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# Adverse Reactions with Covid-19 Vaccine Booster are of Milder Gravity than with First and Second Dose

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**Research Article**

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## Abstract

**Background:** It is not clearly known whether the third doses (booster) of the covid-19 vaccine present more or fewer adverse reactions than those of the first and second doses.

**Objective:** Comparison of self-reported adverse reactions, with first and second versus third (booster) doses of covid-19 vaccine.

**Emplacement:** The population attended in a general medicine consultation in Toledo, Spain.

**Methodology:** Analysis of secondary data from two observational, longitudinal, and prospective studies: 1) Adverse covid-19 vaccines reactions from February to July 2021; And 2) Adverse covid-19 vaccines booster reactions from November 2021 to August 2022.

**Results:** We included 21 cases of adverse covid-19 vaccines booster reactions and 109 cases of adverse covid-19 vaccines reactions (1 and 2 doses). Cases of adverse covid-19 vaccines booster reactions versus cases of adverse covid-19 vaccines reactions (1 and 2 doses) differed only statistically significantly in presenting more mild and less severe adverse reactions.

**Conclusions:** In the context of general medicine in Toledo (Spain), there is a tendency for adverse reactions to be significantly lighter with the booster than with the first or second dose of the covid-19 vaccine.

**Key Words:** COVID-19; SARS-CoV-2; Adverse Drug Events; Post-Vaccination Reactions; Booster; COVID-19 vaccine; General Practice; Secondary Analysis

## Introduction

Since Edward Jenner used the first vaccine in 1796 to prevent smallpox, the development and widespread use of vaccines has prevented mortality and morbidity from at least 25 vaccine-preventable diseases (1). As a result of vaccination programs, smallpox has been eradicated worldwide, polio has been nearly eradicated and is emerging as the next eradication target, and national programs have helped reduce the incidence of tuberculosis in many countries. Other newer vaccines have already made a visible impact, as evidenced by the ability of the hepatitis B vaccine to decrease the number of new hepatitis infections and the incidence of hepatocellular carcinoma (2). But, vaccination, like any other medical intervention, can have adverse effects.

An adverse drug reaction is a broad term that refers to unwanted, uncomfortable, or dangerous effects that a drug can have (3). Since the practice of vaccination emerged, the existence of adverse reactions to vaccines has been recognized. The frequency of adverse reactions to vaccines is directly related to the number of vaccine doses administered (4). Based on currently available data, the benefits of vaccines in preventing covid-19 and disease severity outweigh any current known adverse reactions in most vaccinated individuals. Furthermore, an adverse reaction report does not necessarily mean that the vaccine caused the reactions. A causality assessment should be performed to assess the relationship of the adverse reaction and the vaccine administered. Although a mere suspicion can also be reported. Undiagnosed illnesses, underlying comorbidities, and pre-existing medical conditions may cause symptoms similar to adverse reactions. These conditions can also aggravate potential adverse reactions to vaccines (1, 3).

As of October 28, 2021, 49% of the world's population had received at least one dose of the covid-19 vaccine, of which 38% have been fully vaccinated (5). As of February 2022 there were 10 vaccines approved by the World Health Organization and close to 48% of people were fully vaccinated in the world (6). Results from clinical trials showed that Comirnaty (Pfizer-BioNTech-BNT162b2 mRNA) and Spikevax (mRNA-1273 vaccine Moderna) vaccines had 95% effective and the Janssen vaccine (Johnson & Johnson

vaccine) was 66% effective in protecting against moderate and symptomatic SARS-CoV-2 infection (7).

However, reports of emerging infections and decreased immunity have raised concerns regarding the duration of protection (8). The results strengthen the evidence-based rationale for administering a third dose of vaccine as a booster to specific high-risk populations (8). However, despite these potential benefits, it is essential to monitor the safety of additional doses of vaccines beyond the primary series as they are administered to the general population (9). When covid-19 vaccines became available in early 2021, many experienced side effects, especially after people received their second dose. The Centers for Disease Control and Prevention (CDC) even addressed this issue, noting at the time that side effects from the second dose may be more intense than those experienced by people after the first. Those side effects, the CDC said, are normal signs that your body is creating protection. After two doses, the booster shot became available in October 2021, and it has been reported that probably there is no more side effects with a third dose than with the first or second (10).

In any case, risk communication is necessary to improve the booster vaccination rate (11). In this regard, although it has been reported that the standard 2-dose regimen of mRNA-based COVID-19 vaccines is associated with relatively safe outcomes, serious adverse events such as anaphylaxis, myocarditis, and blood coagulation alterations, have been reported after covid-19 vaccination. The most common adverse reactions occur immediately after vaccination were relatively mild, and include headache, fatigue, aches, low-grade fever, and nausea. In short, results from early studies, including clinical trials and self-report of adverse events in a small cohorts of people who received the third dose of the vaccine, suggest that additional doses of vaccination may also be safe, although further studies are needed (9).

In this context, we present a study whose objective is to provide a general comparison of adverse events after vaccination with the third dose (booster) versus those of the first and second doses against covid-19.

## Material and Methods

The study is a secondary analysis of previously presented data. The study compares an observational, longitudinal and prospective study of self-reported adverse covid-19 vaccines reactions and that were the reason for medical consultation from February to July 2021 with another observational, longitudinal and prospective study of self-reported adverse covid-19 vaccines booster and that were reason for medical consultation from November 2021 to August 2022. Both studies have been previously published (12-14), were carried out on the same population attended in a general medicine consultation, and by the same investigator and general practitioner (GP), which has a list of 2,000 patients > 14 years of age (in Spain, the 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 both studies has been previously published, and here only some specific aspects for this study will be mentioned, to avoid repetition.

### Outcomes of Interest

Evaluation and comparison of self-reported adverse reactions to the first and second versus third (booster) doses of covid-19 vaccine in the same population attended in general medicine.

### First and Second Dose

Vaccination campaign against covid-19 in Spain and Toledo (Castilla La Mancha, Spain), region where the general medicine clinic where the study was conducted is located, 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. Spain managed to have at the end of August 2021 70% of citizens over 12 years of age with the complete guideline (two doses) (15).

### Booster Dose

As of November 23, 2021, in Castilla La Mancha, the region where the study was carried out, 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 and people hospitalized in centers for the elderly and in other socio-health centers (including day centers and occupational centers), regardless of the age , people who received a dose of the Ad26.COV2.S vaccine (Janssen/Johnson & Johnson vaccine) as their primary vaccination and those with a homologous schedule of Vaxzevria as their primary vaccination (first and second doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca), followed by people aged between 79 to 70 years old, 69 to 65 years old, 64 to 60 years old, 59 to 50 years old and 49 to 40 years old, etc. The booster dose was given with mRNA vaccines (0.3 ml Comirnaty or 0.25 ml Spikevax – half the usual primary dose) (16, 17). It must be taken into account that in Spain doses of mRNA-1273 vaccine (Spikevax, Vaccine Moderna) were predominantly given in the first and second doses, while the use of mRNA-1273 vaccine (Spikevax) was predominant in booster. As of December 2, 2021, 73% of covid vaccines administered were from Comirnaty (Pfizer-BioNTech-BNT162b2 mRNA), and 13% from Spikevax (mRNA-1273 vaccine Moderna) (18).

### Collected Variables

Age, sex, symptoms of adverse reactions with covid-19 vaccine, chronic diseases, complex family, prior covid-19, vaccine type,

criteria for the causality, severity and time of appearance of adverse reactions with covid-19 vaccine.

### 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.

## Results

109 cases of adverse covid-19 vaccines reactions (1 and 2 doses) and 21 of adverse covid-19 vaccines booster reactions were included. Probable adverse reactions predominated in both series, with symptoms not elsewhere classified (Injection site pain, arm pain, throat pain, fever, chills, dizziness, headache, asthenia, limb paresthesia), and in women aged 14-49 years with chronic diseases. There were no statistically significant differences by age groups, sex, socio-family factors, previous covid-19, frequency of chronic diseases, and adverse reaction symptoms. Cases of adverse covid-19 vaccines booster reactions versus cases of adverse covid-19 vaccines reactions (1 and 2 doses) differed statistically significantly in presenting more mild and less severe adverse reactions, and in presenting less BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech) and more mRNA-1273 vaccine (Spikevax, Vaccine Moderna) adverse reactions [but this pattern corresponds to the types of vaccines predominantly administered at both times].

**Table 1:** Adverse Covid-19 Vaccines Booster Reactions Versus First and Second Doses.

| VARIABLES | ADVERSE COVID-19 VACCINES REACTIONS (1 AND 2 DOSES) N=109 | ADVERSE COVID-19 VACCINES BOOSTER REACTIONS N=21 | STATISTICAL SIGNIFICANCE |
|---|---|---|---|
| > = 65 years | 8 (7) | 1 (5) | Fisher exact test= 1. NS |
| 49-65 years | 26 (24) | 8 (38) | X2= 1.8492. p= .173877. NS |
| 14-49 years | 75 (69) | 12 (57) | X2= 1.0823. p= .298192. NS |
| Women | 72 (66) | 14 (67) | X2= 0.0029. p= .956746. NS |
| Prior covid-19 | 10 (9) | 2 (9) | Fisher exact test= 1. NS |
| Complex family | 15 (14) | 2 (9) | Fisher exact test= 0.7383. NS |
| Cases with chronic diseases | 60 (82) [N=73]* | 15 (71) | X2 with Yates correction= 0.5991. p= .438903. NS |

( ): Denotes percentages; NS: Not significant; * Casos con enfermedades crónicas en adverse covid-19 vaccines reactions (1 and 2 doses) N=73 (only from February to July 2021).

**Table 2:** Comparison of Causality, Time of Appearance and Gravity between Adverse Covid-19 Vaccine Booster Reactions Versus First and Second Doses.

| VARIABLES | ADVERSE COVID-19 VACCINES REACTIONS (1 AND 2 DOSES) N=109 | ADVERSE COVID-19 VACCINES BOOSTER REACTIONS N=21 | STATISTICAL SIGNIFICANCE |
|---|---|---|---|
| CRITERIA OF CAUSALITY | | | |
| 1.-Certain | 12 (11) | 0 | Fisher exact test= 0.213. NS |
| 2.-Probable | 62 (57) | 9 (42) | X2= 1.397. p= .237226. NS |
| 4.-Unlikely | 13 (12) | 6 (29) | X2= with Yates correction= 2.689. p= .101042. NS |
| 5.-Conditional/ Unclassified) | 0 | 0 | Fisher exact test= 1. NS |
| 6.-Unassessable/Unclassifiable | 0 | 0 | Fisher exact test= 1. NS |
| TIME OF APPEARANCE OF THE ADVERSE COVID-19 VACCINES REACTION | | | |
| 1.-Immediate | 4 (4) | 0 | Fisher exact test= 1. NS |
| 2.-Accelerated | 84 (77) | 16 (76) | X2 with Yates correction= 0.0383. p= .844771. NS |
| 3.-Late | 21 (19) | 5 (24) | X2 with Yates correction= 0.0319. p= .858146. NS |
| GRAVITY OF THE ADVERSE COVID-19 VACCINES REACTION | | | |
| 1.-Mild | 27 (25) | 10 (48) | X2= 4.5146. p= .033607. Significant at p < .05 |
| 2.-Moderate | 56 (51) | 11 (52) | X2= 0.0071. p= .932765. NS |
| 3.- Severe | 26 (24) | 0 | Fisher exact test= 0.0131. Significant at p < .05. |

( ): Denotes percentages; NS: Not significant.

**Table 3:** Comparison of Chronic Diseases between Adverse Covid-19 Vaccine Booster Reactions and Adverse Covid-19 Vaccines Reactions First and Second Doses.

| CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS | ADVERSE COVID-19 VACCINES REACTIONS (1 AND 2 DOSES) N=109 | ADVERSE COVID-19 VACCINES BOOSTER REACTIONS N=21 | STATISTICAL SIGNIFICANCE |
|---|---|---|---|
| -I Infectious | 0 | 1 (2) | Fisher exact test = 0.2274. NS |
| -II Neoplasms | 5 (2) | 1 (2) | Fisher exact test= 1. NS |
| -III Diseases of the blood | 1 (0.5) | 0 | Fisher exact test= 1. NS |
| -IV Endocrine | 40 (19) | 6 (10) | X2= 2.9539. p= .085672. NS |
| -V Mental | 28 (13) | 11 (17) | X2= 0.7705. p= .380054. NS |
| -VI-VIII Nervous and Senses | 28 (13) | 9 (14) | X2= 0.0607. p= .805359. NS |
| -IX Circulatory system | 18 (8) | 4 (6) | X2 with Yates correction= 0.0713. p= .789496. NS |
| -X Respiratory system | 17 (8) | 4 (6) | X2 with Yates correction= 0.0224. p= .881117. NS |
| -XI Digestive system | 19 (9) | 8 (13) | X2= 0.8073. p= .368919. NS |
| -XII Diseases of the skin | 6 (3) | 0 | Fisher exact test= 0.3424. NS |
| -XIII Musculo-skeletal | 26 (12) | 6 (9) | X2= 0.3284. p= .566597. NS |
| -XIV Genitourinary | 25 (12) | 13 (21) | X2= 3.2958. p= .069458. NS |
| -XVII Congenital malformations | 1 (0.5) | 0 | Fisher exact test= 1. NS |
| TOTAL chronic diseases* | 214 (100) | 63 (100) | --- |

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

**Table 4:** Comparison of Symptoms between Adverse Covid-19 Vaccines Booster Reactions and Adverse Covid-19 Vaccines Reactions First and Second Doses.

| SYMPTOMS * ACCORDING TO WHO, ICD-10 GROUPS | ADVERSE COVID-19 VACCINES REACTIONS (1 AND 2 DOSES) N=73** (Data collected only from February to July 2021) | ADVERSE COVID-19 VACCINES BOOSTER REACTIONS N=21 | STATISTICAL SIGNIFICANCE |
|---|---|---|---|
| -V Mental (anxiety) | 1 (1) | 0 | Fisher exact test= 1. NS |
| -VI-VIII Nervous and Senses (Ear plugging, earache, subconjunctival hemorrhage, conjunctivitis) | 6 (4) | 2 (5) | Fisher exact test= 0.6668.NS |
| -IX Circulatory system (superficial phlebitis) | 1 (1) | 0 | Fisher exact test= 1. NS |
| -X Respiratory system (cough, dyspnea, rhinitis) | 6 (4) | 3 (7) | Fisher exact test= 0.3923.NS |
| -XI Digestive system (diarrhea, nausea, vomiting, abdominal pain) | 22 (13) | 2 (5) | X2 with Yates correction= 1.6641. p= .197048. NS |
| -XII Diseases of the skin (urticaria) | 5 (3) | 1 (2) | Fisher exact test= 0.2085. NS |
| -XIII Musculo-skeletal (myalgia, musculoskeletal pain) | 34 (20) | 7 (17) | X2= 0.3466. p= .556047. NS |
| -XIV Genitourinary (hematuria, abortion) | 2 (1) | 0 | Fisher exact test= 1. 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 (53) | 27 (64) | X2= 1.7083. p= .191207. NS |
| TOTAL SYMPTOMS* | 164 (100) | 42 (100) | --- |

( ): Denotes percentages; NS: Not significant; *Patients could have more than one symptom. The percentages are over the total of symptoms; ** Adverse covid-19 vaccines reactions with1 or 2 doses: N=73. (Data collected only from February to July 2021)

**Table 5:** Comparison of Vaccine Types between Adverse Covid-19 Vaccines Booster Reactions Versus First and Second Doses.

| VACCINE TYPES | ADVERSE COVID-19 VACCINES REACTIONS (1 AND 2 DOSES) N=109 | ADVERSE COVID-19 VACCINES BOOSTER REACTIONS N=21 | STATISTICAL SIGNIFICANCE |
|---|---|---|---|
| BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) | 78 (72) | 4 (19) | X2= 20.8474. p < 0.00001. Significant at p < .05. |
| mRNA-1273 vaccine (Spikevax, Vaccine Moderna) | 9 (8) | 17 (81) | X2 with Yates correction= 53.7017. p < 0.00001. Significant at p < .05. |
| ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) | 17 (15) | 0 (It was not used in booster) | NR |
| Janssen (Johnson & Johnson vaccine) | 5 (5) | 0 (It was not used in booster) | NR |
| TOTAL | 109 (100) | 21 (100) | -- |

( ): Denotes percentages; NR: Not Relevant

## Discussion

Based on currently available literature, covid-19 vaccines may cause mild side effects after the first or second dose, including pain, redness, or swelling at the injection site, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and on rare occasions it can also cause anaphylactic shock. The occurrence of adverse events was reported to be lower for the Pfizer/BioNTech vaccine compared to the Moderna vaccine (19).

It has been hypothesized that the side effects of the booster will probably be very similar to those of the second dose for most people; It is even thought that there may be fewer adverse reactions with the booster because there is a lot of time between the second and third doses, compared to the first and second doses. CDC reported that reactions reported after a third dose of the mRNA vaccine were similar to those in the two-dose series; the most common side effects were pain at the injection site, fatigue, and headache. Most of these side effects were mild to moderate and occurred within a day of the booster. Pfizer also provided some details about side effects after the third dose of its vaccine, which were similar to the second dose, including: redness and swelling around the injection site, tiredness, headache, muscle and joint pain and chills (10).

Other authors have reported that the most common local adverse reactions after the third dose were pain at the injection site, tenderness at the injection site, and swelling of the axillary lymph nodes. The most frequent systemic adverse reactions were fatigue, muscle pain, bone pain, headache, and fever below 38ºC. Less common systemic adverse reactions were chills, fever over 38°C, nasal congestion and runny nose, arrhythmia, cough, abdominal pain, chest tightness, nausea, diarrhea, vomiting, and tachypnea. Rare systemic adverse reactions were constipation, dizziness and vertigo, poor concentration, sore throat, excessive hair loss, dysmenorrhea and heavy menstruation, and Bell's palsy. Serious allergic reactions were reported by 2.6% of participants after the second dose, compared to none after the third dose. Nasal congestion and runny nose are more common after the 3rd dose. Adverse reactions of the 2nd and 3rd dose were significantly more frequent in women. People ≤ 60 years were more affected by vaccine adverse reactions (20). Therefore, in general, our results are in line with what was previously published. On the other hand, a higher proportion of lymphadenopathy was observed after the administration of the third doses, which is in line with what was observed in clinical trials (21).

Other studies have shown that reactions reported after getting a booster shot are similar to those after the two-dose or single-dose primary shots. Most side effects were mild to moderate. The most commonly reported side effects were fever, headache, fatigue (tiredness), pain at the injection site (22, 23). However, in another study among 47,999 people who received 3-dose covid-19 mRNA vaccines, although reporting of serious adverse events remained low after the third dose of the vaccine consistent with the results of previous studies, Significantly more people reported low-severity adverse events after the third dose

compared to the second dose, including fatigue (4.92% vs. 3.47%), lymphadenopathy (2.89% vs. 2.07%) , nausea (2.62% vs. 2.04%], headache (2.47% vs. 2.07%, arthralgia (2.12% vs. 1.70%), myalgia (1.99% vs. 1.63 %, diarrhea (1.70% vs. 1.24%), fever (1.11% vs. 0.81%, vomiting (1.10% vs. 0.80%), and chills (0.47% vs. 0.36%) (9).

In another study based on a cross-sectional survey among adults aged ≥18 years, with clinical data collected 14 days after booster vaccination using a standard questionnaire, with 1322 participants, and where AstraZeneca was the most used vaccine for the first and the second dose, while Pfizer was the most commonly used vaccine for booster shots, showed that injection site pain, fatigue, and myalgia were the most common side effects reported (80%, 28%, and 22%, respectively). Compared with previous injections of the covid-19 vaccine, 82% of participants reported their symptoms were similar or milder after receiving the booster dose. But, it was more likely injection site pain and lymphadenopathy after receiving the booster. Fever and fatigue were reported less frequently after booster injections compared to the first and second injections. The severity of symptoms that occurred after the booster dose compared with the first and second doses increased significantly with each additional year of age and among participants who received the Pfizer and Moderna vaccines (11).

It has been proposed that the side effects of the booster are, in general, similar to those of the second dose. This may mean that they are more intense than those of the first one, but that no new adverse event occurs (24). Regarding the homologous or heterologous booster, it has been published that those who received the same type of vaccine for all their doses tended to have fewer reactions after the booster than after the second dose (25). On the other hand, homologous booster schedules reported fewer systemic side effects than heterologous boosters (26).

In Spain, fever or pain in the area of the puncture continue to be the most frequently reported. Until February 6, 2022, a total of 22,307,885 booster doses of Pfizer and Moderna were administered in Spain and only 785 notifications of adverse events associated with the vaccine were registered; the majority of these reactions affected women (69%) and 302 were considered serious. More than half of the third doses inoculated in Spain (56%) corresponded to Moderna, which is precisely the one with the most side effects (64 percent of the total). Specifically, of the 502 notifications related to Moderna's vaccination, the vast majority are transient reactions that can occur in the first days after administration of the vaccine. For this vaccine, the most common adverse reactions were fever, headache, myalgia, nausea, malaise, chills or pain at the injection site. On the other hand, in Spain, of the 282 notifications associated with the third dose of Pfizer, it has also been concluded that general disorders such as fever or pain in the vaccination area continue to be the most frequently reported, followed by systemic disorders, nervous system (mainly headaches and syncope) and the musculoskeletal system (myalgia and arthralgia). However, a higher proportion of lymphadenopathy has been observed after administration of booster doses, which is consistent with what was observed in clinical trials (5.2% vs. 0.4%, respectively) (27).

### Limitations and Strengths of the Study

- It must be taken into account that the results could be minimal data, since adverse reactions to the covid-19 vaccine booster being mostly mild or moderate in nature, and so they could not always generate a consultation with the GP.
- The self-report nature of adverse ractions in this study could be considered a limitation.
- It is a small study to detect rare (serious) adverse events.
- A limitation may be having performed the analysis by adding the cases of adverse reactions to the first and second doses. It can be thought that a disaggregated analysis would give better results. But, it was decided to join the adverse reactions of the first and second doses since their disaggregated number was small (even so, the study has a small number of cases). On the other hand, the statistical interpretation of the results in a 3 x 2 contingency table can be more confusing than in a 2 x 2 one (in addition to reducing the numbers to be compared).
- The study is limited to mRNA vaccines as a booster shot, it can't be extrapolated to other Covid-19 vaccines.
- Our prospective study was based on continued GP care allowed a long follow-up time, and this can be considered strength of the study.

### Conclusion

In the context of general medicine in Toledo (Spain), there were no statistically significant differences by age groups, or sex, socio-family factors, previous covid-19, frequency of chronic diseases, and adverse reaction symptoms between booster vs. first and second doses of covid-19 vaccine. However, there is tendency for adverse reactions to be significantly lighter with the booster than with the first or second dose of the covid-19 vaccine. But this study is not large enough to detect rare (serious) adverse events. In addition, the participants received mRNA vaccines as a booster shot; therefore, our results cannot be translated to other vaccines.

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