetic mean +- Standard deviation; Range)	65.6 +- 22.42 (38-95)	48.41 +- 14.29 (13-74)	t-value= 2.30361. p= .013743. Significant at p < .05.
> = 65 years	2 (40)	5 (16)	Fisher exact test= 0.244. NS
= < 45 years	0	13 (42)	Fisher exact test= 0.1363. NS
Women	3 (60)	22 (71)	Fisher exact = 0.6309. NS
Social-occupancy class of patients (people with some type of labor specialization)	2 (40)	15 (48)	Fisher exact test= 1. NS
Health Care Workers	2 (40)	4 (13)	Fisher exact test=

			0.1858. NS
Moderate-severe severity of primary infection	0	0	Fisher exact test= 1. NS
Chronic diseases	4 (80)	14 (45)	Fisher exact test= 0.3377. NS
Complex family/ Problems in the family context	0	1 (3)	Fisher exact test= 1. NS
Low income household	0	1 (3)	Fisher exact test= 1. NS
Ethnic minority	0	2 (6)	Fisher exact test= 1. NS
Asymptomatic	0	2 (6)	Fisher exact test= 1. NS
Vaccinated only 1 dose	0	1 (3)	NR
Vaccinated only 2 dose	0	4 (13)	NR
Vaccinated only 3 dose	0	26 (84)	NR
Vaccinated 4 dose	5 (100)	0	NR
Infection in 2022	3 (60)	18 (59)	NR
Infection in 2023	2 (40)	13 (42)	NR
Reinfection	1 (20)	7 (23)	Fisher exact test= 1. NS

( ): Denotes percentages; NS: Not significant; NR: Not relevant.

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 February 2023

SYMPTOMS COVID-19 INFECTION* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4TH DOSE N=31	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, artralgias)	9 (41)	35 (35)	X2= 0.2731. p= .601279. NS
Respiratory (cough, dyspnea, chest pain)	6 (27)	25 (25)	X2= 0.0491. p= .824559. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis, ear pain)	6 (27)	30 (30)	X= 0.0645. p= .799547. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	0	2 (2)	Fisher exact test= 1. NS
Neurological (headache, dizziness, mental confusion -brain fog, photopsia, syncope and collapse)	1 (4)	8 (8)	Fisher exact test= 1. NS
Psychiatric (Anxiety, insomnia)	0	0	Fisher exact test= 1. NS

Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Total symptoms*	22 (100)	100 (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 February 2023

CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE N=5	COVID-19 INFECTIONS IN PEOPLE WITHOUT 4TH DOSE N=31	STATISTICAL SIGNIFICANCE
-I Infectious	0	0	Fisher exact test= 1. NS
-II Neoplasms	0	1	Fisher exact test= 1. NS
-III Diseases of the blood	2 (9)	0	Fisher exact test= 0.0904. NS
-IV Endocrine	7 (32)	4 (8)	Fisher exact test= 0.0276. Significant at p < .05.
-V Mental	2 (9)	4 (8)	Fisher exact test= 1. NS
-VI-VIII Nervous and Senses	0	6 (12)	Fisher exact test= 0.168
-IX Circulatory system	7 (32)	7 (14)	X2 with Yates correction= 2.0636. p= .150854. NS
-X Respiratory system	0	4 (8)	Fisher exact test= 0.3058. NS
-XI Digestive system	1 (4)	12 (24)	X2= 3.9082. p= .048052. Significant at p < .05.
-XII Diseases of the skin	0	1 (2)	Fisher exact test= 1. NS
-XIII Musculo-skeletal	2 (9)	3 (6)	Fisher exact test= 0.6379. NS
-XIV Genitourinary	1 (4)	8 (16)	Fisher exact test= 0.2593. NS
TOTAL chronic diseases*	22 (100)	50 (100)	---

( ): 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.

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 February 2023.

Discussion

1. Main findings

The main results of our study were that cases with 4th dose had:

1) Higher average age (which is normal, since older people received this dose as a priority on the dates of the study).

2) More chronic diseases (which is logical, since older people who consequently have more chronic diseases were vaccinated with that dose), significantly more Endocrine and less Digestive.

3) In both groups general symptoms predominated followed by those of ENT.

4. Finally, the 4VE was high (84%).

To correctly assess these findings, two important aspects must be taken into account. On the one hand, the small number of cases included in our study may mask statistical significance between differences that by common sense turn out to be important. And on the other hand, we must remember that 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.[42] And, 4th dose of the covid-19 vaccine began to be given to the elderly and social-health workers.[21,27,28] This meant in practice that in many cases of symptoms of viral infections in the community, no diagnostic tests were carried out and that those that were carried out were more likely in older patients.

Therefore, it can be thought that 1) there were more covid-19 cases in both groups; 2) the cases of covid-19 in older people are probably closer to reality than the cases in young people who had not received 4th dose (and thus, the number of cases in the group of patients without 4th dose, who are younger, it will be underrepresented). All this indicates that 4VE was underestimated in our study (the numerator will be almost correct, but the denominator will be really higher), so the 4VE will really be > 84%.

On the other hand, our results must be related to variants that were circulating in Spain at the time of the study. From January 2022 to October 2022, the omicron variant predominated.[43-45] According to the weekly report, published on December 12, 2022, on the update of variants by sequencing of random samples in week 47 of 2022 (21 to 27 November), the omicron percentage stood at 100%. Lineages BQ.1 and its derivatives of it, including BQ.1.1 accounted for 78.4%. The BA.4 and BA.5 lineages ranged from 87% to 96.3% and for the BA.2 lineage, from 0% to 39.9%.[27]

In this regard, the severity of disease associated with alpha, gamma, and delta variants has been reported to be comparable, whereas Omicron infections are significantly less severe. But, breakthrough disease is significantly more common in patients with Omicron infection.[46,47]

2. Comparison with other studies

Bivalent omicron BA.1 vaccines when administered as a fourth dose have been reported to induce substantial neutralizing responses against ancestral strains and omicron BA.1 and, to a lesser extent, they neutralized BA.4, BA.5, and BA.2.75 strains. Among adults 55 years and older who had previously received three 30 μg doses of BNT162b2, the increase in immunogenicity against omicron BA.1 was substantially greater with the omicron BA.1-adapted BNT162b2 vaccines than with the original 30 μg dose from BNT162b2.[9]

Likewise, serological data show a general neutralization benefit with bivalent booster immunizations, revealing a strong immune response against BA.1 and the parent virus, as well as a good immune response against other omicron subvariants BA.4 and BA.5.[48,49] In addition, it is accepted that the bivalent vaccine quadruples the antibodies against BA.4 and BA.5 omicron subvariants in people over 55.[50] The additional efficacy of a booster dose (third, fourth, or fifth dose) has been estimated at 69% in the first two months after injection. Protection increases with bivalent vaccines, but it also

declines over time and more rapidly in those over 80 years of age.[51]

In a US Centers for Disease Control and Prevention (CDC) study conducted between October 3 and December 24, 2022, during the dominance of omicron subvariants BA.2, BA.4, and BA.5., people who received bivalent covid-19 booster at the end of 2022 were 3 times less likely to die from the disease than people who only received the original monovalent vaccines, although the protection begins to be lost after two months.[52] In another CDC study between December 1, 2022 and January 13, 2023, the bivalent vaccine protected against XBB.1.5 infection, halving the risk of symptomatic XBB.1 infection.[53]

The BA.4-BA.5 bivalent vaccine has been reported to elicit higher neutralizing responses against the BA.5-derived sublines (BA.4.6, BQ.1.1, and XBB.1) and the BA.2-derived subline (BA .2.75 .2) than the parent vaccine when given as 4th dose.[54] Up to 70 days after its application, the bivalent or omicron-adapted booster of the Pfizer/BioNTech vaccine reduced hospitalizations by 81% and mortality by 86% in patients older than 65 years.[55] The effectiveness of a bivalent booster dose of mRNA vaccines against severe infection with omicron BA.4.6, BA.5, BQ.1, and BQ.1.1 that caused hospitalization, has been published was 58.7%. Estimates of vaccine efficacy were similar for the Moderna and Pfizer-BioNTech boosters.[7] Vaccine efficacy increased in most groups after a 4th dose in which this booster was recommended.[16] In short, studies of the 4VE in real life leave no doubt, in selected patients that it is still necessary to continue with boosters.[56] Our results also go in this direction.

Study limitations

1. Infections were not genetically sequenced.
2. The number of cases was small and may be "minimal" figures due to underreporting. So the statistical significance of some variables could be hidden, and an imprecise determination of vaccine effectiveness may be obtained.

Conclusion

In the general practice setting in Toledo, Spain, from October 1, 2022 to February 28, 2023, effectiveness of the 4th dose of mRNA bivalent vaccine against covid-19 was high, probably >87%. Consequently, it can be said that bivalent boosting with mRNA vaccines achieved substantial additional protection against infection. However, the number of cases was small, and they may be "minimal" figures due to underreporting. So an imprecise determination of vaccine effectiveness may be obtained. Despite these limitations, and in the absence of further data, our results suggest that it is reasonable to recommend a second booster dose (fourth dose) for the population at higher risk."

References

1. Loewy MA (2022) [COVID-19: the weekly summary (October 28 to November 3, 2022)]. Medscape; 4 de nov. https://espanol.medscape.com/verarticulo/5909930?src=mkm_ret_221106_mscpmrk-ES_ExcNews&uac=327178AR&impID=4824850&faf=1
2. El-Sadr WM, Vasan A, El-Mohandes A (2023) Facing the New Covid-19 Reality. N Engl J Med; 388: 385-7. doi: https://doi.org/10.1056/NEJMp2213920
3. Callaway E (2022) COVID 'variant soup' is making winter surges hard to predict Descendants of Omicron are proliferating worldwide — and the same mutations are coming up again and again. Nature; 611: 213-4. https://doi.org/10.1038/d41586-022-03445-6
4. Willyard C (2023) How quickly does COVID immunity fade? What scientists know. Vaccination, infection with SARS-CoV-2 and a combination of both provide varying degrees of protection. Nature; 02 February. https://doi.org/10.1038/d41586-023-00124-y
5. de Francisco ALM (2022) [Autumn 2022: bivalent Covid vaccine]. In: Lorenzo V,

López Gómez JM (Eds). Nefrología al día. https://www.nefrologiaaldia.org/507

6. Offit PA (2023) Bivalent Covid-19 Vaccines — A Cautionary Tale. N Engl J Med 2023; 388: 481-3. doi: https://doi.org/10.1056/NEJMp2215780
7. Lin DY, Xu Y, Gu Y, et al. (2023) Effectiveness of Bivalent Boosters against Severe Omicron Infection. N Engl J Med; 388: 764-6. doi: https://doi.org/10.1056/nejmc2215471
8. Wang Q, Bowen A, Valdez R, et al. (2023) Antibody Response to Omicron BA.4–BA.5 Bivalent Booster. N Engl J Med; 388: 567-9. doi: https://doi.org/10.1056/nejmc2213907
9. Winokur P, Gayed J, Fitz-Patrick D, et al. (2023) Bivalent Omicron BA.1–Adapted BNT162b2 Booster in Adults Older than 55 Years. N Engl J Med; 388:214-27. doi: https://doi.org/10.1056/NEJMoa2213082
10. Collier AY, Miller J, Hachmann NP, et al. (2023) Immunogenicity of BA.5 bivalent mRNA vaccine boosters. N Engl J Med; 388:565-7. doi: https://doi.org/10.1056/NEJMc2213948
11. El Sahly H, Glück T, Sakoulas G (2022) Vaccine Effectiveness Against SARS-CoV-2 Variants, Revisited. NEJM Journal Watch; November 2. https://www.jwatch.org/na55378/2022/11/02/vaccine-effectiveness-against-sars-cov-2-variants
12. Javierre Miranda AP, Aldaz Herce P, Gómez Marco JJ (2022) Is the fourth dose justified for SARS-CoV-2? Between necessity and evidence. Aten Primaria; 54(12). doi: https://doi.org/10.1016/j.aprim.2022.102517
13. Loewy MA (2022) [COVID-19: the weekly summary (October 21-27, 2022)]. Medscape; 28 de oct. https://espanol.medscape.com/verarticulo/5909892?src=mkm_ret_221030_mscpmrk-ES_ExcNews&uac=327178AR&impID=4798361&faf=1#vp%E2%82%82
14. Hansen CH, Friis NU, Bager P, et al. (2023) Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark. Lancet Infect Dis; 23(2): 167-76. doi: https://doi.org/10.1016/S1473-3099(22)00595-3
15. Looi M, Mahase E (2022) What next for covid-19 vaccines? BMJ; 379: o2422. doi: https://doi.org/10.1136/bmj.o2422
16. Ferdinands J M, Rao S, Dixon BE, et al. (2022) Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study. BMJ: 379: e072141. doi: https://doi.org/10.1136/bmj-2022-072141
17. Chalkias S, Harper C, Vrbick k, et al. (2022) A bivalent Omicron-containing booster vaccine against Covid-19. N Engl J Med; 387:1279-91. doi: https://www.nejm.org/doi/10.1056/NEJMoa2208343
18. Loewy MA (2022) [COVID-19: the weekly summary (September 16-22, 2022)]. Medscape; 23 de sep. https://espanol.medscape.com/verarticulo/5909741?src=mkm_ret_220925_mscpmrk-ES_ExcNews&uac=327178AR&impID=4668857&faf=1#vp%E2%82%82
19. Grewal R, Kitchen SA, Nguyen L, et al. (2022) Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: test negative design study. BMJ; 378: e071502. doi: https://doi.org/10.1136/bmj-2022-071502
20. Glück T (2022) Effectiveness of a Fourth Dose of COVID-19 mRNA Vaccine in Older Long-Term Care Residents: More

Evidence. Reviewing Grewal R et al. BMJ; 2022 Jul 6. Journal Wach. https://www.jwatch.org/na55131/2022/07/14/effectiveness-fourth-dose-covid-19-mrna-vaccine-older-long?query=topic_respinf&jwd=000012293400&jspc=GP&cid=DM1261776_Non_Subscriber&bid=1072010000

21. Jiménez AL (2022) [Portfolio of omicron-adapted vaccines expands: how does each one work? The EMA has already recommended the authorization of the vaccines against Covid-19 adapted from Comirnaty Original/Omicron BA.1, Spikevax bivalent Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5]. ConSalud.es. https://www.consalud.es/pacientes/especial-coronavirus/como-funcionan-vacunas-adaptadas_120131_102.html
22. Ledford H (2022) Which COVID boosters to take and when: a guide for the perplexed. A diverse menu of vaccine options leaves people searching for the best route to protection. Nature; 609: 18-9. doi: https://doi.org/10.1038/d41586-022-02221-w
23. Vogel G (2022) Omicron booster shots are coming—with lots of questions. COVID-19 vaccines get their first update since the pandemic began. Here's what you need to know about them. Science; 30 AUG 2022. https://www.science.org/content/article/omicron-booster-shots-are-coming-lots-questions
24. Robitzski D (2022) What We Know About Getting a Second Booster Shot of COVID-19 Vaccines. The Scientist; Aug 11. https://www.the-scientist.com/news-opinion/what-we-know-about-getting-a-second-booster-shot-of-covid-19-vaccines-70350
25. Consejo interterritorial de salud (2022) [COMIRNATY BIVALENTE, Original/Omicron BA.4-5 (COVID-19 mRNA Vaccine, Pfizer-BioNTech) Technical Guide December 27, 2022]. Sistema Nacional de Salud. España. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Guias_Tecnicas/docs/Guia_Tecnica_COMIRNATY_bivalente.pdf
26. Consejo interterritorial de salud (2023) [SPIKEVAX BIVALENT, Original/Omicron BA.1 and Original/Omicron BA.4-5 (Modern mRNA COVID-19 Vaccine) Technical Guide January 23, 2023]. Sistema Nacional de Salud. España. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Guias_Tecnicas/docs/Guia_Tecnica_vacuna_Moderna_bivalente.pdf
27. Consejo Interterritorial (2022) [Update of the vaccination recommendations against COVID-19 for autumn-winter in Spain Approved by the Public Health Commission on December 15, 2022. Prepared by the Report on the Vaccination Program and Registry]. Sistema Nacional de Salud. España. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/Recomendaciones_vacunacion_Otono_Invierno_Covid.pdf
28. ATLAS ESPAÑA (2022) [The new vaccination campaign for the fourth dose of Covid19 starts throughout Spain]. ABC; 25/09. https://www.abc.es/espana/arranca-espana-nueva-campana-vacunacion-cuarta-dosis-20220925183607-vi.html
29. European Medicines Agency (2022) ECDC-EMA statement on booster vaccination with Omicron adapted bivalent COVID-19 vaccines. News 06/09. https://www.ema.europa.eu/en/news/ecdc-ema-statement-booster-vaccination-omicron-adapted-bivalent-covid-19-vaccines
30. Ministerio de Sanidad (2021) [COVID-19 early detection, surveillance and control strategy. Updated December 1, 2021]. Instituto de Salud Carlos III. https://www.mscbs.gob.es/profesionales

/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Estrategia_vigilancia_y_control_e_indicadores.pdf

31. Ayoub HH, Tomy M, Chemaitelly H, et al. (2022) Estimating protection afforded by prior infection in preventing reinfection: applying the test-negative study. doi: https://doi.org/10.1101/2022.01.02.22268622
32. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, et al. (2021) Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. Euro Surveill; 26(39): pii=2100894. https://doi.org/10.2807/1560-7917.ES.2021.26.39.2100894
33. Snijders BEP, van Lier A, van de Kassteele J, et al. (2012) Mumps vaccine effectiveness in primary schools and households, the Netherlands, 2008. Vaccine; 30(19):2999-3002. doi: https://doi.org/10.1016/j.vaccine.2012.02.035
34. de Gier B, Andeweg S, Joosten R, et al. (2021) Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveill; 26(31): pii=2100640. doi: https://doi.org/10.2807/1560-7917.ES.2021.26.31.2100640
35. Strauss AL (1984) Chronic illness and the quality of life. St Louis: The C.V. Mosby Company. https://catalogue.nla.gov.au/Record/2489376
36. WHO. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version: 2019. https://icd.who.int/browse10/2019/en
37. Donaldson RJ, Donaldson LJ (1983) Essential Community Medicine. Lancaster: MTP Press.
38. Turabian JL (2017) Family Genogram in General Medicine: A Soft Technology that can be Strong. An Update. Res Med Eng Sci; 3(1). doi: http://dx.doi.org/10.31031/RMES.2017.03.000551
39. Russell LT (2020) Capturing Family Complexity in Family Nursing Research and Practice. J Fam Nurs; 26(4):287-93. doi: http://dx.doi.org/10.1177/1074840720965396
40. Diccionario panhispánico del español jurídico (2022) [Ethnic minority]. https://dpej.rae.es/lema/minor%C3%ADa-%C3%A9tnica
41. Mao S, Huang T, Yuan H, et al. (2020) Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. BMC Public Health; 20: 1525. doi: https://doi.org/10.1186/s12889-020-09606-4
42. Turabian JL (2022) An ostrich strategy for covid-19 is too risky. BMJ; 377: o1112. doi: https://doi.org/10.1136/bmj.o1112
43. Evaluación rápida de riesgo (2022) [SARS-CoV-2 variants in Spain: Ómicron lineages BA.2.12.1, BA.4 and BA.5 11th update, June 28, 2022]. Centro de Coordinación de Alertas y Emergencias Sanitarias. Ministerio de Sanidad. España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/20220628-ERR.pdf
44. Centro de Coordinación de Alertas y Emergencias Sanitarias (2022).[Update of the epidemiological situation of SARS-CoV-2 variants in Spain. May 17, 2022]. Ministerio de Sanidad. España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20220517.pdf
45. Centro de Coordinación de Alertas y Emergencias Sanitarias (2022) [October 17, 2022 Update on the epidemiological situation of SARS-CoV-2 variants in Spain]. Ministerio de Sanidad. España. https://www.sanidad.gob.es/profesional

es/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20221017.pdf

46. Esper FP, Adhikari TM, Tu ZJ, et al. (2023) Alpha to Omicron: Disease Severity and Clinical Outcomes of Major SARS-CoV-2 Variants. J Infect Dis; 227(3): 344–52. doi: https://doi.org/10.1093/infdis/jiac411
47. Trobajo-Sanmartín C, Miqueleiz A, Guevara M, et al. (2023) Comparison of the Risk of Hospitalization and Severe Disease Among Co-circulating Severe Acute Respiratory Syndrome Coronavirus 2 Variants. Int J Infect Dis; 227(3): 332–8. doi: https://doi.org/10.1093/infdis/jiac385
48. Meredith ED-G, Lai L, Wali B, et al. (2022) Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster. N Engl J Med; 388:183-5. doi: https://doi.org/10.1056/NEJMc2214293
49. Mahase E (2022) Covid-19: Booster vaccines rolled out as hospital admissions rise. BMJ; 379: o2484. doi: https://doi.org/10.1136/bmj.o2484
50. Loewy MA (2022) [COVID-19: The Weekly Summary (November 4-10, 2022)]. Medscape; 11 de nov. https://espanol.medscape.com/verarticulo/5909971?src=mkm_ret_221113_mscpmrk-ES_ExcNews&uac=327178AR&impID=4851592&faf=1
51. Loewy MA (2023) [COVID-19: the weekly summary (February 24 to March 2, 2023)]. Medscape; 3 de marzo. https://espanol.medscape.com/verarticulo/5910508?ecd=mkm_ret_230305_mscpmrk-ES_ExcNews&uac=327178AR&impID=5209399&faf=1#vp$_1$
52. Loewy MA (2023) [COVID-19: The Weekly Summary (February 10-16, 2023)]. Medscape; 17 de feb. https://espanol.medscape.com/verarticulo/5910436?ecd=mkm_ret_230218_mscpmrk-ES_ExcNews&uac=327178AR&impID=5173986&faf=1
53. Loewy MA (2023) [COVID-19: the weekly summary (January 20-26, 2023)]. Medscape; 27 de enero. https://espanol.medscape.com/verarticulo/5910337?src=mkm_ret_230128_mscpmrk-ES_ExcNews&uac=327178AR&impID=5115493&faf=1
54. Zou J, Kurhade C, Patel S, et al. (2023) Neutralization of BA.4–BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with Bivalent Vaccine. N Engl J Med; 388:854-7. doi: https://doi.org/10.1056/NEJMc2214916
55. Reuters Staff (2023) Omicron COVID Booster Cuts Hospitalization in Over 65s, Israeli Study Finds. Medscape; January 10. https://www.medscape.com/viewarticle/986682
56. Roa E (2022). Cuarta dosis de vacuna Covid-19, La biblioteca de Springfield. https://rubenroa.blogspot.com/2022/09/cuarta-dosis-de-vacuna-covid-19.html

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