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Adverse Covid-19 Vaccines Reactions in General Medicine: A Clinical-Epidemiological Case Series Reporting of 73 Patients in Toledo's (Spain) from February to July 2021

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Abstract

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

Objective: To study, in general medicine, clinical-epidemiological characteristics of patients who consulted for self-reported adverse reactions to COVID-19 vaccines.

Methodology: An observational, longitudinal and prospective case series study of patients with adverse COVID-19 vaccines reactions (ACVRs) based on a cohort of patients in a family medicine office in Toledo (Spain) was carried out from February 1, 2021 to July 31, 2021.

Results: During the 6 months of the study, 73 cases were included. The patients had an average age of 50 years; they were predominantly women, without previous COVID-19, of medium socio-economic level, with 20% ethnic minorities. The majority had a history of chronic diseases, especially endocrinological and Nervous and Senses. The reported symptoms were mostly labelled in the group of symptoms, signs not otherwise specified: Pain injection site, arm pain, fever, chills, dizziness, headache, asthenia, limb paresthesia, lymphadenopathy and edema. 16% were considered definitive and 44% probable. Severity moderate was predominated. Most occurred in the first dose.

Conclusion: In the context of general medicine in Toledo (Spain), during the first 6 months of COVID-19 vaccination, no serious adverse effects were found, which were mostly symptoms and signs not otherwise specified, more frequent with the first dose, and affecting to middle-aged women with chronic diseases.

Keywords: COVID-19; Adverse Drug Events; Post-Vaccination Reactions; Vaccine Safety; COVID-19 Vaccine; General Practice; Case Series

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; GPs: General Practitioners; ADRs: Adverse Drug Reactions; AVRs: Adverse Vaccines Reactions; ACVRS: Adverse COVID-19 Vaccines Reactions; CDC: Center of Disease Control; AESI: Adverse Events of Special Concern; MMR: Measles, Mumps, And Rubella.

Introduction

More than a year after its emergence as a global pandemic, severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) infection has been associated with more than 177 million cases, resulting in more than 3.8 million deaths worldwide as of June 21, 2021 [1,2]. To control this pandemic, efforts to develop safe and effective vaccines against SARS-CoV-2 were accelerated [3]. By early 2021 several candidate vaccines had emerged as safe and effective in preventing coronavirus disease 2019 (COVID-19) [4-7]. Very seldom in the history of vaccination has there been a time when vaccines were administered to so many people in a relatively short time. In this way, the generation of information on the safety of COVID-19 vaccines and its dissemination is essential. The massive application of vaccines requires robust pharmacovigilance systems and global coordination of post-license surveillance, both for governments to make appropriate decisions and to maintain or win public confidence in vaccines [8].

On the other hand, general practitioners (GPs) have accumulated experience in the continued care of patients, and when they think that there is an effect possibly linked to the vaccine, should report it, for ruling it out or maintain it. It is advisable not to initially rule out any possible adverse effects, but to enter them into the registers and leave them to another level, where there is a more global vision, to decide whether to discard it or not. There is a whole system process to filter and determine if the data really constitutes a signal. The precautionary side is always better: report, rather than not do it, especially at the beginning, when any effect, even mental health, could be related. When the product is on the market, and this is seen with other vaccines, some effects are no longer reported as much.

The problem of drug use is one of the most socially relevant in all countries, and adverse drug reactions (ADRs) are an important part of this problem, being frequent in clinical practice [9]. An ADR is any harmful and unintended response to a drug that occurs in doses normally applied to humans for the prophylaxis, diagnosis, or treatment of disease, or for the restoration, correction, or modification of disease; this term also includes all the harmful clinical consequences derived from the dependence, abuse and incorrect use of medicines, including those caused by the use outside the authorized conditions and those caused by medication errors. Virtually all drugs can produce some ADRs, and even pharmacologically inert substances can cause side effects in certain people [10]. Sometimes it is difficult to establish the clinical diagnosis of a ADR since these have characteristics similar to any disease not related to drug exposures [11].

Since the practice of vaccination emerged, the existence of adverse vaccines reactions (AVRs) has been recognized. The frequency of AVRs is directly related to the number of vaccine doses administered. AVRs may have a coincidental relationship with the inherent properties of the vaccine, or be linked to errors in the administration, quality, storage and transport of the vaccine, but it must be recognized that when large populations are vaccinated they will be observed, after vaccination, fortuitously, some serious events that occur sporadically with or without vaccination. For this reason, the investigation of the causality of AVRs, especially that of the most serious ones, is a difficult task [12].

Even if they are mild side effects, it is important to report them. In addition to identifying the occurrence of serious and rare adverse events in phase 4 of the studies, knowing whether minor events are within the expected range is also part of the goals of pharmacovigilance. It is important that the GP understands that notification is essential when we have new vaccines. The more notifications there are and the larger the database, the more properly it can be said that vaccines are safe [13].

On the other hand, patient reporting of non-specific side effects when taking medications, which are not a direct result of the pharmacological action of the drug, is a common, and costly phenomenon. Several factors appear to be related: the patient's expectations of adverse effects at the beginning 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 somatize; and circumstantial and contextual factors [14-16].

On February 2021 Spain began a mass vaccination campaign against COVID-19. As of June 30, 2020, the Spanish Ministry of Health had supplied 45,924,484 doses of vaccines; More than 20 million Spaniards had the complete vaccination schedule against the coronavirus on that date, 43% of the population (20,528,505 people). With at least one dose, there were 27.2 million, 57% (27,277,127 inhabitants). By age group, 71% of the population over 40 years of age already had the complete vaccine schedule, while 89% of that same group had at least one dose. Vaccination in young people is slower; only 15% of the population between 20 and 29 years old (740,347 people) had received at least one dose, while only 2% of young people between 12 and 19 years old (75,090) had one dose of the vaccine [17]. Also, on that date of June 30, 2021, the vaccination started in people over 20 years of age in Castilla-La Mancha, Spain. 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 July 31, 2021, which aimed to knowing and describing the clinical-epidemiological characteristics of patients who consult for self-reported adverse reactions after COVID-19 vaccination.

Material and Methods

Design and Emplacement

An observational, longitudinal and prospective case series study of patients with adverse COVID-19 vaccines reactions (ACVRs), based on a cohort of patients was carried out from February 1, 2021 to July 31, 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).

Events of Interest

The events of interest in this study were the spontaneous communications of the patients in consultation with the GP in general medicine.

Diagnosis of ACVRs

Reports of ACVRs that were reason for consultation with the GP by vaccinated patients 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 [10].

Collected Variables

1. Data were extracted from the medical records of the general medicine practice under study. The following variables were collected:
2. Age and sex
3. Symptoms of ACVRs and 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" [18], both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [19].
4. Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [20,21].
5. 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) [22-25].
6. Ethnic minority
7. Sick leave due to ACVRs
8. Symptomatic/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 [26]; 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 [27].
9. Severity of COVID-19 in the cases that had passed it (mild cases: clinical symptoms are mild and no manifestation of pneumonia could not be found on images; moderate cases: with symptoms such as fever and respiratory tract symptoms, and the manifestation of pneumonia can be seen on the imaging tests; and severe cases: respiratory distress, respiratory rate ≥ 30 breaths/min., pulse oxygen saturation ≤ 93% with room air at rest, arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg.) [28]. To simplify comparison, moderate and severe cases were counted together.
10. Vaccine type: Comirnaty (Pfizer-BioNTech-BNT162b2 mRNA; Pfizer/BioNTech), Moderna-mRNA-1273 mRNA, Vaxzevria (AstraZeneca), and Janssen/Johnson & Johnson vaccine (Currently, the European Commission has licensed four vaccines: Comirnaty, Pfizer/BioNTech, licensed December 21, 2020; Moderna vaccine, licensed January 6; AstraZeneca vaccine, licensed 29 December and the 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) [29].
11. Criteria for the causality of ACVR, classified as [30-32]:

- 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 analyzed.
- 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
- Severity or intensity of ACVR, classified as Mild, Moderate, Severe [33]:
- 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.

12. Time of appearance of ACVR, classified as [34]:

- 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 COVID-19 vaccination adverse reaction from February 1, 2021 to July 31, 2021 were included, and that they were seen in the consultation object of the study and their medical documentation was available.

Results

73 cases were included. The patients had an average age of 50 years, they were predominantly women, without previous COVID-19, of medium socio-economic level, with 20% ethnic minorities. A fourth of them required medical leave. Most had a history of chronic diseases, especially endocrinological and Nervous and Senses, the reported symptoms were mostly labelled in the group of Symptoms and Signs: Injection site pain, arm pain, fever, chills, dizziness, headache, asthenia , paraesthesia in limbs, lymphadenopathy, edema in feet. Regarding the causality criteria, 16% were considered definitive and 44% probable. According to the time of appearance, most were accelerated. Regarding the severity, the moderate ones predominated. Most occurred in the first dose, and the vaccines were predominantly in absolute numbers from Pfizer, but proportionally to the number of vaccines administered to the population [in May 2021 in Castilla-La Mancha, Spain, more than half a million doses of the Pfizer vaccine (> 500,000;> 67%), 162,000 of AstraZeneca (22%), 72,000 of Moderna (10%), and 12,000 of Janssen (1%) [35], this vaccine was the least ACVRs presented (Tables 1-4).

Variables	Adverse Covid-19 Vaccines Reactions N=73
Age in years (Arithmetic mean + - Standard deviation)	49.39 +- 11.64
> = 65 years	8 (11)
= < 45 years	27 (37)
= < 18 years	0
Women	51 (70)
Men	22 (30)
Previous symptomatic COVID-19	7 (10)
Previous COVID-19 asymptomatic	1 (1)
Previous COVID-19 with moderate-severe severity	3 (4)
Social-occupancy class of patients (people with some type of labor specialization)	27 (37)
sick leave for adverse COVID-19 vaccine reaction	19 (26)
Ethnic minority	15 (20)
Low income household	6 (8)
Complex family	11 (15)
Chronic diseases presence	60 (82)

( ): Denotes percentages

Table 1: General Variables Of Patients With Adverse Covid-19 Vaccines Reactions.

Symptoms * According To Who, Icd-10 Groups	Adverse Covid-19 Vaccines Reactions N=73
V Mental (anxiety)	1 (1)
VI-VIII Nervous and Senses (Ear plugging, subconjunctival hemorrhage, odynophagia)	6 (4)
IX Circulatory system (superficial phlebitis)	1 (1)
X Respiratory system (cough, dyspnea, rhinitis)	6 (4)
XI Digestive system (diarrhea, nausea, vomiting, abdominal pain)	22 (13)
XII Diseases of the skin (urticaria)	5 (3)
XIII Musculo-skeletal (myalgia, musculoskeletal pain)	34 (20)
XIV Genitourinary (hematuria, abortion)	2 (1)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (Injection site pain, arm pain, fever, chills, dizziness, headache, asthenia, limb paresthesia, lymphadenopathy, foot edema)	87 (53)
Total Symptoms*	164 (100)

( ): Denotes percentages

* Patients could have more than one symptom. The percentages are over the total of symptoms

Table 2: Symptoms Of Adverse Covid-19 Vaccines Reactions.

Chronic Diseases* According To Who, Icd-10 Groups	Adverse Covid-19 Vaccines Reactions N=73
-II Neoplasms	5= (3)
-III Diseases of the blood	1 (1)
-IV Endocrine	34 (19)
-V Mental	21 (11)
-VI-VIII Nervous and Senses	27 (15)
-IX Circulatory system	15 (8)
-X Respiratory system	15 (8)
-XI Digestive system	16 (9)
-XII Diseases of the skin	4 (2)
-XIII Musculo-skeletal	22 (12)
-XIV Genitourinary	21 (12)
TOTAL chronic diseases*	181 (100)

( ): Denotes percentages

*Patients could have more than one chronic disease. The percentages are over the total of chronic diseases.

Table 3: Chronic Diseases Of Patients With Adverse Covid-19 Vaccines Reactions.

Criteria Of Causality	Adverse Covid-19 Vaccines Reactions N=73
Definitive (Certain)	12= (16)
Probable (Likely)	32 (44)
Possible	19 (26)
Unlikely	10 (14)
Conditional / Unclassified	0
Not evaluable / Unclassifiable	0
Time Of Appearance Of The Adverse Covid-19 Vaccines Reaction	
Immediate	3 (4)
Accelerated	54 (74)
Late	16 (22)
Gravity Of The Adverse Covid-19 Vaccines Reaction	
Mild	23 (31)
Moderate	29 (40)
Severe (Bronchospasm, urticaria, dyspnea, hematuria, abortion, fever, phlebitis, anxiety)	21 (29)
Type Of Vaccine Involved In The Adverse Covid-19 Vaccines Reaction	
Pfizer-BioNTech-BNT162b2 (Pfizer / BioNTech) mRNA	47 (64)
Moderna mRNA- mRNA-1273	5 (7)
AstraZeneca - ChAdOx1 nCoV-19 (AZD1222)	17 (23)
Johnson & Johnson COVID-19 Vaccine Janssen	4 (6)
Covid-19 Vaccine Dose (Johnson & Johnson COVID-19 Vaccine Janssen has a single dose)	
First	59 (80)
Second	27 (37)
Both doses	13 (18)

( ): Denotes percentages.

Table 4: Criteria For Causation, Time To Occur, Type Of Vaccine And Dose Of The Vaccine Of Adverse Covid-19 Vaccines Reactions.

Discussion

Vaccination Campaign against COVID-19 in Spain and Toledo (Castilla La Mancha, Spain)

Once the Pizfer/BioNTech vaccine was approved on December 21 by the European Medicines Agency, the vaccination campaign began in Spain on December 27, 2021. It was carried out in a staggered manner and prioritizing the groups of people most exposed to COVID-19. As of June 21,

2020, vaccination began in the age range of 30 to 39 years. Meanwhile, the 40 to 49-year-old group was still being vaccinated and second doses were inoculated to those over 50 and 60 years of age. Residents and staff of centers for the elderly and care for dependents, first-line health and social health personnel and non-institutionalized dependents have been vaccinated. By age group, 58% of those over 50 years of age already have the complete regimen and 42% of the 40-49 group already have at least one dose [36].

Drug-Related Problems are Common in General Medicine: The Role of the GP

COVID-19 vaccine is the hope for containment of disease outbreak. The post vaccination adverse effect is an important consideration [37-39]. In general, out of every 100 courses of drug treatment, there are 20 adverse drug reactions (ADRs), between 5 and 25 clinically observable drug interactions (DDIs) (of which 5 are due to ADRs) and between 15 and 50 potential DDIs, which reach to 100 in geriatric patients [40,41]. Among the advantages of GP are the continuous care and the possibility of improving knowledge of ADRs avoiding the difficulties of interpreting symptoms or diseases that are not due to medicines but psychosocial effects. Among the methods aimed at identifying and quantifying the ACVRs, in the GP consultation, we used two of them in this study: 1) Data derived from pure clinical observation; 2) Voluntary spontaneous notification by the patient in the consultation or as a direct reason for the consultation [42].

Causation of Adverse Events After Vaccination

The clearest and most reliable way to determine whether an adverse event is causally related to a vaccine is to compare the incidence of the event in two groups, vaccinated and unvaccinated, in a randomized clinical trial. These trials, however, can never be large enough to assess very rare events and pharmacovigilance systems are needed to identify events possibly related to vaccination. We use the WHO criteria as causality categories [12,31,32]. Accordin these causality criteria, we find 16% were considered definitive and 44% probable.

Most Frequently Reported Adverse Events

Reporting of incidence of adverse events to official surveillance systems after COVID-19 vaccination varies between countries: from 0.43% in the UK, 0.41% in Australia, 0.31% in Italy and 0.24 % in Argentina to 0.12% in Spain, 0.10% in Brazil and 0.07% in Mexico. In all cases, the sensitivity is higher for serious adverse events [13]. A Center of Disease Control (CDC) analysis of adverse event data during the first month of COVID-19 vaccination in the US offered reassurance on the use of the two licensed mRNA vaccines: Between December 14, 2020 and December 13 January 2021, for 14,000,000 vaccine doses and approximately 7,000 adverse events were reported. Of these, 91% were considered not serious. The most common were headache, fatigue, and dizziness [43].

The two messenger RNA (mRNA) vaccines, made by Moderna and Pfizer-BioNTech, appear to cause similar reactions. A significant portion of people experience non-serious reactions, such as arm pain or headache. That ratio is higher than that of the annual flu vaccine, perhaps because COVID-19 mRNA vaccines elicit a particularly strong immune response. Compared to Moderna, the most common adverse reactions included injection site pain, fatigue, headache, muscle pain, joint pain, and chills; these were generally short-lived. It has been reported that compared to the Pfizer-BioNTech vaccine, Moderna's was more likely to cause headaches, arm pain, and related side effects [44]. Until April 25, 2021, 14,290,507 doses of vaccines against COVID-19 had been administered in Spain, with 17,297 notifications of adverse events having been registered. The most frequently reported events are still general disorders (fever, pain in the vaccination area), of the nervous system (headache, dizziness) and of the musculoskeletal system (myalgia and arthralgia) [45].

After reviewing the available safety data, the following has been established:

- Comirnaty (BioNTech/Pfizer): rash and pruritus (rare) and urticaria (rare) have been incorporated into the technical data sheet and package leaflet as possible adverse reactions. The possible occurrence of localized inflammation after vaccination in people who had previously received filler injections in the face will also be incorporated [45]. Likewise, it is considered probable Link Between Pfizer Vaccine and Myocarditis Cases [46-48].
- Vaxzevria (AstraZeneca): the appearance of thrombosis accompanied by thrombocytopenia in unusual places such as the cerebral venous sinuses and splanchnic veins, is a possible adverse reaction of the vaccine. Its frequency of occurrence is very rare and the majority of cases reported at the time of evaluation occurred within 14-27 days of vaccination and under 60 years of age. This information has been incorporated into the technical sheet with recommendations for healthcare professionals and citizens. The possible appearance of isolated thrombocytopenia has also been incorporated into the technical data sheet and the package leaflet. The estimated frequency was 1.13 cases per 100,000 first dose vaccinations [49-53]. Of the approximately 10,000 healthcare professionals who received the first dose of the Oxford/AstraZeneca vaccine in France between February 6 and 10, the drug regulatory agency received

149 reports of pharmacovigilance for influenza-like signs and symptoms, often severe, with an average temperature of 39°C. Effects occurred within 24 hours in 127 cases, and most cases were seen in people with an average age of 34 years (range: 20 to 63) [54]. Likewise, the possible association with the appearance of capillary leak syndrome is under study after some isolated cases have been reported [44].

- COVID-19 Vaccine Janssen: The development of thrombosis accompanied by thrombocytopenia in unusual places such as the cerebral venous sinuses and splanchnic veins is a possible adverse reaction of the vaccine. Its frequency of appearance is very rare. At the time of evaluation, the cases reported with this vaccine occurred within 21 days of vaccination and, mostly, in women under 60 years of age. This possible adverse reaction is described in the technical data sheet and the package insert for this vaccine, with recommendations for healthcare professionals and citizens [45,55].

In our study, the reported symptoms were mostly labelled in the group of Symptoms and Signs: Injection site pain, arm pain, fever, chills, dizziness, headache, asthenia, paraesthesia in limbs, lymphadenopathy, edema in feet, etc.

Each new vaccine has potential adverse events of special concern (AESI) that warrant a focused evaluation, based on what is known about previous vaccines and vaccine development. In relation to the so-called events of interest (non-hemorrhagic and hemorrhagic stroke, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, anaphylaxis, Bell's palsy, myocarditis or pericarditis, narcolepsy, appendicitis, immune thrombocytopenia, disseminated encephalomyelitis), syndrome Guillain-Barré and transverse myelitis) [56], in our series none were found any of them within the categories of certain, probable and possible.

Allergic Reactions to COVID Vaccines

A small number of people have experienced severe allergic reactions to these vaccines. They are extremely rare and no one has died. Fewer than five people per million administered doses of Moderna or Pfizer - BioNTech experienced anaphylactic reactions. That's based on self-reported data from healthcare workers and vaccinated people. For the Oxford-AstraZeneca vaccine, 30 cases of anaphylaxis have been confirmed so far, out of just over 3 million doses administered [57]. It has been communicad 2.1% acute allergic reactions. These included itching or a rash outside the injection site, respiratory symptoms, hives, and swelling; 16 confirmed cases of anaphylaxis (rate: 0.027% with Pfizer-BioNTech, 0.023% with Moderna). Of these, 94% were women, the mean age was 41 years, 63% had a history of allergy, and 31% had a history of anaphylaxis [58]. The CDC's reports in late December 2020 and January 2021 indicated rates of 11.1 and 2.5 anaphylaxis cases per million vaccine doses of the Pfizer-BioNTech and Moderna vaccines, respectively, with no fatalities [59]. The rate of anaphylactic reactions to the application of messenger RNA vaccines against COVID-19 is only 7.9 cases per million inoculations [60], which, according to the researchers, is "within the range" of rates observed with other common vaccines. People that developed an allergic reaction after the first dose of a messenger RNA vaccine, including erythema, dizziness, tingling, shortness of breath, and even anaphylaxis, seem to tolerate the second dose better [61]. In our study, there were 4% of bronchial hypersensitivity reactions with cough, dyspnea or rhinitis, and 3% of urticaria.

Among Pfizer-BioNTech vaccine recipients enrolled in CDC's "v-safe" program, a smartphone-based tool that enables automated health checks after COVID-19 vaccination, reactions were more common after vaccination. Second dose than after the first [62]. Both Moderna and Pfizer/BioNTech vaccines require two doses several weeks apart. Although reactogenicity is usually higher after a second dose, side effects seem to mean that the vaccine is working well [63]. In our case series, the majority of ADVRs were with the first dose (80%). It has been reported that in Moderna's clinical trial, 10% of vaccine recipients developed axillary swelling or tenderness ipsilateral to the vaccination arm within 7 days of the first dose, and 14% within 7 days of the second dose. Rates in the Pfizer-BioNTech trial were lower, but probably an underestimate, they note [64]. In our series of cases, we found 2 cases of lymphadenopathy (3%).

Vaccination during Pregnancy

Regarding vaccination during pregnancy, local and systemic events after vaccination appear to be similar between pregnant and non-pregnant people. The miscarriage rate was 13% among the v-safe pregnancy registry participants with complete pregnancies, with the majority occurring before 13 weeks' gestation. By comparison, published miscarriage rates range from 10% to 26% [65]. In our series of cases, 1 spontaneous abortion was found, but with an unlikely causality criterion.

Women Report More and Worse Acvrs

Men and women offer a responder differently to many types of vaccines. It is probably due to a combination of factors, including hormones, genes, and the dose of the injections. Researchers at the CDC analyzed safety data for 13.7 million Covid-19 vaccines and found that 79% of reported side effects came from women, although only 61% of vaccines were administered to women. In general,

women have more reactions to a variety of vaccines. That includes flu vaccines given to adults, as well as some given in childhood, such as the hepatitis B and measles, mumps, and rubella (MMR) vaccines. But the side effects are usually mild and short-lived. And these physical reactions are a sign that a vaccine is working, that it is generating a very robust immune response [66]. In our case series, these data were repeated, with a majority of women (70%) reporting ACVRs.

Non-Pharmacological Effects of COVID-19 Vaccines

The mechanisms that produce ADRs are extraordinarily numerous and of very diverse origin, although they can be classified as dependent on the drug used or on the patient himself [67]. Some ADRs cannot strictly be ascribed to pharmacological effects, so other non-specific mechanisms, such as nocebo effects or cultural factors, also give rise to ADRs experienced by patients. It has been reported that the presence ofADRs is related to the greater presence of anxiety and depression and a predominance of the female sex. Likewise, a high level of anxiety has been reported during provocation tests in "false allergy" ("pseudo-allergy") and may be related to the nocebo effect as a mechanism for producing ADR symptoms.

Limitations and Strengths of the Study

- It must be taken into account that the results presented are minimal data, since the ACVRs being mostly mild or moderate in nature, they could not generate a consultation with the GP.
- On the other hand, a strength of the study lies in being forward-looking and longitudinal. The follow-up period is important to interpret adverse events to vaccines appropriately. For example, the risk of Bell's palsy has been reported to be greatest within the first month of a second dose of mRNA vaccine [68].

Conclusion

In the context of general medicine in Toledo (Spain), during the first 6 months of COVID-19 vaccination, no serious adverse effects were found in the ACVRs of the definitive, probable and possible cases, which were mostly symptoms and signs not otherwise specified, of unknown etiology or transient. With much less frequency the ACVRs musculoskeletal, digestive and respiratory. These ACVRs were injection site pain, arm pain, fever, chills, myalgia, nausea, vomiting, diarrhea, dizziness, headache, asthenia, paraesthesia in limbs, lymphadenopathy, urticaria, cough and bronchospasm, occurred preferentially in middle-aged women with chronic diseases (mainly endocrinological, nervous and senses, musculo-skeletal, genitourinary and mental). Most occurred in the first dose, and the vaccines were predominantly in absolute numbers from Pfizer, but proportionally to the number of vaccines administered to the population, this vaccine was the one with the lowest ACVRs.

References

1. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins. The Center for Systems Science and Engineering (CSSE) at JHU.

2. WHO (2021) WHO coronavirus disease (COVID-19) dashboard.

3. Lan J, Ge J, Yu J, Shan S, Zhou H, et al. (2020) Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 581(7807): 215-220.

4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, et al. (2021) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 384: 403-416.

5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, et al. (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 383: 2603-26015.

6. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, et al. (2021) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397(10269): 99-111.

7. (2021) Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. FDA Briefing Document.

8. Tabakman R (2021) Anti-COVID-19 vaccines: the challenge of knowing them better. Medscape.

9. Taché SV, Sönnichsen A, Aschcroft DM (2011) Prevalence of adverse events in ambulatory care: a systematic review. Ann Pharmacother 45(7-8): 977-989.

10. Colloca L, Millar FG (2011) The nocebo effect and its relevance for clinical practice. Psychosom Med 73(7): 598-603.

11. Farcas A, Bojita M (2009) Adverse drug reactions in clinical practice: a causality assessment of a case of drug-induced pancreatitis. J Gastrointestin Liver Dis 18(3): 353-358.

12. WHO (2021) Adverse Events Following Immunization (AEFI).

13. Loewy MA (2021) COVID-19: The Weekly Summary (July

30 - August 5, 2021). Medscape.

14. Barsky AJ, Saintfort R, Rogers MP, Borus JF (2002) Nonspecific medication side effects and the nocebo phenomenon. JAMA 287(5): 622-627.

15. Wu ZY, Li K (2009) Issues about the nocebo phenomenon in clinics. Chin Med J 122(9):1102-1106.

16. Islas EJ, Báez Montiel BB, Turabian JL, Maldonado MB, Herrera Ontañón JR, et al. (2012) Patients with adverse drug reactions have a higher prevalence of emotional disorders. Primary Care 44(12): 720-726.

17. (2021) Ministry of Health.

18. Strauss AL (1984) Chronic illness and the quality of life. St Louis: The C.V. Mosby Company.

19. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version: 2019.

20. Royal Collage of General Practitioners (1986) The Classification and Analisis of General Practice Data. Occasional Paper 26.

21. Donaldson RJ, Donaldson LJ (1983) Essential Community Medicine. Lancaster: MTP Press.

22. Turabian JL (2017) Family Genogram in General Medicine: A Soft Technology that can be Strong. An Update. Res Med Eng Sci 3(1): 186-191.

23. Russell LT (2020) Capturing Family Complexity in Family Nursing Research and Practice. J Fam Nurs 26(4): 287-293.

24. Watts C, Shrader E (1998) How to do (or not to do)… The genogram: a new research tool to document patterns of decision-making, conflict and vulnerability within households. Health Policy and Planning 13: 459-464.

25. McIlvain H, Crabtree B, Medder J, Stange KC, Miller WL (1998) Using practice genograms to understand and describe practice configurations. Fam Med 30(7): 490-496.

26. Montenegro P, Brotons C, Serrano J, Fernández D, Ramos CG, et al. (2021) Community seroprevalence of COVID-19 in probable and possible cases at primary health care centres in Spain. Family Practice 38(2): 153-158.

27. (2020) Strategy for early detection, surveillance and control of COVID-19. Instituto de Salud Carlos III.

28. Mao S, Huang T, Yuan H, Li M, Huang X, et al. (2020) Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. BMC Public Health 20: 1525.

29. (2021) Castilla La Mancha Ministry of Health.

30. Kyonen M, Folatre I, Lagos X, Vargas S (2015) Comparison of two methods to assess causality of adverse drug reactions. Rev Médic Chile 143(7).

31. WHO (2012) Medicines safety surveillance: notification system for the general public.

32. Tarapués M (2017) Analisis de Causalidad RAM. Conference: I Scientific Conference of Pharmaceutical Sciences Loja-Ecuador 2017.

33. Definitions In Pharmacovigilance.

34. Pelta Fernandez R, Vivas Rojo E (1992) Adverse drug reactions. Clinical assessment. Madrid: Díaz de Santos.

35. (2021) Complete vaccination reaches 11% of Castilla-La Mancha. Diario Sanitario.

36. (2021) Who is vaccinated now in Spain?. The rate of vaccination in each community. RTVE.

37. Joob B, Wiwanitkit V (2021) Expected Viscosity After COVID-19 Vaccination, Hyperviscosity and Previous COVID-19. Clinical and Applied Thrombosis/Hemostasis 27: 1-2.

38. Kamat P (2021) Adverse Drug Reactions, a Significant Health Problem in Primary Care. Medscape.

39. Insani WN, Whittlesea C, Alwafi H, Man KKC, Chapman S, et al. (2021) Prevalence of adverse drug reactions in the primary care setting: A systematic review and meta-analysis. PLoS One 16(5): e0252161.

40. Turabian JL (2019) Reactions Adverse to Drugs and Drug-drug Interactions: A "Wonderful" Spiral of Geometric Growth Produced by Multimorbidity and Polypharmacy. J Community Prev Med 2(2): 1-5.

41. Turabian (2018) Strategies to Increase Opportunities to Identify and Communicate Adverse Drug Reactions and Drug Related Problems in General Medicine. J Family Med Community Health 5(6): 1165.

42. Turabian JL (2019) The role of general practitioner in the study of adverse drug reactions epidemiology in ambulatory care setting. Arch Community Med Public Health 5(1): 003-007.

43. Gee J, Marquez P, Su J, Calvert GM, Liu R, et al. (2021) First Month of COVID-19 Vaccine Safety Monitoring-United States, December 14, 2020-January 13, 2021. MMWR Morb Mortal Wkly Rep 70(8): 283-288.

44. Weiland N, Grady D, Zimmer C (2020) Moderna Vaccine

Is Highly Protective Against Covid-19, the F.D.A. The New York Times.

45. (2021) 5th Pharmacovigilance Report on COVID-19 Vaccines. Spanish Agency for Medicines and Health Products.

46. Heller J (2021) Israel Sees Probable Link Between Pfizer Vaccine and Myocarditis Cases. Medscape.

47. Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, et al. (2021) Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol.

48. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, et al. (2021) Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol.

49. O'Shea D (2021) Scottish Study Estimates Risk of Bleeding and Clotting Disorders After AstraZeneca Vaccine. Medscape.

50. Pishko AM, Bussel JB, Cines DB (2021) COVID-19 vaccination and immune thrombocytopenia. Nat Med; 27: 1145-1146.

51. Grady D (2021) A Few Covid Vaccine Recipients Developed a Rare Blood Disorder. A link to the vaccines is not certain, and investigations are underway in some reported cases.The New York Times.

52. Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, et al. (2021) Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med.

53. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, et al. (2021) First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Med 27: 1290-1297.

54. Lecrubier A (2021) Flu syndromes with the AstraZeneca vaccine, hypertension with the Pfizer vaccine: the ANSM takes stock. Medscape.

55. Grens K (2021) US Health Authorities Ask for Pause in J&J COVID-19 Vaccination. The Scientist.

56. Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, et al. (2021) Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ 373: 1435.

57. Remmel A (2021) COVID vaccines and safety: what the research says. It is clear that coronavirus vaccines are safe and effective, but as more are rolled out, researchers are learning about the extent and nature of side effects. Nature pp: 1-3.

58. Blumenthal KG, Robinson LB, Camargo CA, Shenoy ES, Banerji A, et al. (2021) Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA 325(15):1562-1565.

59. (2021) Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine-United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep 70(2): 46-51.

60. Reuters (2021) Experts Warn Serious Allergic Reactions to COVID-19 Vaccines Are Rare. Medscape.

61. McNamara D (2021) Second mRNA Dose Safe After Allergic Reaction to First: Study. Medscape.

62. (2021) Possible Side Effects After Getting a COVID-19 Vaccine. CDC.

63. Wadman M (2020) Public needs to prep for vaccine side effects. Science 370(6520): 1022.

64. Edmonds CE, Zuckerman SP, Conant EF (2021) Management of Unilateral Axillary Lymphadenopathy Detected on Breast MRI in the Era of COVID-19 Vaccination. AJR 217: 1-4.

65. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, et al. (2021). Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med 384: 2273-2282.

66. Moyer MW (2021) Women Report Worse Side Effects After a Covid Vaccine. The New York Times.

67. Lee A (2007) Adverse drug reactions. In: 1st (Edn.), in Spanish of the 2nd (Edn.), in English. Barcelona: Pharma Editores.

68. Ozonoff A, Nanishi E, Levy O (2021) Bell's palsy and SARS-CoV-2 vaccines-an unfolding story-Authors' reply. Lancet Infect Dis 21(8): 1211-1212.