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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)

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Abstract

Background: Information on the safety of vaccines against COVID-19 is essential.

Objective: To describing the incidence rates (IR) and risk factors for adverse COVID-19 vaccines reactions in general medicine.

Methodology: An observational, longitudinal and prospective study of patients que consuln por adverse reactions to COVID-19 vaccines in a general medicine office in Toledo (Spain) was carried out from February to September 2021.

Results: We found an IR of 5% cases of adverse COVID-19 vaccines reactions in people = <14 years x 8 months, the highest figure being between 14-49 years, in women, and with Pfizer-BioNTech-BNT162b2 and AstraZeneca-ChAdOx1 nCoV- 19 vaccines. Regarding gravity, the highest IR was 3 cases of moderate adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months. Statistically significant protective factors were: > = 65 years, 14-49 years, or 14-18 years, male, some type of labour specialization, complex family, and chronic diseases of Circulatory system; and risk factors: age 14-65 years, female, chronic diseases of Endocrine, and Nervous and Senses. Vaccine Moderna- mRNA-1273 was the only one that showed a protective Relative Risk of of adverse COVID-19 vaccines reactions, but without statistical significance.

Conclusion: In the context of general medicine in Toledo (Spain), during the 8-month follow-up, the IR of adverse COVID-19 vaccines reactions is low. The risk estimates clearly favour vaccination.

Keywords: COVID-19; SARS-CoV-2; Adverse Drug Events; Post-vaccination Reactions; Vaccine Safety, COVID-19 vaccine; General Practice; Epidemiology; Risk Factors

Abbreviations: WHO: World Health Organization; COVID-19: Coronavirus Disease 2019; PCR: Polymerase Chain Reaction.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak, caused by the SARS-CoV-2 virus, a global pandemic. Vaccines for COVID-19 have been developed at unprecedented speed, and phase III clinical efficacy trials reported results for some vaccines less than a year after the WHO declared the pandemic. Since December 2020, various vaccines have been licensed by regulators such as the European Medicines Agency, the US Food and Drug Administration, and the UK Medicines and Health Products Regulatory Agency. New COVID-19 vaccines are beginning to change this situation [1-5], and numerous new vaccines are in the final stages of clinical trials [6,7]. Currently, the European Commission has licensed four vaccines: BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech) licensed December 21, 2020; mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), licensed January 6; ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), licensed 29 December and Janssen (Johnson & Johnson vaccine), authorized on March 11. In Spain, these four vaccines are currently available, all of which have been approved by the European Medicines Agency [8].

The Janssen (Johnson & Johnson vaccine) vaccine against COVID-19 is a vector vaccine. ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca) is also a vector vaccine against COVID-19. In this type of vaccine, the genetic material of the COVID-19 virus is placed in a modified version of another virus (viral vector). When the viral vector enters cells, it delivers the genetic material from the COVID-19 virus that instructs cells to make copies of protein S. Once cells display S proteins on their surface, the immune system It responds by creating defence antibodies and white blood cells [9]. A second approach is employed by BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech) and mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), which have produced the first licensed vaccines using synthetic mRNA technology. The mRNA is inside a lipid droplet, which protects it from enzymatic degradation and allows it to enter cells. The mRNA chain induces peak protein synthesis without entering the cell nucleus or affecting the genetic material [10].

Mass vaccination campaigns to prevent COVID-19 are now occurring in many countries [11]. Existing vaccine-effectiveness estimates have focused on the BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) and Janssen (Johnson & Johnson vaccine) [12-17]. Accelerated development and regulatory evaluation, as well as rapid deployment of vaccines, have exposed both the strengths and limitations of current safety monitoring systems [18]. Thus, although the speed of development of the vaccines must be recognized, there is still uncertainty about the safety and efficacy of these vaccines in populations other than those tested in the trials. As with all medicines, vaccine safety should continue to be monitored after regulatory clearance to complement what has been learned during clinical development [19].

Phase 3 trials may have inherent limitations in evaluating vaccine safety due to a small number of participants and a healthier than average population sample. Post-marketing surveillance is required to monitor the safety of new vaccines in real-world settings [20]. As new knowledge about the safety and benefits of vaccines continues to evolve, the benefit-risk balance must be reassessed, refined, and communicated as the burden of disease changes and new variants emerge [21].

On February 2, 2021 Spain began a mass vaccination campaign. As of September 3, 2021, in Spain there were 36,696,877 people (77.3% of the population) with at least one dose, and 33,940,053 (71.5% of the population) with a complete regimen [22]. And with data of September 30, 2021, in Castilla La Mancha, (Spain), 85% of the population has a complete COVID-19 vaccination schedule. In this context, we present an observational, longitudinal and prospective study in general medicine in Toledo, Castilla La Mancha (Spain), based on a cohort of patients from February 1, 2021 to September 30, 2021, which aimed to know and describe the incidence rates (IR) and the risk factors for adverse COVID-19 vaccines reactions of patients who consult for reported adverse reactions after COVID-19 vaccination.

Material and Methods

The methodology has already been exposed in part, in a preliminary study with a series of cases smaller than the current one [23].

Design and Emplacement

An observational, longitudinal and retrospective case series study of patients with RA a vacunas COVID-19 syndrome, based on a prospective cohort of patients was carried out from February 1, 2021 to September 30, 2021, 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 [24]. The number of residents of the neighbourhood that is treated at the Health

Center, by 2020, was 22,553 people [25].

Outcome of Interest

The outcomes of interest were:

1. Determine IR of adverse COVID-19 vaccines reactions. IR of adverse reactions to COVID-19 vaccines was calculated at the GP's office by dividing the number of infection events by the person follow-up time [26].
2. Study some of the possible risk factors for COVID-19 vaccines reactions. In this sense, the variables collected were compared by calculating the relative risk (RR) as the Incidence among the exposed population/Incidence among the population not exposed to possible risk factors, in patients with adverse COVID-19 vaccines reactions and those who had not adverse COVID-19 vaccines reactions. RR expresses to the clinician the excess risk that a patient has for being exposed to the risk factor, and also serves to identify people at high risk, but does not measure the probability that someone with the risk factors will acquire the disease. The RR was interpreted as follows [27]:

- 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 adverse reactions to COVID-19 vaccines who had accessed medical care were considered cases. Control patients were the rest of the people without with adverse COVID-19 vaccines reactions, from the GP's list of patients, who did not go to medical attention or were diagnosed at another level of the health system. As explained below, at the date of data analysis (September 30, 2021) 89% of the patients in the consultation received the first dose; 85% received the 2 doses. It can be said that a negative symptoms or no-consultation design was used for adverse reactions to COVID-19 vaccines [28].

Calculation of Rate Denominators

The total number of patients assigned to the consultation (2000 people) was used as an approximation to the denominator of rates. Spain began its mass immunization program on December 27, 2020, shortly after the first COVID-19 vaccine (BNT162b2 mRNA vaccine; Comirnaty, Pfizer/BioNTech) was approved earlier that month. With data of September 30, 2021, in Castilla La Mancha, (Spain), 85% of the population has a complete COVID-19 vaccination schedule. In the consultation object of the study had 295 cases de COVID since May 15, 2020 (date from which the consultation has records, since they begin to perform PCR on suspected COVID-19 cases, and as of December 22, 2020 they also begin to perform rapid antigen tests for symptoms of less than 5 days of evolution) until September 30, 2021.

The population for the neighbourhood that depends on the consultation object of the study and Toledo (Castilla La mancha) was considered based on official statistical data to obtain approximations of the data of the age groups attended in the consultation. Thus, adverse COVID-19 vaccines (cases) were compared with the total population attended in the consultation (controls) (2,000 people minus the cases of adverse COVID-19 vaccines reactions) whose data regarding some variables of interest (as complex family, and chronic diseases) were previously published [29,30]. For the denominators of the types of vaccines applied in the total population, official vaccination data were used [31].

Diagnosis of Adverse COVID-19 Vaccines 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 [32].

COVID-19 Diagnosis

COVID-19 diagnosis was performed with polymerase chain reaction (PCR) oropharyngeal swab test or antigen test for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. A symptomatic 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, musc le 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 [33].

Collected Variables

Data were extracted from the medical records of the general medicine practice under study. 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" [34], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [35].

3. Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [36,37].
4. Complex family and low income household based on the genogram and in the experience of the general practitioner about continuity of care and knowledge of the family (genogram was a schematic model of the structure and processes of a family, which included the family structure , life cycle and family relational patterns. It was understood that "complex" genogram identified complex families with psychosocial problems) [38-41].
5. Symptomatic or asymptomatic prior COVID (the diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing or antibody test. Spain had not initially devised an intensive testing strategy for suspected cases of COVID-19 infections [42]. Since the beginning of the pandemic in mid-March 2020, PCR tests were only performed in the hospital context until mid-May 2020, when they began to be performed in general medicine as well. In mid-December 2020, rapid antigen tests began to be carried out for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. A symptomatic 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, musc le 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 [33].
6. Vaccine type: BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), and Janssen (Johnson & Johnson vaccine). In Spain, these four vaccines are currently available, all of which have been approved by the European Medicines Agency).
7. Criteria for the causality of adverse COVID-19 vaccines reactions, classified as [43-45]:

- Definitive (Certain): Event or alteration of laboratory tests with plausible temporal sequence in relation to the administration of the suspected drug. It cannot be explained by the concurrent disease, or by other drugs or substances. It can be a clinical syndrome associated with the use of drugs; Recovery after drug withdrawal (positive withdrawal effect); Positive re-exposure effect.
- Probable (Likely): Event or alteration of laboratory tests with plausible temporal sequence in relation to the administration of the suspect drug. It is unlikely to be attributed to the concurrent disease to other drugs or substances. There is a clinically reasonable response to drug withdrawal. Re-exposure not analysed.
- Possible: Event or alteration of laboratory tests with a plausible temporal sequence in relation to the administration of the suspected drug, but which can also be explained by the concurrent disease, or by other drugs or substances. No information is available regarding the effect of the withdrawal.
- Unlikely: Improbable time sequence. It can be more plausibly explained by the concurrent disease, or by other drugs or substances.
- Conditional/Unclassified: It is essential to obtain more data in order to make a proper evaluation, or the additional data is under analysis.
- Not evaluable/Unclassifiable: It cannot be judged because the information is insufficient or contradictory, and that it cannot be verified or completed in your data.

8. Severity or intensity of adverse COVID-19 vaccines reactions, classified as [46]:

- **Mild:** There are easily tolerated signs and symptoms. They do not require therapy or medical intervention.
- **Moderate:** Signs and symptoms that interfere with normal activities. They require intervention or medical treatment.
- **Severe:** Signs or symptoms that incapacitate and disable to carry out habitual activities. They require medical intervention or therapy.

9. Time of appearance of adverse COVID-19 vaccines reactions, classified as [47]:

- **Immediate:** Present within the first 60 minutes (includes urticaria, angioedema, and anaphylaxis)
- **Expedited:** They manifest 1-72 h. after starting treatment (correspond to urticaria, angioedema, pruritus, laryngeal edema and bronchospasm, etc.)
- **Late:** They appear 3 days or more after starting treatment (their most common manifestations are urticaria, angioedema, rash, other skin eruptions, reactions similar to those of serum sickness, interstitial nephritis, hemolytic anemia, neutropenia , thrombocytopenia, Stevens-Johnson syndrome, exfoliative dermatitis, drug fever, etc.).

Sample

All patients who consulted for adverse COVID-19 vaccines reactions from February 1, 2021 to September 30, 2021 were

included, and that they were seen in the consultation object of the study and their medical documentation was available.

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X2) with Yates correction or Fisher Exact Test when necessary, (according to the number the expected cell totals) for percentages, and the Student t test for the mean.

Results

Incidence Rates

We found an IR of 5 cases of adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines in people = <14 years x 8 months, the highest figure being between 14-49 years (7 cases of adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines in people of 14-49 years x 8 months) and less between 14-18 years (0 cases of adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines in people of 14-18 years x 8 months). The RI was higher in women vs. men (5 cases of adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines in women x 8 months vs. 2 cases of adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines in men x 8 months). According to the criteria of causality, the highest IR was 3 cases of probable adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months. According to time of appearance of the adverse COVID-19 vaccines reaction, the highest IR was 4 cases of Accelerated adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months. Regarding the gravity of the adverse COVID-19 vaccines reaction, the highest IR was 3 cases of Moderate adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months. Regarding the type of vaccine involved in the adverse COVID-19 vaccines reaction, the highest IRs were 6 cases of adverse vaccines reactions per 100 COVID-19 vaccines x 8 months for both Pfizer-BioNTech-BNT162b2 vaccines and AstraZeneca-ChAdOx1 nCoV-19 (AZD1222); the lowest IR was for Moderna mRNA-1273 vaccine: (3 cases of adverse Moderna mRNA-1273 vaccines reactions per 100 COVID-19 Moderna mRNA-1273 vaccines x 8 months) (Table 1).

Variables	Adverse Covid-19 Vaccines Reactions N=109	Estimated Population Of GP Office N=2.000	Incidence Rates Of Adverse Covid-19 Vaccines Reactions X 8 Months
=< 14 years	109 (100)	2.000 (100)	5 cases per 100 COVID-19 vaccines in people = <14 years x 8 months
> = 65 years	8 (7)	349 (17)	2 cases per 100 COVID-19 vaccines in people >= 65 years x 8 months
14-65 years	101 (93)	1651 (83)	6 cases per 100 COVID-19 vaccines in people of 14-65 years x 8 months
49-65 years	26 (24)	511 (26)	5 cases per 100 COVID-19 vaccines in people of 49-65 years x 8 months
14-49 years	75 (69)	1140 (57)	7 cases per 100 COVID-19 vaccines in people of 14-49 years x 8 months
14-18 years	0	120 (6)	0 cases per 100 COVID-19 vaccines in people of 14-18 years x 8 months
Women	51 (70)	1060	5 cases per 100 COVID-19 vaccines in women x 8 months
Men	22 (30)	940	2 cases per 100 COVID-19 vaccines in men x 8 months
Criteria of Causality			
1.-Certain	12 (11)	2000	1 case of Certain adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
2.-Probable	62 (57)	2000	3 cases of Probable adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months

3.-Possible	22 (20)	2000	1 cases of Possible adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
4.-Unlikely	13 (12)	2000	1 case of Possible adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
5.-Conditional/ Unclassified)	0	2000	0
6.-Unassessable/ Unclassifiable	0	2000	0
Time of Appearance of the Adverse Covid-19 Vaccines Reaction			
1.-Immediate	4 (4)	2000	0.2 cases of Immediate adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
2.-Accelerated	84 (77)	2000	4 cases of Accelerated adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
3.-Late	21 (19)	2000	1 case of Late adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
Gravity of the Adverse Covid-19 Vaccines Reaction			
1.-Mild	27 (25)	2000	1 case of Mild adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
2.-Moderate	56 (51)	2000	3 cases of Moderate adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
3.- Severe Bronchial hyperresponsiveness, urticaria, dyspnea, hematuria, abortion, fever, phlebitis, anxiety, vertigo, syncope, cellulitis	26 (24)	2000	1 case of Severe adverse COVID-19 vaccines reactions per 100 COVID-19 vaccines x 8 months
Type of Vaccine Involved in the Adverse Covid-19 Vaccines Reaction			
Pfizer-BioNTech-BNT162b2 (Pfizer/BioNTech) mRNA	78 (72)	1380 (69)	6 cases of adverse Pfizer-BioNTech-BNT162b2 vaccines reactions per 100 COVID-19 Pfizer-BioNTech-BNT162b2 vaccines x 8 months
Moderna mRNA-1273	9 (8)	260 (13)	3 cases of adverse Moderna mRNA-1273 vaccines reactions per 100 COVID-19 Moderna mRNA-1273 vaccines x 8 months
AstraZeneca - ChAdOx1 nCoV-19 (AZD1222)	17 (15)	260 (13)	6 cases of adverse AstraZeneca - ChAdOx1 nCoV-19 vaccines reactions per 100 COVID-19 AstraZeneca - ChAdOx1 nCoV-19 vaccines x 8 months
Johnson & Johnson COVID-19 Vaccine Janssen vaccine	5 (5)	100 (5)	5 case of adverse Janssen vaccines reactions per 100 COVID-19 Janssen vaccines x 8 months

( ): Denotes percentages

Table 1: Incidence Rates of Adverse Covid-19 Vaccines Reactions in General Medicine for the Period February-September 2021.

Protection Factors and Risk Factors

The following statistically significant factors were found: A) Protective factors for adverse COVID-19 vaccines reactions: age >= 65 years, 14-49 years, or 14-18 years; male; people with some type of labour specialization; complex family (Potential problems familiar context of the patient based on the genogram); and chronic diseases of Circulatory system. B) Risk factors for adverse COVID-19 vaccines reactions: age 14-65 years; woman; chronic diseases of Endocrine, Nervous and Senses. The Spikevax mRNA vaccine (formerly COVID-19 Vaccine Moderna-mRNA-1273 was the only one that showed a protective relative risk (RR) of adverse COVID-19 vaccines reactions, but without statistical significance (Tables 2-4).

Risk Factors	Adverse Covid-19 Vaccines Reactions N=109	Without Adverse Covid-19 Vaccines Reactions n=1.891	Statistical Significance	Relative Risk (Rr)
> = 65 years	8 (7)	321 (17)	X2= 6.9621. p= .008325. Significant at p < .05.	RR= 0.4 (CI 95%: 0.82, 0.2). Protection factor effectively
14-65 years	101 (93)	1570 (83)	X2= 6.9621. p= .008325. Significant at p < .05.	RR= 2.5 (CI 95%: 1.22, 5.08). Moderate risk
49-65 years	26 (24)	492 (26)	X2= 0.2516. p= .615917. NS	RR= 0.9 (CI 95%: 1.53, 0.53). Not significant
14-49 years	75 (69)	1078 (57)	X2= 5.8781. p= .015331. Significant at p < .05.	RR= 1.6 (CI 95%: 1.08, 2.44). Weak risk
14-18 years	0	113(6)	Fisher exact test= 0.0023. Significant at p < .05.	RR= 0 (CI 95%: 0, 0). Protection factor effectively
Women	72 (66)	988 (52)	X2= 7.8877. p= .004977. Significant at p < .05.	RR= 1.7 (CI 95%: 1.16, 2.55). Moderate risk
Men	37 (34%)	903 (48)	X2= 7.8877. p= .004977. Significant at p < .05.	RR= 0.6 (CI 95%: 0.86, 0.39). True benefits
Symptomatic and asymptomatic prior COVID	10 (9)	295 (16)	X2= 3.2927. p= .06959. NS	RR= 0.6 (CI 95%: 1.1, 0.28). True benefits
Social-occupancy class of patients (people with some type of labor specialization)	33 (30)	864 (46)	X2= 9.9006. p= .001652. Significant at p < .05.	RR= 0.5 (CI 95%: 0.8, 0.35). Protection factor effectively
Complex family (Potential problems familiar context of the patient based on the genogram)	15 (14)	576 (31)	X2= 13.8042. p= .000203. Significant at p < .05.	RR= 0.4 (CI 95%: 0.64, 0.22). Protection factor effectively

( ): Denotes percentages
RR: relative risk

Table 2: Comparison of the Variables Studied Between Adverse Covid-19 Vaccines Reactions And Without Adverse Covid-19 Vaccines Reactions And Relative Risk Calculation.

Chronic Diseases* According To Who, Icd-10 Groups	Adverse Covid-19 Vaccines Reactions N=109	Without Adverse Covid-19 Vaccines Reactions N=1.891	Statistical Significance	Relative Risk (RR)
-I Infectious	0	19 (0.5)	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-II Neoplasms	5 (2)	145 (3)	X2= 0.5247. p= .468864. NS	RR= 0.7 (CI 95%: 2.34, 0.23). True benefits
-III Diseases of the blood	1 (0.5)	82 (2)	X2 with Yates correction= 1.46. p= .226922. NS	RR= 0.3 (CI 95%: 2.3, 0.03). Protection factor effectively
-IV Endocrine	40 (19)	523 (12)	X2= 9.6539. p= .00189. Significant at p < .05.	RR= 1.7 (CI 95%: 1.2, 2.38). Moderate risk
-V Mental	28 (13)	592 (13)	X2= 0.0014. p= .969991. NS	RR= 1 (CI 95%: 1.31, 0.75). Not significant
-VI-VIII Nervous and Senses	28 (13)	347 (8)	X2= 8.0137. p= .004643. Significant at p < .05.	RR= 1.7 (CI 95%: 1.16, 2.6). Moderate risk
-IX Circulatory system	18 (8)	819 (18)	X2= 13.4569. p= .000244. Significant at p < .05.	RR= 0.4 (CI 95%: 0.68, 0.26). Protection factor effectively
-X Respiratory system	17 (8)	372 (8)	X2= 0.03. p= .862436. NS	RR= 1 (CI 95%: 4.76, 0.19). Not significant
-XI Digestive system	19 (9)	366 (8)	X2= 0.1467. p= .701719. NS	RR= 1 (CI 95%: 0.54, 2.26). Not significant
-XII Diseases of the skin	6 (3)	113 (2)	X2 with Yates correction= 0.0016. p=.967676. NS	RR= 1 (CI 95%: 0.01, 184.56). Not significant
-XIII Musculo-skeletal	26 (12)	681 (15)	X2= 1.4444. p= .229424. NS	RR= 0.8 (CI 95%: 1.21, 0.5). True benefits
-XIV Genitourinary	25 (12)	384 (8)	X2= 2.5349. p= .111352. NS	RR= 1.4 (CI 95%: 0.9, 2.16). Weak risk
-XVII Congenital malformations	1 (0.5)	19 (0.5)	Fisher exact test= 0.6064. NS	RR= 1 (CI 95%: 0.72, 1.68). Not significant
-XIX Injury, poisoning and certain other consequences of external causes	0	19 (0.5)	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XXI Factors influencing health status	0	13 (0.5)	Fisher exact test= 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
TOTAL chronic diseases*	214 (100)	4494 (100)	-	-

( ): Denotes percentages
RR: relative risk
*Patients could have more than one chronic disease. The percentages are over the total of chronic diseases

Table 3: Comparison of Chronic Diseases between Adverse Covid-19 Vaccines Reactions and Without Adverse Covid-19 Vaccines Reactions and Relative Risk Calculation.

Vaccine Types	Adverse Covid-19 Vaccines Reactions N=109	Without Adverse Covid-19 Vaccines Reactions N=1.891	Statistical Significance	Relative Risk (RR)
BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)	78 (72)	1380 (69) 1380-78=1302 vacunados con ARNm de Pfizer si RA	X2= 0.1048. p= .7461. NS	RR= 0.9 (CI 95%: 1.67, 0.53). Not significant
mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna)	9 (8)	251 (13)	X2= 2.2931. p= .129947. NS	RR= 0.6 (CI 95%: 1.25, 0.29). True benefits
ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca)	17 (15)	260 (13) 260-17=243	X2= 0.2947. p= .587253. NS	RR= 1.1 (CI 95%: 0.58, 2.28). Not significant
Janssen (Johnson & Johnson vaccine)	5 (5)	100 (5) 100-5=95	X2= 0.1018. p= .749652. NS	RR= 0.9 (CI 95%: 13.33, 0.06). Not significant
TOTAL	109 (100)	1891 (100)		

( ): Denotes percentages
RR: relative risk

Table 4: Comparison of Vaccine Types between Adverse Covid-19 Vaccines Reactions and Without Adverse Covid-19 Vaccines Reactions and Relative Risk Calculation.

Discussion

Pharmacovigilance is the science related to the collection, detection, evaluation, monitoring and prevention of adverse reactions with pharmaceutical products. The collection and evaluation of adverse reactions is particularly important in the first decade after the marketing authorization of a medicine, since the information collected in this period could help, for example, to identify complications of its use that were unknown before its commercialization [48]. Approximately 25% of patients experience adverse drug reactions in primary care and more than a quarter of these could be avoided if risk situations were detected earlier. Collecting adverse drug reactions from the patient's perspective is essential to reduce its occurrence [49]. In just over a year, SARS-CoV-2 and the disease it causes have led to a massive worldwide research effort that has resulted in a large body of evidence. The field of vaccines is a particularly dynamic field of great interest to public health [7]. Substantial variability has been reported characterizing the initial incidence of potential adverse effects from COVID-19 vaccines. The incidence of the 15 pre-specified adverse events of special interest (eg, stroke, myocardial infarction, thrombosis deep vein, immune thrombocytopenia) was markedly heterogeneous both within and between databases by age and sex. Thus, the true links between COVID-19 vaccines and adverse events can be difficult to define [19].

Until September 5, 2021, 66,835,878 doses of vaccines against COVID-19 have been administered in Spain, having registered 41,751 notifications of adverse events, which would correspond to 62 notifications per 100,000 doses administered. Most of the notifications correspond to people between 18 and 65 years of age (88%) and mostly women (76%). 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) [50]. We find data similar to these officially communicated for Spain on the same dates; Although, we detected an IR of 5% cases of adverse COVID-19 vaccines reactions in people = <14 years, figure higher to communicated, but it must be taken into account that our data refers to consultation with the GP and not to declaration of adverse reaction. It is known that adverse events are generally not reported relative to the actual rate of an event [51-53]. The frequency of vaccine-related serious adverse events has been reported to be low (<0.1%) and balanced between treatment groups [53]. In Spain, of the 41,751 notifications of adverse events, 8,515 were considered serious [50]. Our results are in the same line, finding, regarding the severity of adverse COVID-19 vaccines reactions: an IR of 3 cases of Moderate severity per 100 COVID-19 vaccines x 8 months.

After reviewing the available safety data, the following has been established: Very rarely myocarditis and/or pericarditis may occur after administration of the BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech) or mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) [54,55]. BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech) is being studied for the possible appearance of asthenia, lethargy, decreased appetite and night sweats.

ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca) have been identified as possible cause of adverse reactions of pain in the extremities, pain in the abdomen and flu-like symptoms (such as fever, sore throat, cough and chills). The possible association with the appearance of Guillain-Barré syndrome, acute disseminated encephalomyelitis and encephalitis, immune thrombocytopenia, and acute macular neuroretinopathy is currently under evaluation. The ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), is associated with a risk of immune thrombosis with vaccine-induced thrombocytopenia syndrome in the range of one to two cases per 100,000 vaccinations, and younger women present the greatest risk. Additional cases have been reported for the adenoviral vector-based vaccine COVID-19 Ad26.CoV2.S from Janssen (Johnson & Johnson vaccine) [50,56,57].

Pooled rates of local and systemic reactions have been reported to be significantly different between vaccine platforms. Inactivated vaccines, protein subunit vaccines, and DNA vaccines had lower rates of local and systemic reactions compared to RNA vaccines, non-replicating vector vaccines, and virus-like particulate vaccines. The safety profiles of BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), Janssen (Johnson & Johnson vaccine) were relatively benign [53]. We found, regarding the type of vaccine involved in the adverse COVID-19 vaccines reactions, that the highest IRs were 6 cases of adverse vaccines reactions per 100 COVID-19 vaccines x 8 months for both Pfizer-BioNTech-BNT162b2 vaccines and for AstraZeneca-ChAdOx1 nCoV-19 (AZD1222); and the lowest IR was for Moderna mRNA-1273 vaccine: (3 cases of adverse Moderna mRNA-1273 vaccines reactions per 100 COVID-19 Moderna mRNA-1273 vaccines x 8 months). Spikevax mRNA vaccine (formerly COVID-19 Vaccine Moderna- mRNA-1273 was the only one that showed a protective RR of adverse COVID-19 vaccines reactions, but without statistical significance.

Finally, we found mixed results regarding the RR of chronic diseases and social factors on adverse COVID-19 vaccines reactions (people with some type of labour specialization, complex family and chronic diseases of Circulatory system, were protective factors; whereas chronic diseases of Endocrine, Nervous and Senses was risk factors). We hypothesize that medical care seeking and use behaviors associated with these factors would be responsible for the results [58].

Limitations and Strengths of the Study

- Registries in general practice are key sources for morbidity estimates, especially if all people are registered in a general practice and if GP is the gatekeeper of health care; so, diagnoses from medical specialists and other health care providers will also be known by the GP [24,59].
- However, the frequency figures of adverse COVID-19 vaccines reactions obtained from the GP consultation may not represent their total incidence, but the proportion which is presented at this level of care, being a “minimum incidence”. In addition, it has been argued that medical morbidity registers have a high under-registration of diseases (between 25 and 40%) [60].
- The follow-up period for reporting security events is important to interpret event rates appropriately. Our prospective study based on continued GP care allows a long follow-up time [61].
- Although active surveillance can help highlight suspicious trends, the lack of a rigorously constructed comparable control group limits the ability of such surveillance to identify causal effects of vaccination.

Conclusion

In the context of general medicine in Toledo (Spain), during the 8-month follow-up, the IR of adverse COVID-19 vaccines reactions was low and their severity was moderate. The risk estimates clearly favour vaccination. Our results seem to indicate that Spikevax mRNA vaccine exhibits lowest IR of adverse COVID-19 vaccines reactions, and it showed a protective RR of adverse COVID-19 vaccines reactions; however, the small numbers available do not allow definitive conclusions to be drawn.

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