Adverse Reactions Incidence Rates of Covid-19 Vaccination in First and Second Doses, First Booster and Fourth Doses in General Medicine

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ABSTRACT

Background: It is not clearly known the variation in the incidence of adverse reactions during the different doses of the COVID-19 vaccine.
Objective: Determine the incidence rate of adverse COVID-19 vaccine reactions.
Emplacement: The population attended in a general medicine consultation in Toledo, Spain.
Methodology: Secondary analysis of observational, longitudinal, and prospective studies of self-reported adverse COVID-19 vaccine reactions, from February to September 2021 (first and second doses), from November 2021 to August 2022 (first booster), and from October 1, 2022 to February 28, 2023 (fourth dose; second booster).
Results: The total incidence rate of adverse reactions in the vaccinated population was higher for the first and second doses (5%), and lower for the second booster (0.4%). The figures for the first booster were intermediate between the two (2%). This pattern was maintained in people over and less than 65 years of age and by gender. The incidence rate by age was always higher in <65 years in all doses. By sex, the incidence rate was always higher in women vs. men. The total incidence rate of adverse reactions with respect to the total population attended in the general medicine practice maintained the same pattern, except in those >=65 years of age who had the same incidence in the third and fourth doses.
Conclusion: The incidence rate of adverse covid-19 vaccine reactions, both in figures with respect to the vaccinated population and with respect to the total population dependent on the general medicine consultation, has been decreasing from the first doses to the last ones. This is possibly due 1) to a real decrease in the immunogenicity of the boosters, and 2) a lower demand for this reason that entails a lower number of adverse reactions in the general practitioner's office.
Keywords: Adverse Drug Events; COVID-19 Vaccine; General Practice; Secondary Analysis, Post-vaccination Reactions; SARS-CoV-2.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 600 million people worldwide and has been shown to cause increased severity and disease mortality in patients with active cancer versus healthy individuals. Vaccines are one of the most effective approaches to preventing infectious diseases and have helped eradicate conditions, such as smallpox, and reduce the incidence of various other infections.[1]

In the midst of the COVID-19 pandemic, mass immunization campaigns have become the most

promising public health measure. During clinical trials, certain adverse effects were observed; however, acceptable safety profiles led to the authorization for the distribution and use of the vaccines. Scientific evidence suggests that vaccines are generally safe. While mild complications, such as injection site pain or bruising, can occur, more serious events remain rare. Furthermore, Vaccination is important to reduce the morbidity and mortality associated with COVID-19.[2,3]

Millions of people have been vaccinated against SARS-CoV-2. Different platforms have been used for COVID-19 vaccines currently being administered, such as replication-deficient viral vectors (for example, ChAdOx1-S developed by Oxford/AstraZeneca, Ad26.COV2.S developed by Janssen, and new mRNA-based vaccines such as BNT162b2 developed by Pfizer/BioNTech and mRNA-1273 developed by Moderna).[4]

An adverse reaction (AR) to a drug is a harmful and unintended reaction that occurs at doses normally used in man for the prophylaxis, diagnosis, treatment of diseases, or modification of a physiological function (vaccines are included as preventive or therapeutic). The AR to vaccines is generally very varied, from a mild local reaction to a fatal outcome causing death.[5,6] Vaccination is one of the most effective public health strategies; however, it can produce AR.[7] Any medicine, including vaccines, can cause mild, moderate, or severe AR. It can therefore be stated that absolute safety (absence of any AR) does not exist when a vaccine or any other medical device is administered. Vaccines, unlike other medicines, are administered to healthy people for preventive purposes and therefore their safety profile must be as high as possible. This is an essential requirement for a healthy population to accept preventive vaccination.[8]

Proof that vaccines activate the immune system is the appearance of AR that follows their application.[7] When the immune system first comes into contact with an (immunobiological) antigen, a primary response is produced; mediated by IgM antibodies. The secondary response occurs in a subsequent event of recontact with that antigen; it is more vigorous and lasts longer, due to the presence of sensitized cells that have stored antigenic memory.[5,6]

Cases of serious side effects are very rare. However, a significant percentage of people are still nervous and undecided about the vaccine. One of the main reasons cited to explain this behavior is the fear of dangerous or unexpected adverse side effects.[9,10] While the efficacy of a second dose of booster vaccine (i.e., the fourth inoculation) is well established, its safety is still not fully understood.[10] Also, to the best of our knowledge, no comparisons of the incidence rates (IR) of AR to different doses of COVID-19 vaccines have been made. In this context, we present a secondary analysis of several longitudinal and prospective studies, carried out in different periods of time, in the same population and with the same methodology, whose objective was to compare the incidence rate of the AR, that led to consultation with the general practitioner (GP), between first and second dose, first booster, and second booster of covid-19 vaccine.

Material and Methods

Several observational, longitudinal, and prospective studies of self-reported adverse covid-19 vaccines reactions are compared and that were the reason for medical consultation: 1) from February to July 2021 (first and second doses)[11,12]; 2) from November 2021 to August 2022 (first booster)[13]; and 3) from October 1, 2022 to February 28, 2023 (fourth dose -second booster- of bivalent mRNA).[14] All of them were carried out on the same population who attended a general medicine consultation and by the same investigator and GP, which has a list of 2,000 patients > 14 years of age (in Spain, the GPs care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP; the GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and

each person is assigned to GP). The methodology of these studies has been previously published, and here only some specific aspects of this study will be mentioned, to avoid repetition.[14]

Outcome of Interest

Determine IR of adverse covid-19 vaccine reactions. IR of AR to COVID-19 vaccines was calculated at the GP's office by dividing the number of infection events by the person's follow-up time.[15]

Diagnosis of adverse covid-19 vaccine reactions

Reports of adverse COVID-19 vaccine reactions that were the reason for consultation with the GP were included. An AR 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.[16]

Results

The total IR of RA in the vaccinated population was higher for the first and second doses, and lower for the second booster. The figures for the first booster were intermediate between the two (5%, 2%, 0.4%). This pattern was maintained in people over and less than 65 years of age and by gender. The IR by age was always higher in <65 years in all doses. By sex, the IR was always higher in women vs. men (**Table 1, Figure 1**). The total IR of RA with respect to the total population attended in general medicine practice maintained the same pattern, except in those >=65 years of age who had the same incidence in the third and fourth doses (**Table 2, Figure 2**).

Variables	Incidence Rates of Adverse Reactions with First and Second Doses	Incidence Rates of Adverse Reactions with Third Dose	Incidence Rates of Adverse Reactions with Fourth Dose
Total= >14 years	5 %	2%	0.4%
>= 65 years	2%	0.3%	0.2%
<65 years	6%	3%	0.5%
Women	5%	3%	0.5%
Men	2%	1.5%	0.2%

Table 1: Comparison of Incidence Rate of Adverse Covid-19 Vaccines Reactions with First and Second Doses, First Booster and Fourth Dose Regarding the Vaccinated Population.

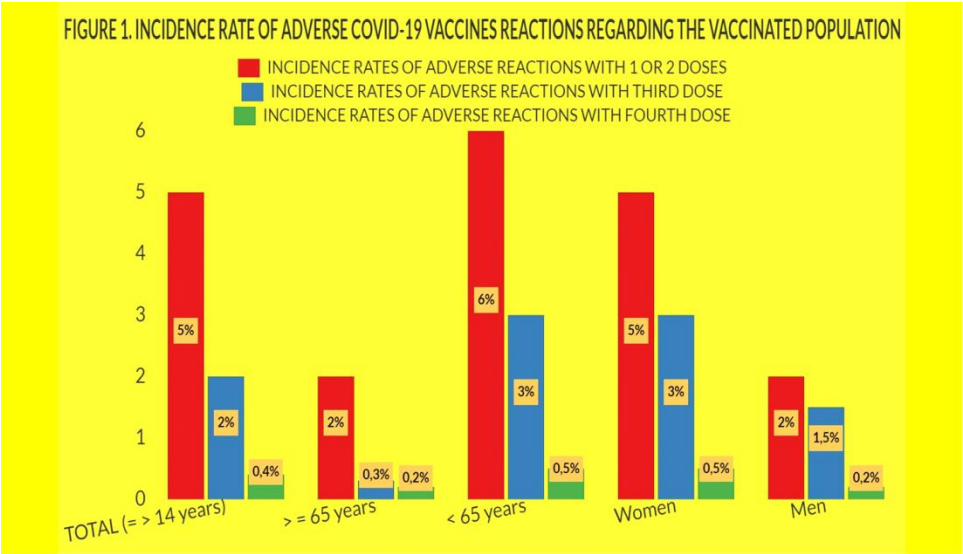

Figure 1: Comparison of Incidence Rate of Adverse Covid-19 Vaccines Reactions with First and Second Doses, First Booster and Fourth Dose Regarding the Vaccinated Population.

Variables	Incidence Rates of Adverse Reactions with 1 or 2 Doses	Incidence Rates of Adverse Reactions with Third Dose	Incidence Rates of Adverse Reactions with Fourth Dose
Total= >14 years	5 %	1.0%	0.2%
>= 65 years	2%	0.2%	0.2%
<65 years	6%	1.3%	0.2%
Women	5%	1.4%	0.3%
Men	2%	0.7%	0.1%

Table 2: Comparison of Incidence Rate of Adverse Covid-19 Vaccines Reactions with First and Second Doses, First Booster and Fourth Dose Regarding the Total Population of the Practice.

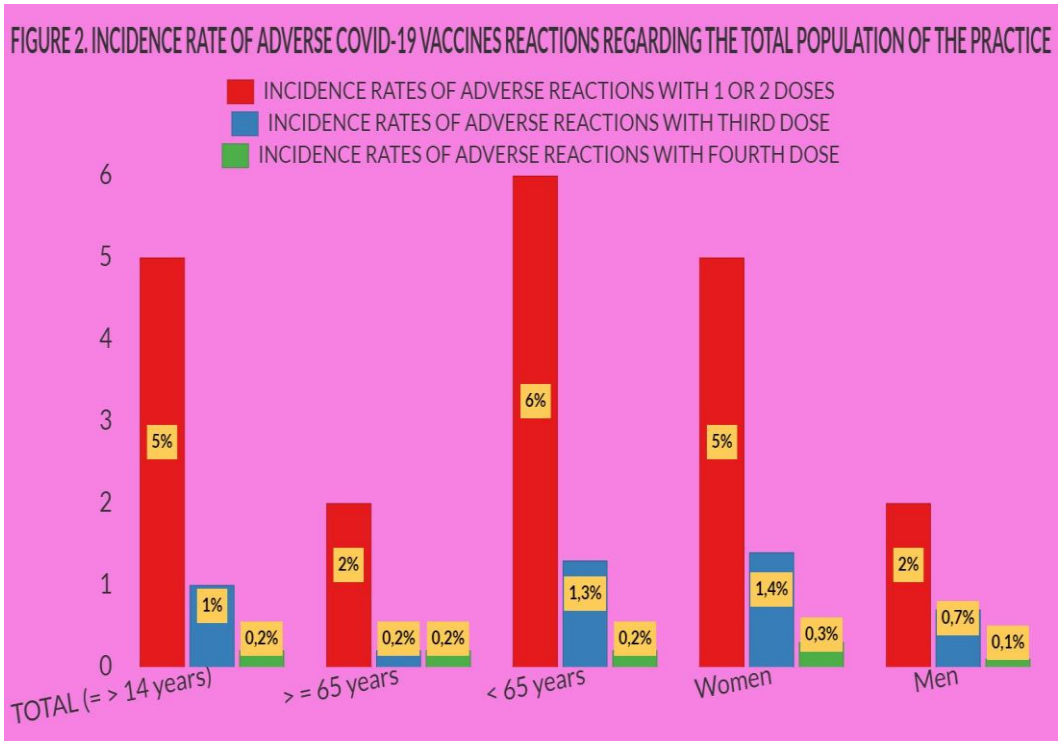

Figure 2: Comparison of Incidence Rate of Adverse Covid-19 Vaccines Reactions with First and Second Doses, First Booster and Fourth Dose Regarding the Total Population of the Practice.

Discussion

1. Main findings

Our main result is that the IR of COVID-19 vaccine adverse reactions that were the reason for consulting the GP (which would be a proxy indicator of the minimum incidence) is decreasing from the first dose to the fourth dose. A permanent pattern is observed where they are higher in men <65 years and in women. But these results must be taken with caution. These results may suggest both a real progressive reduction in the number of AR (possibly due to decreased immunogenicity of the boosters), and a reduction in general practitioner visits for this reason, possibly as a learning effect for patients, in the course of successive doses of vaccines, and thus, people, over time, would

consult the GP only for some AR, perhaps only for severe AR.

2. Comparison with other studies

Adverse effects of COVID-19 vaccines are mild in most cases, consisting of a local reaction at the injection site and/or minor systemic effects such as fatigue or headache. They are most likely the result of the initial immune response, characterized by the production of antiviral cytokines, particularly interferons.[3,17]

The anecdotal comments from patients about their feelings after receiving the booster dose of the COVID-19 vaccine are like: "The first dose did not give me any kind of reaction. With the second I had arm pain. But the third one left me fatal, with chills and numbness that I had never had before." If this fact were true, why is it that there may be a greater general reaction when inoculating the third or fourth dose? One explanation may be that in many boosters, Moderna is used, which is a more reactogenic vaccine and with a greater immune response than that of Pfizer or AstraZeneca, which were inoculated at the time as the first or second dose. In any case, theoretically, it is the normal reaction of the immune system, which is already stimulated.[18]

After the administration of a vaccine for the first time and after a more or less prolonged latency period, the production of antibodies takes place at a weak rate; after subsequent contact with the same antigen, a much more intense and rapid response takes place. This is a consequence of the presence of cells that have stored the antigenic memory, that is, the primary reaction is a consequence of the first antigenic contact as opposed to the secondary response due to repetitive stimulations.[5]

Thus, it has been published that AR was more frequent after the second dose.[19] According to a systematic review, after the second dose, there was more AR than the first.[19-21] However, other studies show different results. It has been published that 56% presented AR with the first dose and 46% with the second. Likewise, presenting AR in the first dose was associated with presenting them with the second dose.[7] In addition, the AR in the fourth dose seems to be linked to the AR in the third administered (the first booster) to each person.[10] In any case, it seems that it is the minor, local, and common AR of the vaccines, which have higher rates with the booster dose.[8]

On the other hand, there are differences according to the type of vaccine. For mRNA-based vaccines, side reactions are usually stronger with the second dose. In contrast, with the AstraZeneca vaccine, they seem to be stronger with the first dose.[22,23] Likewise, it has been reported that no significant differences were observed in the reactions between the first and second reinforcement.[10,24,25] In our study we found relevant differences in these data, obtaining progressively lower incidence rates of AR when repeating doses.

Regarding age, it is accepted that the younger the person who is vaccinated, the more noticeable the AR is since there are still antibodies in the body. Older people have a less reactive immune system and therefore tend to have fewer AR.[7,18,22,23] Men and women tend to respond differently to many types of vaccines. This is probably due to a mix of factors, including hormones, genes, and the dose of vaccines. In general, the majority of people who report AR to COVID-19 vaccines are women.[7,26-28] Women produce more antibodies possibly related to reproductive hormones. It is also possible that genetic differences between men and women have some influence on immunity. Variations according to sex in pharmacokinetics and pharmacodynamics have also been observed, with women being more susceptible to AR.[7,29] But, part of the answer could be behavioral; it is possible that women communicate and see the doctor about ARs more than men even when their symptoms are the same.[30] Our results coincide with what has been published regarding age and sex.

In our context, 4 vaccines have been used: Pfizer Moderna, Janssen, and AstraZeneca. For the first and second doses, Pizfer / BioNTech vaccine and

Spikevax (mRNA-1273 vaccine Moderna) were predominantly used; ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) was finally destined for the age group between 60 and 69 years old. Later, the Janssen vaccine (Johnson & Johnson vaccine) vaccine arrived, aimed at more age groups than AstraZeneca, and designed for people with difficult uptake, taking advantage of its inoculation in a single dose.[31] For the Booster dose, only messenger RNA (mRNA) vaccines (0.3 ml Comirnaty or 0.25 ml Spikevax – half the usual primary dose)[32-34] were used. In the fourth booster dose for fall-winter 2022, only Moderna and Pfizer-BioNTech's bivalent COVID-19 vaccines were used.[35] In this way, the analysis of the incidence of AR can be more complex, since the reactogenicity can vary from one brand of vaccine to another; although, most mild AR has been reported to be similar.[8,36]

Conclusion

Bearing in mind that safety is one of the key factors in deciding whether or not to get vaccinated, in our context booster doses appear to be increasingly safer. The IR of AR to the COVID-19 vaccines, both in figures with respect to the vaccinated population and with respect to the total population dependent on the general medicine consultation, have been decreasing from the first doses to the last, where they show very low figures in the fourth dose. A permanent pattern is observed where they are higher in men <65 years and in women. In our context, the magnitude of the reduction and the trend in the IR of AR to the different doses of the COVID-19 vaccine suggest the coexistence of both a progressive real reduction in the number of AR (possibly due to a decrease in the immunogenicity of the boosters) and a reduction in the number of visits to the general practitioner for this reason, possibly as a learning effect of the patients in the course of the vaccine doses, about when to consult the GP.

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