Research Article

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Comparison of Adverse COVID-19 Vaccines Reactions between First and Second Doses, First Booster and Fourth Doses in General Medicine

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ABSTRACT

Background: *Differential characteristics of the adverse reactions between the different COVID-19 vaccinations shots are not clearly known.*

Objective: *Comparison of adverse reactions that led to consultation with the general practitioner between first and second, third (first booster) and fourth (second booster) doses of COVID-19 vaccines.*

Methodology: *Several longitudinal studies are compared, with the same methodology and population, of adverse COVID-19 vaccines reactions that were the reason for medical consultation, in people with first and second doses from February to July 2021, first booster from November 2021 to August 2022 and fourth dose (second booster) of bivalent mRNA from October 1, 2022 to February 28, 2023.*

Results: *A total of 109 adverse COVID-19 vaccines reactions with the first and second doses, 21 adverse COVID-19 vaccines reactions in vaccinated people with first booster, and 4 adverse COVID-19 vaccines reactions in vaccinated people with fourth dose (second booster) were included. The only statistically significant differences were that the adverse reactions of first and second doses vs. first and second boosters were occurred in people < 65 years [p= .00041], were more certain and probable [p= .027042], and more mild and moderate [p= .005912]. There were no differences by chronic diseases or symptoms.*

Conclusion: *Adverse reactions were more severe, more unlikely/conditional, and occurred in older people with the boosters than with the first or second dose of the COVID-19 vaccine. However, these differences must be taken with caution and could be explained by older people being more vaccinated with booster, and by the knowledge of the population over time, which may change the reason for consultation with general practitioner towards adverse reactions severe and less known. Our data support the safety of COVID-19 vaccines, including the first and second booster.*

Keywords

COVID-19, SARS-CoV-2, Adverse Drug Events, Post-vaccination Reactions, Booster, COVID-19 vaccine, General Practice, Secondary Analysis.

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected more than 676 million people worldwide to date, being the cause of more of 6 million deaths [1]. Vaccination is important to reduce the morbidity and mortality associated with COVID-19 [2], having administered more than 13,338 million doses of vaccines [1].

The main function of vaccines is to provide protection against the pathogen to which they are directed, and it is one of the most effective public health strategies [3]. Any medicine, including

vaccines, can cause mild, moderate, or severe adverse reactions. It can therefore be stated that absolute safety (absence of any adverse reaction) does not exist when a vaccine is administered. Vaccines, unlike other medicines, are administered to healthy people for preventive purposes and therefore their safety profile must be as high as possible. This is an essential requirement for a healthy population to accept preventive vaccination [4].

The safety of a vaccine is studied throughout its development, from its in vitro laboratory evaluation until, once the clinical trials have been completed, its commercialization is authorized and its results are used to prepare its technical data sheet. Only post-marketing follow-up, once it has been applied to a large number of people, will allow us to know the reality of the adverse reactions of a vaccine [5,6].

On the other hand, it is very important that the personnel involved in vaccination, especially the general practitioner (GP) who is usually the first professional the patient sees, knows what adverse reactions may occur after the administration of the vaccine. Through this knowledge, unexpected adverse events can be detected and differentiated [7,8].

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 to restore protection that might have diminished since the last previous dose, but its possible adverse effects are not well known compared to previous COVID-19 vaccines shots [9-13]. In addition, the lack of sufficient information on vaccine safety is one of the main factors contributing to vaccine doubt [14].

In this context, we present a secondary analysis of several longitudinal and prospective studies, carried out in different periods of time, in the same population and with the same methodology, whose objective was to compare the characteristics of the adverse reactions that led to consultation with the general practitioner, between first and second (from February to July 2021), first booster (from November 2021 to August 2022) and second booster (from October 1, 2022 to February 28, 2023) of the shots of COVID-19 vaccine.

Material and Methods

A longitudinal study of adverse COVID-19 vaccines reactions in people with fourth dose (second booster) of bivalent mRNA from October 1, 2022 to February 28, 2023 is compared to several observational, longitudinal and prospective studies of adverse COVID-19 vaccines reactions, with were the reason for medical consultation from February to July 2021 (first and second dose) and first booster adverse COVID-19 vaccines reactions from November 2021 to August 2022 (15-19). All studies were carried out on the same population attended in a general medicine consultation, and by the same investigator and GP, which has a list of 2,000 patients > 14 years of age. The methodology of all studies has been previously published, and here only some specific aspects will be mentioned to avoid repetition.

Outcomes of interest

Description of characteristics and comparison of self-reported adverse reactions to the first and second, third (first booster) and fourth dose (second booster) COVID-19 vaccine shot in the same population attended in general medicine.

First and second dose

Vaccination campaign against COVID-19 in Spain began on December 27, 2021, once the Pizfer / 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. It began with the residents and staff of the centers for the elderly, front-line health and socio-health personnel, non-institutionalized dependent people, and older population groups, progressively lowering the ages for vaccination. Following the strategy of expanding the vaccination of younger age groups, as of June 21, 2020, vaccination began in the age range of 30 to 39 years. Meanwhile, the group between 40 and 49 years of age continued to be vaccinated and second doses were inoculated for those over 50 and 60 years of age. In the midst of this process, doubts arose with ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca), a drug that was finally destined for the age group between 60 and 69 years old and essential groups. Later, the Janssen vaccine (Johnson & Johnson vaccine) vaccine arrived, aimed at more age groups than AstraZeneca and designed for people with difficult uptake, taking advantage of its inoculation in a single dose [20,21].

Booster dose

As of November 23, 2021, in Castilla La Mancha, booster doses against COVID-19 were started only with messenger RNA (mRNA) vaccines 6 months after the end of 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 actively carried out by descending age cohorts, starting with those over 80 years of age. The booster dose was given with mRNA vaccines (0.3 ml Comirnaty or 0.25 ml Spikevax – half the usual primary dose) [22-24].

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 [25].

Diagnosis of adverse COVID-19 vaccine reactions

Reports of adverse COVID-19 vaccines reactions that were reason for consultation with the GP were included. An adverse reaction was defined as any response to a vaccine that is harmful and unintended, and that occurs in doses that are normally applied in humans for the prophylaxis of COVID-19 [26].

Collected variables

Age and sex; symptoms of adverse reaction and chronic diseases [27], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [28]; Problems in the family context and low income household based on the genogram [29,30]; criteria for the causality of adverse reactions, classified as definitive (certain), probable (likely), possible, unlikely, conditional / unclassified, not evaluable / unclassifiable [31-33]; severity or intensity of adverse reactions, classified as mild, moderate and severe [34]; and time of appearance of adverse reactions, classified as immediate, expedited and late [35].

Results

A total of 109 adverse COVID-19 vaccines reactions with the first and second doses, 21 adverse COVID-19 vaccines reactions in vaccinated people with first booster, and 4 adverse COVID-19 vaccines reactions in vaccinated people with fourth dose (second booster) were included. The following statistically significant differences were found in the first and second dose vs. first and second booster: more adverse reactions in younger people (< 65 years) (X2 (1, N=134) = 15.6003. p= .00041), and more adverse reactions certain and probable (X2 (1, N=134) = 7.2207. p= .027042). There were more Mild and Moderate adverse reactions in the first and second doses and first booster vs. second booster (X2 (1, N=134) = 10.2616. p= .005912). There were no differences due to severity of the adverse COVID-19 vaccines reaction, neither due to chronic diseases nor symptoms of adverse reactions (TABLE 1, TABLE 2, TABLE 3, TABLE 4).

Discussion

Main findings

Our main result is that adverse reactions in the first and second booster were more severe, more unlikely/conditional, and in older people. But these results must be taken with caution. Since our study does not include denominators, the results may lead to erroneous conclusions, since they can be explained by other reasons. It must be taken into account that people preferably

Table 1: Comparison of Characteristics of Adverse COVID-19 Vaccines Reactions in First and Second Doses, First Booster and Second Booster.

Variables	Cases of adverse reactions in a population vaccinated with 1 or 2 doses from february to september 2021 N=109	Cases of adverse reactions in population vaccinated with booster for the period december 1, 2021-september, 1 2022 N=21	Cases Of Adverse Reactions In Population Vaccinated With Fourth Dose From October 2022 To February 2023 N=4	Statistical significance
> = 65 years	8 (7)	8 (38)	1 (25)	X2 (2, N=134)= 15.6003. p= .00041. Significant at p < .05
< 65 years	101 (93)	13 (62)	3 (75)	X2 (2. N=134)= 15.6003. p= .00041. Significant at p < .05.
Women	51 (70)*	14 (67)	3 (75)	X2 (2, N=98)= 0.1403. p= .932264. NS
Men	22 (30)*	2 (9)	1 (25)	X2 (2, N=98)= 0.1403. p= .932264. NS
Complex family	15 (14)	2 (9)	1 (25)	X2 (2, N=134)= 0.7463. p= .688553. NS
Cases with chronic diseases	60 (82) [N=73]	15 (71)	3 (75)	X2 (2, N=98)= 1.2173. p .544097.

( ): Denotes percentages; NS: Not significant

Table 2: Comparison of Causality, Time of Appearance and Gravity between Adverse COVID-19 Vaccines Reactions in First and Second Doses, First Booster and Second Booster.

Variables	Cases of adverse reactions in a population vaccinated with 1 or 2 doses from february to september 2021 N=109	Cases of adverse reactions in population vaccinated with booster for the period december 1, 2021-september, 1 2022 N=21	Cases of adverse reactions in population vaccinated with fourth dose from october 2022 to february 2023 N=4	Statistical Significance
CRITERIA OF CAUSALITY				
-Certain and Probable	74 (68)	9 (42)	1 (25)	X2 (2, N=134)= 7.2207. p= .027042. Significant at p < .05.
- Possible	22 (20)	6 (29)	2 (50)	X2 (2, N=134)= 2.5221. p= .283357. NS
-Unlikely, Conditional/ Unclassified) and Unassessable/Unclassifiable	13 (12)	6 (29)	1 (25)	X2 (2, N=134)= 4.1714. p= .124221. NS
TIME OF APPEARANCE OF THE ADVERSE COVID-19 VACCINES REACTION				
-Immediate and Accelerated	88 (81)	16 (76)	3 (75)	X2 (2, N=134)= 0.2862. p .866663. NS
-Late	21 (19)	5 (24)	1 (25)	X2 (2, N=134)= 0.2862. p= .866663. NS
GRAVITY OF THE ADVERSE COVID-19 VACCINES REACTION				
-Mild and Moderate	83 (76)	20 (95)	1 (25)	X2 (2, N=134)= 10.2616. p= .005912. Significant at p < .05.
- Severe	26 (24)	1 (5)	3 (75)	X2 (2, N=134)= 10.2616. p= .005912. Significant at p < .05.

( ): Denotes percentages; NS: Not significant

Table 3: Comparison of Chronic Diseases between Adverse COVID-19 Vaccines Reactions in First and Second Doses, First Booster and Second Booster.

Chronic diseases* # According to who, Icd-10 groups	Cases of adverse reactions in population vaccinated with 1 or 2 doses from february to september 2021 N=109	Cases of adverse reactions in population vaccinated with booster for the period december 1, 2021-september, 1 2022 N=21	Cases of adverse reactions in population vaccinated with fourth dose from october 2022 to february 2023 N=4	Statistical significance
-II Neoplasms	5 (3)	1 (2)	1 (7)	X2 (2, N=289)= 1.3188. p= .517156. NS
-IV Endocrine	40 (19)	6 (10)	1 (7)	X2 (2, N=289)= 4.0452. p= is .13231. NS
-V Mental	28 (13)	11 (18)	3 (20)	X2 (2, N=289)= 1.1748. p= .55577. NS
-VI-VIII Nervous and Senses	28 (13)	9 (14)	3 (20)	X2 (2, N=289)= 0.5722. p .751197. 0.5722. NS
-IX Circulatory system	18 (8)	4 (6)	1 (7)	X2 (2, N=289)= 0.3083. p= .857144. NS
-X Respiratory system	17 (8)	4 (6)	1 (7)	X2 (2, N=289)= 0.1877. p= .910436. NS
-XI Digestive system	19 (9)	7 (11)	1 (6)	X2 (2, N=289)= 0.4407. p= .802228. NS
-XII Diseases of the skin	6 (3)	1 (2)	2 (13)	X2 (2, N=289)= 5.7116. p= .05751. NS
-XIII Musculo-skeletal	26 (12)	6 (10)	1 (6)	X2 (2, N=289)= 0.6706. p= .715141. NS
-XIV Genitourinary	25 (12)	13 (21)	1 (7)	X2 (2, N=289)= 4.0913. p= .129294. NS
TOTAL chronic diseases*	212 (100)	62 (100)	15 (100)	---

*Patients could have more than one chronic disease; The percentages are over the total of chronic diseases
Only chronic diseases are shown with a number of cases > 0
( ): Denotes percentages; NS: Not significant

Table 4: Comparison of Symptoms between Adverse COVID-19 Vaccines Reactions in First and Second Doses, First Booster and Second Booster.

Symptoms * # According to who, Icd-10 groups	Cases of adverse reactions in population vaccinated with 1 or 2 doses from february to september 2021 N=109	Cases of adverse reactions in population vaccinated with booster for the period december 1, 2021-september, 1 2022 N=21	Cases of adverse reactions in population vaccinated with fourth dose from october 2022 to february 2023 N=4	Statistical Significance
-VI-VIII Nervous and Senses (Ear plugging, earache, subconjunctival hemorrhage, conjunctivitis)	6 (4)	2 (5)	1 (13)	X2 (2, N= 210)= 1.4511. p= .484064. NS
-X Respiratory system (cough, dyspnea, rhinitis)	6 (4)	3 (7)	1 (13)	X2 (2, N= 210)= 1.9425. p= .378609. NS
-XI Digestive system (diarrhea, nausea, vomiting, abdominal pain)	22 (14)	2 (5)	1 (13)	X2 (2, N= 210)= 2.5654. p= .277287. NS
-XII Diseases of the skin (urticaria)	5 (3)	1 (2)	1 (12)	X2 (2, N= 210)= 2.226. p= .328574. NS
-XIII Musculo-skeletal (myalgia, musculoskeletal pain)	34 (21)	7 (17)	1 (12)	X2 (2, N= 210)= 0.7292. p= .694486. NS
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (Injection site pain, arm pain, throat pain, fever, chills, dizziness, headache, asthenia, limb paresthesia, lymphadenopathy, foot edema)	87 (54)	27 (64)	3 (37)	X2 (2, N= 210)= 2.4426. p= .294844. NS
TOTAL SYMPTOMS*	160 (100)	42 (100)	8 (100)	---

*Patients could have more than one symptom. The percentages are over the total of symptoms
Only groups of symptoms with a number of cases > 0 are shown
( ): Denotes percentages; NS: Not significant

vaccinated with booster are older and it can be thought that there is greater knowledge in the population, over time, regarding consulting the GP only for adverse reactions that are more severe and less well known.

Comparison with other studies

A proof that vaccines activate the immune system is the appearance of side effects that follow their application. These effects range from mild to severe, so the application of biologicals can cause fear among the population. Undoubtedly, any vaccination will induce transient side effects due to the activated immune response and tissue trauma at the injection site [3].

Males and females respond differently to vaccination. Biological differences, such as endocrine and sex hormones, play an important role in the high response of women to bacterial and viral vaccines. Variations according to sex in pharmacokinetics and pharmacodynamics have also been observed, with women being more susceptible to adverse effects. These effects have been attributed to women having a significantly higher percentage of body fat than men, which affects the volume of distribution and elimination of the drugs [36-38]. However, we did not find gender differences in the adverse reactions between first and second doses, first booster and fourth shot.

Regarding age, older people have a less reactive immune system and therefore tend to have fewer side reactions [39]. However, it has been reported that the elderly group, which is characterized by a higher rate of underlying medical conditions, might be more sensitive to changes caused by vaccine reactions [14]. In our study we found that in the first and second booster vs. first and second dose, there were more adverse reactions in older people (> 65 years). However, it must be taken into account that, as in many studies, participants were over 50 years of age, according to the vaccine administration guidelines, in the first and second boosters [25,40,41]. In addition, it has been reported that the incidence of the 15 pre-specified adverse events of special interest (e.g., stroke, myocardial infarction, thrombosis deep vein, immune thrombocytopenia) was markedly heterogeneous both within and between databases by age and sex [4].

For the first and second doses, adverse reactions to vaccine are generally mild and self-limited [3]. The most frequently reported events continue to be general disorders (fever and pain in the vaccination area), of the nervous system (headache and dizziness) and of the musculoskeletal system (myalgia and arthralgia) [42]. In our study, there were milder and moderate adverse reactions in the first and second dose and first booster vs. second booster, coinciding with the studies consulted [43]. Our results also coincide with what was published for the first and second doses [3,45]. The most common side effects after the third and fourth doses of the vaccine are fever, headache, malaise, vomiting, diarrhea, hives, fatigue, abdominal pain, dizziness, chills, and joint pain [46].

The updated or bivalent booster vaccines are similar to their now-retired predecessors. However, instead of providing a single set of instructions, they provide two sets: one specific to the parent coronavirus strain and one specific to omicron subvariants. Despite this difference, all side effects of the bivalent booster have been very similar to those of the regular booster, and even with the original vaccine [47]. The most common side effects for adults receiving bivalent injection were arm pain at the injection site, fatigue, headache, muscle aches, and joint pain [48]. It has been published that the appearance of side effects in the fourth dose was linked to the third administered (the first booster) to each person [14,47].

Regarding patients with chronic diseases, it has been reported that the adverse effect profile of vaccines in these patients is similar to that of people without chronic diseases [2]. Finally, it can be thought that people now know better than at the beginning of the vaccinations (first and second doses) the possible adverse reactions of the COVID-18 vaccines [49] and this fact may influence that they are more frequent reasons for consult with the GP the severe and unlikely/conditional adverse reactions in the first and second booster.

Study limitations

1. The small number of COVID-19 adverse reactions may mask statistical significance between variables.
2. The sample size of our study might not be sufficient to identify rare serious events
3. Adverse reactions that were the reason for consulting the GP were collected, so these are not all the adverse reactions that occurred, but rather those that at each point in time the patients considered to be the reason for consultation. Although serious events after vaccination are likely to prompt a medical consultation, milder reactions may not be a reason for consultation.
4. Our analysis may be biased in that people who had a serious adverse response to one dose (for example the first booster) might have opted not to receive a new dose (for example the second booster) and therefore some potential new adverse reactions are not represented in our data.
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 context of general medicine in Toledo (Spain), there seems to be a tendency for adverse reactions to be significantly more severe, more unlikely/conditional, and in older people with the boosters than with the first or second dose of the COVID- 19 vaccinate. But, these differences may be spurious and explained by other confounding factors. Thus, the ages of the people preferably vaccinated with booster were older. On the other hand, probably the population's knowledge about adverse COVID-19 vaccines reactions, over time from the first vaccinations in 2021 to the second booster in 2023, has changed people's behavior regarding when to consult with the GP for an adverse reaction; this can

cause that more severe and lesser known adverse reactions to be consulted with the first and second booster vs. first and second dose. In short, taking into account the results and the possible confounding variables, it is conceivable that there may be no relevant differences, due exclusively to the vaccine, between the adverse reactions of the first, second, third and fourth doses of COVID-19 vaccine. Consequently, our conclusions support the safety of COVID-19 vaccines, including the second booster.

References

1. https://coronavirus.jhu.edu/map.html
2. Seneviratne SL, Yasawardene P, Wijerathne W, et al. COVID-19 vaccination in cancer patients: a narrative review. Int J Med Res. 2022; 50: 3000605221086155.
3. Galeano RA, Antúnez K, Chamorro ON, et al. Efectos adversos a las vacunas contra la COVID-19 en Paraguay en el 2021. Rev cient cienc salud. 2023; 5: e5102.
4. Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ. 2021; 373: n1435.
5. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Eng J Med. 2021; 385: 1078-90.
6. Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health. 2021; 194: 245-251.
7. https://vacunasaep.org/printpdf/profesionales/reacciones-adversas-de-las-vacunas
8. Lee GM. The Importance of Context in Covid-19 Vaccine Safety. N Eng J Med. 2021; 385: 1138-1140.
9. Lin DY, Xu Y, Gu Y, et al. Durability of Bivalent Boosters against Omicron Subvariants. N Engl J Med. 2023; 388: 1818-1820.
10. European Medicines Agency ECDC-EMA statement on booster vaccination with Omicron adapted bivalent COVID-19 vaccines. 2022.
11. https://www.consalud.es/pacientes/especial-coronavirus/como-funcionan-vacunas-adaptadas_120131_102.html
12. https://webcache.googleusercontent.com/search?q=cache:kZEI2MAHtYQJ:https://www.independent.co.uk/news/health/uk-covid-variant-omicron-new-wave-b2183934.html&cd=2&hl=es&ct=clnk&gl=es
13. Chalkias S, Harper C, Vrbicky K, et al. A bivalent Omicron-containing booster vaccine against Covid-19. N Engl J Med. 2022; 387: 1279-1291.
14. Yechezkel M, Mofaz M, Painsky A, et al. Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study. Lancet Respir Med. 2023; 11: 139-150.
15. Turabian JL. Risk Factors and Incidence Rates of Adverse Covid-19 Vaccines Reactions: a Longitudinal Study of 109 Adverse Reactions Cases from February to September 2021 in General Medicine of Toledo (Spain). Epidemol Int J. 2022; 6: 000219.
16. Turabian JL. Adverse Covid-19 Vaccines Reactions in General Medicine: A Clinical Epidemiological Case Series Reporting of 73 Patients in Toledo's (Spain) Epidemol Int J. 2021; 5: 000204.
17. Turabian JL. Adverse Covid-19 Vaccines Booster Reactions Case Series, In a General Medicine Office in Toledo, Spain. Medp Public Health Epidemiol. 2022; 1: 202210001.
18. Turabian JL. Incidence Rates and Risk Factors for Covid-19 Booster Adverse Reactions in General Medicine. Medp Public Health Epidemiol. 2022; 1: 202210007.
19. Turabian JL. Adverse Reactions with Covid-19 Vaccine Booster are of Milder Gravity than with First and Second Dose. Medp Public Health Epidemiol. 2022; 1: 202210005.
20. https://sanidad.castillalamancha.es/ciudadanos/enfermedades-infecciosas/coronavirus/preguntas-frecuentes-sobre-el-coronavirus-covid-19/campa%C3%B1a-vacunacion
21. https://www.rtve.es/noticias/20210620/ritmo-vacunacion-comunidades/2083665.shtml#vacuna-castilla-mancha
22. https://www.elespanol.com/eldigitalcastillalamancha/region/20211125/sanitarios-castilla-la-mancha-recibiran-inmediata-tercera-vacuna/629937547_0.html
23. https://api.asclepiusopen.com/storage/articles/jcpm/volume5-issue1/jcpm-5103.pdf
24. https://www.elmundo.es/ciencia-y-salud/salud/2021/01/29/60141474fc6c834e268b4666.html
25. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/Recomendaciones_vacunacion_Otono_Invierno_Covid.pdf
26. Colloca L, Millar FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011; 73: 598-603.
27. Strauss AL. Chronic illness and the quality of life. St Louis: The C.V. Mosby Company. 1984.
28. https://icd.who.int/browse10/2019/en
29. Turabian JL. Family Genogram in General Medicine: A Soft Technology that can be Strong. An Update. Res Med Eng Sci. 2017; 3: 000551.
30. Russell LT. Capturing Family Complexity in Family Nursing Research and Practice. J Fam Nurs. 2020; 26: 287-293.
31. Kyonen M, Folatre I, Lagos X, et al. [Comparison of two methods to assess causality of adverse drug reactions]. Rev méd Chile. 2015; 143: 880-886.
32. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHO-UMC_ReportingGeneralPublic-ESP-GRA3Final.pdf?ua=1
33. https://www.researchgate.net/publication/321490997_Analisis_de_Causalidad_RAM
34. http://www.anmat.gov.ar/Publicaciones/Definiciones_farmacovigilancia_graf.pdf:
35. Pelta Fernandez R, Vivas Rojo E. [Adverse drug reactions. Clinical assessment]. Madrid: Díaz de Santos. 1992.
36. Schwartz JB. The Influence of Sex on Pharmacokinetics. Clin Pharmacokinet. 2003; 42: 107-121.

37. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ. 2020; 11: 32.

38. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2020; 16: 626-638.

39. https://www.isglobal.org/preguntas-frecuentes-vacuna

40. https://corona.health.gov.il/en/vaccine-for-covid/

41. https://www.cdc.gov/media/releases/2022/s0519-covid-booster-acip.html

42. https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/8o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/

43. Álvarez Collado L. [Adverse reactions reported after the administration of the vaccine against Covid-19 in workers of a tertiary hospital]. Rev Asoc Esp Espec Med Trab. 2021; 30: 227-238.

44. García Alonso E, Sánchez Peinador C, García Luengo A, et al. [Analysis of the adverse reactions to the COVID-19 vaccine in the population of the Basic Health Area of Cantalejo]. Med Gen Fam. 2022; 11.

45. https://www.aemps.gob.es/informa/19o-informe-de-farmacovigilancia-sobre-vacunascovid-19/

46. https://as.com/actualidad/los-efectos-secundarios-mas-comunes-tras-la-tercera-y-cuarta-dosis-de-la-vacuna-n/

47. https://www.aarp.org/espanol/salud/enfermedades-y-tratamientos/info-2021/efectos-secundarios-vacuna-refuerzo-covid.html

48. https://www.verywellhealth.com/new-bivalent-booster-side-effects-6665439

49. https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/vacunas-contra-la-covid%E2%80%9119/farmacovigilancia-de-vacunas/respuestas-a-preguntas-frecuentes-relacionadas-con-la-seguridad-de-vacunas-frente-a-la-covid-19/