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Incidence Rates and Risk Factors for Covid-19 Booster Adverse Reactions in General Medicine

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Research Article

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Abstract

Background: Data on the incidence rate and risk factors of covid-19 booster adverse reactions are critical to success vaccination programs.

Objective: To describing the incidence rates and risk factors for covid-19 booster adverse reactions in general medicine.

Methodology: An observational, longitudinal and prospective study of patients who self-report covid-19 booster adverse reactions as a reason for visiting in a general medicine office in Toledo (Spain) was carried out from December 1, 2021-September, 1 2022.

Results: Statistically significant factors found for the covid-19 booster adverse reactions were: 1) Protective factors: age > = 65 years, complex family, chronic diseases of circulatory system, and vaccine booster with Comirnaty, Pfizer / BioNTech); And 2) Risk factors: age 14-64 years, presence of chronic diseases, chronic diseases of genitourinary, and vaccine booster with Moderna mRNA-1273. The incidence rates of covid-19 booster adverse reactions were: 2% >=14 years, 0.3% >= 65 years, 3% in women, 1.5% in men, 1% in Comirnaty (Pfizer / BioNTech), and 3 % in Moderna mRNA-1273.

Conclusions: In the context of general medicine in Toledo (Spain), for the period December 1, 2021-September, 1 2022, the incidence rates of covid-19 booster adverse reactions was low, especially in >= 65 years and men. Risk factors focus on women aged 16-64 years, with chronic diseases, and vaccine booster with Moderna mRNA-1273. The risk estimates clearly favour vaccination. However, the small number of cases limits the conclusions that can be drawn.

Key Words: COVID-19; SARS-CoV-2; Post-Vaccination Reactions; COVID-19 vaccines; Adverse Events Reaction; Booster Vaccination; General Practice; Risk Factors

Introduction

The coronavirus disease of 2019 (covid-19) remains a current threat to public health. Vaccination may provide more extraordinary safety measures against hospitalizations related to the covid-19 virus. By April 22, 2022, about 11.2 billion covid-19 vaccines had been administered in more than 197 countries. The percentage of individuals fully vaccinated worldwide is 60% of the total world population (1, 2). Randomized clinical trials have shown high efficacy of covid-19 vaccines, and observational studies have estimated high real-world effectiveness. However, reports of emerging infections and the decreased immunity have raised concerns regarding the duration of protection (3-5). Boosters achieve strong protection against covid-19-related hospitalization and death (6) and produce a greatest escalation of antibody and cellular immune responses, restoring the efficacy of the vaccine (7-9). These data have led to the approval and implementation of additional doses and booster vaccines (10).

In this scenario, post vaccination adverse effect is an important issue (11-13). Many people have a history of a significant adverse reaction to a specific food, drug, or vaccine; therefore, people around the world have serious concerns about licensed vaccines (14). A post-vaccination adverse event is any adverse medical event that follows immunization and is not necessarily causally related to the use of the vaccine. The adverse event can be any unfavourable or unwanted sign, abnormal laboratory result, symptom or disease (15). The detection, reporting, analysis and communication of post-vaccination adverse effects constitute the basis of vaccine pharmacovigilance (15). Pharmacovigilance is the science related to the collection, detection, evaluation, monitoring and prevention of adverse reactions with pharmaceutical products (16).

Data on the incidence rate and risk factors of covid-19 booster adverse reactions are critical to the successful promotion of the covid-19 vaccine booster program. The more information that can be obtained, the better it will be for people to select the

appropriate brand of vaccine. However, research on adverse events of booster doses is still scarce (17). In this context, we present an observational, longitudinal and prospective study of patients who self-reported covid-19 booster adverse reactions as a reason for visiting in a general medicine office in Toledo (Spain) from December 1, 2021-September, 1 2022, to determine incidence rates (IR) and possible risk factors for covid-19 booster vaccines reactions.

Material and Methods

Design and Emplacement

An observational, longitudinal and retrospective case series study of patients with covid-19 booster adverse reactions, based on a prospective cohort of patients was carried out from December 1, 2021-September, 1 2022, in a family medicine office in the Health Center Santa Maria de Benquerencia, 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). The methodology has already been exposed in part, in a preliminary study with a series of cases (18).

Outcomes of Interest

The outcomes of interest were:

1. Determine incidence rates (IR) of adverse covid-19 booster vaccines reactions.
2. Study some of the possible risk factors for covid-19 booster vaccines reactions.

In this sense, the variables collected were compared by calculating the relative risk (RR) as incidence of covid-19 booster with adverse reactions / incidence of covid-19 booster without adverse reactions. RR expresses excess risk that a patient has for being exposed to the risk factor, but does not measure the probability. The RR was interpreted as follows (19):

- From 0 to 0.5 protection factor effectively
- From 0.6 to 0.8 true benefits
- From 0.9 to 1.1 not significant
- From 1.2 to 1.6 weak risk
- From 1.7 to 2.5 moderate risk
- More than 2.5 strong risk

Definition of Cases and Controls

Patients with covid-19 booster adverse reactions who had accessed medical care were considered cases. Control patients were the rest of the people who received booster but without covid-19 booster adverse reactions (who did not go to medical attention for covid-19 booster adverse reactions).

Calculation of the Incidence Rate (IR) of Adverse Effects to the Covid-19 Booster Vaccine

IR of adverse events was calculated as the sum of all reported adverse events divided by the number of people vaccinated with booster, at follow-up time, and expressed as the fraction of 100 people vaccinated with booster (17, 29).

Calculation of Denominators for Relative Risks (RRs)

The total number of patients assigned to the consultation (2000 people) was used as an approximation to the denominator. Nationally published data (21-25) were used to infer booster doses administered in general practice and types of vaccines applied. Other data in relation to other variables of interest (as complex family, and chronic diseases) in the medical office object of the study, were based on the results from previously published studies (26, 27).

Diagnosis of Adverse Covid-19 Vaccines Reactions

Reports of covid-19 booster adverse 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 (28, 29).

Collected Variables

The following variables were collected: 1) Age and sex; 2) 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) (30), classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (31); 3) Complex family based on the genogram (It was understood that "complex" genogram identified complex families with psychosocial problems) (32); 4) Prior covid-19 (diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing or antibody test) (33); 5) Vaccine type (Only mRNA vaccines: Pfizer / BioNTech or Moderna mRNA-1273) (34).

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X2) with Yates correction or Fisher Exact Test when necessary.

Results

Incidence rates of covid-19 booster adverse reactions for the period December 1, 2021-September, 1 2022, was 2% >=14 years, 0.3% >= 65 years, 3% in women and 1.5% in men, 1 % in Comirnaty (Pfizer / BioNTech), and 3% (Moderna mRNA-1273 (TABLE 1). The following statistically significant factors were found: A) Protective factors for covid-19 booster adverse reactions: age >= 65 years, complex family (Potential problems familiar context of the patient based on the genogram), chronic diseases of circulatory system, and vaccine booster with Pfizer/BioNTech; B) Risk factors for covid-19 booster adverse reactions: age 14-64 years, presence of chronic diseases, chronic diseases of genitourinary, and vaccine booster with Moderna mRNA-1273 (TABLE 2, TABLE 3).

Discussion

No vaccine is perfectly safe. Most vaccines have side effects, and those for covid-19 are no different. A clinical or epidemiological study is needed to find out if the reaction rate in vaccinated individuals exceeds that expected (35). Mild to moderate effects indicate that the immune system is responding to the vaccine (36). Clinical trials of the vaccine conducted by Pfizer show that 50% experienced no significant side effects during the trials, yet 90% of participants built up immunity against the virus. Moderna's mRNA-1273 vaccine protocol notes that common side effects may be experienced by one in ten people, yet the vaccine

Table 1: Incidence Rates of Covid-19 Booster Adverse Reactions in General Medicine (Toledo, Spain) for the Period December 1, 2021-September 1, 2022.

VARIABLES	COVID-19 BOOSTER ADVERSE REACTIONS N=21	ESTIMATED POPULATION OF GP OFFICE WITH BOOSTER SHOT N=1.021 booster en la consulta	WITHOUT COVID-19 BOOSTER ADVERSE REACTIONS N=1.000 booster SIN RA	INCIDENCE RATES OF COVID-19 BOOSTER ADVERSE REACTIONS FOR THE PERIOD DECEMBER 1, 2021-SEPTEMBER, 1 2022
=< 14 years	21 (100)	1.021 (100)	1.000 (100)	2%
> = 65 years	1 (5)	325 (32)	324 (32)	0.3%
14-65 years	20 (95)	696 (68)	676 (68)	3%
Women	14 (67)	541 (53)	527 (53)	3%
Men	7 (33)	480 (47)	473 (47)	1,5%
Complex family	2 (9)	333 (30)	333 (30)	1%
Cases with chronic diseases	15 (71)	153 (15)	150 (15)	10%
Vaccine booster with BNT162b2 mRNA (Comirnaty, Pfizer / BioNTech)	4 (19)	449 (44%)	445 (99)	1%
Vaccine booster with mRNA-1273 (Spikevax, Moderna)	17	572 (56)	555 (97)	3%

( ): Denotes percentages.

Table 2: Comparison of Selected Variables between Covid-19 Booster Adverse Reactions and Covid-19 Booster without Adverse Reactions and Relative Risk Calculation in General Medicine for the Period December 1, 2021-September, 1 2022.

VARIABLES	COVID-19 BOOSTER ADVERSE REACTIONS N=21	COVID-19 BOOSTER WITHOUT ADVERSE REACTIONS N=1.000	STATISTICAL SIGNIFICANCE	RELATIVE RISK (RR)
> = 65 years	1 (5)	324 (32)	X2= 7.2405. p= .007128. Significant at p < .05.	RR= 0.11 (CI 95%: 0.64, 0.02). Protection factor effectively
14-65 years	20 (95)	676 (68)	X2= 7.2405. p= .007128. Significant at p < .05.	RR= 7.19 (CI 95%: 1.08, 47.85). Strong risk
Women	14 (67)	527 (53)	X2= 1.6106. p= .204405. NS	RR= 1.77 (CI 95%: 0.61, 5.14). Moderate risk
Complex family	2 (9)	333 (30)	X2= 5.2742. p= .021643. Significant at p < .05.	RR= 0.22 (CI 95%: 0.93, 0.05). Protection factor effectively
Cases with chronic diseases	15 (71)	150 (15)	X2 with Yates correction is 44.2626. p < 0.00001. Significant at p < .05.	RR= 12.99 (CI 95%: 6.1, 27.66). Strong risk
Vaccine booster with BNT162b2 mRNA (Comirnaty, Pfizer / BioNTech)	4 (19)	445 (99)	X2= 5.4083. p= .020041. Significant at p < .05.	RR= 0.3 (CI 95%: 0.92, 0.1). Protection factor effectively
Vaccine booster with mRNA-1273 (Spikevax, Moderna)	17	555 (97)	X2= 5.4083. p= .020041. Significant at p < .05.	RR= 3.34 (CI 95%: 1.08, 10.29). Strong risk

( ): Denotes percentages; RR: relative risk; NS: Not significant.

Table 3: Comparison of Chronic Diseases between Covid-19 Booster Adverse Reactions and Covid-19 Booster without Adverse Reactions and Relative Risk Calculation in General Medicine for the Period December 1, 2021-September, 1 2022.

CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 BOOSTER ADVERSE REACTIONS N=21	COVID-19 BOOSTER WITHOUT ADVERSE REACTIONS N=1.000	STATISTICAL SIGNIFICANCE	RELATIVE RISK (RR)
-I Infectious	1 (2)	10 (1)	Fisher exact test= 0.2552. NS	RR= 3.48 (CI 95%: 0.01, 1567.9). Strong risk
-II Neoplasms	1 (2)	77 (3)	Fisher exact test= 0.7216. NS	RR= 0.48 (CI 95%: 17.5, 0.01). Protection factor effectively
-III Diseases of the blood	0	43 (2)	Fisher exact test= 0.628. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-IV Endocrine	6 (10)	274 (12)	X2= 0.3017. p= .582792. NS	RR= 0.79 (CI 95%: 2.96, 0.21). True benefits
-V Mental	11 (17)	310 (13)	X2= 0.9007. p= .342593. NS	RR= 1.37 (CI 95%: 0.61, 3.09). Weak risk
-VI-VIII Nervous and Senses	9 (14)	181 (8)	X2= .5446. p= .059741. NS	RR= 1.93 (CI 95%: 0.88, 4.21). Moderate risk
-IX Circulatory system	4 (6)	429 (18)	X2= 6.0462. p= .013936. Significant at p < .05.	RR= 0.3 (CI 95%: 0.84, 0.11). Protection factor effectively
-X Respiratory system	4 (6)	195 (8)	X2= 0.3324. p= .564235. NS	RR= 0.75 (CI 95%: 3.76, 0.15). True benefits
-XI Digestive system	8 (13)	191 (8)	X2= 1.6172. p= .203484. NS	RR= 1.6 (IC 95%: 0.66, 3.88). Weak risk
-XII Diseases of the skin	0	59 (3)	Fisher exact test= 0.4048. NS	RR= 0 (IC 95%: Infinity, 0). Protection factor effectively
-XIII Musculo-skeletal	6 (9)	356 (15)	X2= 1.5947. p= .206658. NS	RR= 0.56 (IC 95%: 1.43, 0.22). True benefits
-XIV Genitourinary	13 (21)	201 (9)	X2= 10.8189. p= .001005. Significant at p < .05.	RR= 2.64 (IC 95%: 1.42, 4.91). Strong risk
TOTAL chronic diseases*	63 (100)	2326 (100)	---	---

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

protects 95% (37).

It is the innate immune response that causes the usual side effects that people experience a day or two after being vaccinated. Long-lasting specific immunity, which is the ultimate goal of any vaccination, is only achieved by activating the adaptive immunity. Unlike innate immunity, adaptive immunity cannot initiate inflammation, although recent studies suggest that it may significantly contribute to it. In some people, this inflammatory response of the innate and adaptive immune systems is exaggerated and manifests as a secondary effect. In others, although it works normally, it does not work at levels that can cause noticeable side effects (37).

Population heterogeneity in relation to infection, covid-19 vaccination, and host characteristics is likely to be reflected in the underlying antibody responses to virus, and consequently in the frequency of reactions adverse (38). It has been observed that people over 65 years of age have fewer side effects from the vaccine. This may be attributed to the age-related gradual decline in immune activity (37). Sex can also play a role. It has been published 79% of side effect reports came from women. This bias may be related to testosterone, which tends to dampen inflammation and therefore the side effects associated with it. Men have more testosterone than women, which could contribute to fewer cases of side effects (37). People with chronic inflammatory diseases (such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis) who take immunosuppressive drugs to control their symptoms may experience fewer side effects due to a decreased inflammatory response (37).

The objective of our study was to analyze the incidence rate and factors associated with covid-19 booster adverse reactions as reason for visiting in a general medicine office in Toledo (Spain) from December 1, 2021-September, 1 2022. Our main findings are that young people <= 65 years old, with chronic diseases and with Moderna mRNA-1273 booster had a higher risk for covid-19 booster adverse reactions. On the other hand, our calculation of the IR of covid-19 booster adverse reactions suggests that these are not frequent (2%), although somewhat more in women (3%) and with Moderna mRNA-1273 (3%). These data are in line with what has been reported by other authors (13, 39).

Thus, vaccine type has been reported to be the main modifiable factor in antibody responses after vaccination, and Moderna mRNA-1273 was found to give the highest responses (37). People aged 60 years or older had lower antibody levels after vaccination compared with younger participants, and increasing age has been associated with reduced responses to the vaccine in several studies, regardless of vaccine type (37, 40, 41). In several studies, women had higher IgG levels after covid-19 vaccination than men (37, 42, 43). In Spain at the end of March 2022, 37% of covid-19 booster adverse reactions corresponded to the administration of Comirnaty (Pfizer / BioNTech) and 63% to Spikevax (Moderna mRNA-1273). Of these, the majority occurred in women (69%) and in people between the ages of 18 and 65 (87%) (21, 22).

People who reported mental health illnesses (depression, chronic stress, schizophrenia, bipolar disorder, etc.) had lower antibody levels in multivariable models. This association can be attributed to specific diagnoses, medications, and other underlying characteristics of those people (37, 44). On the other hand, patient reporting of side effects when taking medications may be influenced by a number of factors: the patient's expectations of adverse effects at the start of treatment, a conditioning process in which the patient learns from previous experiences and associates taking medication with somatic symptoms, certain psychological characteristics such as anxiety, depression, and the tendency to somatise, and circumstantial and contextual factors (45). We found that the presence of mental illness implies a weak risk, but not statistically significant. Perhaps the tendency to have lower antibody levels (and fewer adverse reactions) is offset by the tendency to report more non-pharmacological adverse reactions in these patients.

People with cardiovascular disease have been reported to have increased IgA and IgG responses after vaccination; although these did not report symptoms more frequently or cardiovascular sequelae (37, 42, 46). We found the presence of chronic diseases of circulatory system as protective factors for covid-19 booster adverse reactions. The safety of the booster dose should be especially considered in special populations, such as people with autoimmune diseases (17). It has been reported that a booster vaccination was not associated with an increased risk of adverse effects in patients with various immune-mediated inflammatory diseases (39). We did not find this possible risk either, showing chronic musculoskeletal diseases as a protective factor, but not statistically significant.

A limitation of our study is the small number of cases of covid-19 booster adverse reactions included; consequently, it is not large enough to assess rare and very rare events (47), such as Bell's palsy, anaphylaxis, and myopericarditis (48-52).

Finally, it is keep in mind that on August 31, 2022, the U.S. FDA authorized emergency use of two novel bivalent mRNA covid-19 vaccines for boosting previous immunizations. The original covid-19 monovalent mRNA vaccines from Pfizer and Moderna, which are the ones analyzed in our study, are no longer licensed for use as boosters in the US for adolescents (age, ≥12) and adults. In these patients the new bivalent vaccines are the only options reinforcement (53).

Conclusion

In the context of general medicine in Toledo (Spain), from December 1, 2021 to -September, 1 2022, the IR of covid-19 booster adverse reactions was low, especially in >= 65 years and men. Risk factors focus on women aged 16-64 years, with chronic diseases. Our results seem to indicate that vaccine booster with BNT162b2 mRNA (Comirnaty, Pfizer / BioNTech) exhibits lowest IR of adverse and it showed a protective RR versus Spikevax (Moderna mRNA-1273). The risk estimates clearly favour vaccination. However, the small numbers available do not allow definitive conclusions to be drawn.

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