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Research Article

Case series of covid-19 infections with fourth dose of bivalent mrna vaccine in the period from october 2022 to october 2023 in a general medicine office of toledo (spain)

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Abstract

Background

The effectiveness of administering booster doses with vaccines adapted to new variants and subvariants is still a matter of debate.

Objective

To describe the cases of covid-19 infections in vaccinated people with 4th dose.

Methodology

An observational, longitudinal and prospective case series study of adult patients with covid-19 infections in vaccinated people with 4th dose in general medicine from October 1, 2022 to October 1, 2023. Descriptive epidemiological analysis considered a set of selected demographic and clinical features.

Results

21 covid-19 infections were included in vaccinated people with 4th dose from October 2022 October 2023. The main characteristics were: 67% > = 65 years, 62% women, 24% Socio-Health Care Workers, 9% with Moderate-severe severity (hypoxia, pneumonia), 86% had Chronic diseases [mainly Circulatory system (22%) and Endocrine (20%)]. There were practically no psychosocial risk factors [Complex family/ Problems in the family context, Low-income household, Ethnic minority (5, 0% and 0% respectively)], and 24% were re-infections. General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) (42%) and Respiratory symptoms (cough, dyspnea, chest pain) (31%) predominated.

Conclusion

In our series from October 2022 October 2023, in the context of a general medicine consultation in Toledo (Spain), the risk profile of the cases, the frequency of reinfections and the infrequency of severity, suggests that revaccination is still advisable in vulnerable people such as older people, women, socio-health care workers and chronically ill people.

Keywords: COVID-19; SARS-CoV-2; Epidemiological characteristic; Symptoms; Case Series; General Practice

Introduction

Since March 2020, when the World Health Organization declared the state of pandemic for the coronavirus disease 2019 (covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has evolved in several periods of different duration and repercussions in terms of morbidity and mortality (1). One of the determinants of morbidity and mortality has been the behavior of the virus during the pandemic from the original strain (Wuhan-alpha) to the currently predominant Omicron. Said behavior of the virus, in addition to the health measures implemented, especially vaccination, explain the differences between the pandemic and currently endemic period with respect to symptomatic infection, morbidity and deaths [2-4].

Currently, the predominant variant in Spain is Omicron, which has a greater immune escape capacity than previous variants, is more transmissible and has less severity. It comprises five lineages-mutations: BA.1, BA.2, BA.3, BA.4 and BA.5. So far no differences in the severity of the cases have been observed for any of them. Currently, the BA.5 variant is the dominant one [5]. In Spain, from the beginning of vaccination until September 14, 2022, 93% of citizens over 12 years of age had the complete vaccination schedule

[6]. The Health Authorities decided to start vaccinating the fourth dose to people over 80 years of age and institutionalized with a bivalent vaccine available. Depending on the availability of vaccines, it was extended to people over 60 years of age, immunosuppressed people, social health workers and pregnant women, and finally rest of population [7].

The previous monovalent boosters had managed to recover vaccine effectiveness up to 85-90% against hospitalization and death, which had decreased over the months and coinciding with the circulation of the Omicron variant and its immune evasion [8]. For the second booster (fourth dose) bivalent vaccines were used [9]. Since September 1, 2022, the European Commission and the European Medicines Agency (EMA) authorized the use of the adapted covid-19 vaccines Comirnaty Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.1, as vaccines for a second booster dose in people over 12 years of age with the complete primary vaccination schedule and at least 3 months after the last dose of vaccine administered. Likewise, the EMA approved the adapted bivalent covid-19 vaccine Comirnaty Original/Omicron BA.4- BA.5 for use in people over 12 years of age who have received at least one primary cycle of vaccination against coviod-19 [10, 11].

With the adaptation of vaccines, the aim was to expand protection against different variants. Predictive studies of the efficacy of bivalent boosters in the vaccinated population concluded that protection against serious infection rose from 50% to 87% with monovalent booster, while it would reach 98% when using bivalent booster. Furthermore, the lower the preboost immunity, the greater the relative benefit of a bivalent booster would be [12]. Its approval was based on clinical data available with Comirnaty Original/Omicron BA.1 and laboratory immunogenicity studies. Studies showed that the bivalent vaccine can trigger strong immune responses against Omicron BA.1 and the original SARS-CoV-2 strain in previously vaccinated people, and greater responses against subvariant BA.1 than the original vaccines [13].

However, applying a fourth dose in general population has the disadvantages that it can lead to low vaccine coverage due to pandemic fatigue, and that repetition with new doses can cause a phenomenon of immune tolerance. A repeat dose of the bivalent BA.5 mRNA vaccine, as recommended for some populations, may not be sufficient to broaden neutralizing antibody responses and overcome immunological imprinting in elderly but healthy individuals [14].

In this changing scenario, where clinical studies are still ongoing, and where epidemiological surveillance has been greatly reduced, causing a lack of data regarding many population groups (2, 15, 16), sustained clinical-epidemiological surveillance are needed, which could include longitudinal cohort studies. In this context, we present an observational, longitudinal and prospective case series study of adult patients with covid-19 infections in vaccinated people

with 4th dose in general medicine from October 1, 2022 to October 1, 2023.

Material And Methods

Design and emplacement

An observational, longitudinal and prospective study of Covid-19 infections in vaccinated people with 4th dose was conducted from October 1, 2022 to October 1, 2023, in a general medicine office in 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 [17]. Data from this series of cases were previously published from a shorter period of time than that of the current study, and global data on all covid infections in people with and without a fourth dose of vaccination [18-20].

Outcome of interest

To describe the cases of covid-19 infections in vaccinated people with 4th dose.

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [21] performed in health services or at home.

Collected variables

The following variables were collected:

-Age and sex

-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" [22], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [23]

-If they were Health Care Workers

-Problems in the family context and low-income household based on the genogram and in the experience of the GP for their continuity of care and knowledge of the family (genogram is 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" genograms present families with psychosocial problems) [24, 25]

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [26]

-Disease severity (classified according to: 1. mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; 2. moderate cases: with symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests; and 3. 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.) [27]; to simplify comparison, moderate and severe cases were counted together;

-Date of covid-19 infection diagnosis

-Presence of reinfection (SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection) [28, 29]

-Vaccination status against covid-19 at the date of acute infection: vaccinated with fourth dose (second booster) for fall-winter 2022 [30]

Epidemiological analysis

Descriptive epidemiological analysis considered a set of selected demographic and clinical features. Excessive fragmentation of the data was avoided to avoid showing a small number of cases. The age of 65 years was used as the beginning of old age [31]

Ethical issues

No personal data of the patients were used, but only group results, which were taken from the clinical history.

Results

21 covid-19 infections were included in vaccinated people with 4th dose from October 2022 October 2023. The main characteristics were: 67% > =

65 years, 62% women, 24% Socio-Health Care Workers, 9% with Moderate-severe severity (hypoxia, pneumonia), 86% had Chronic diseases [mainly Circulatory system (22%) and Endocrine (20%)]. There were practically no psychosocial risk factors [Complex family/ Problems in the family context, Low-income household, Ethnic minority (5, 0% and 0% respectively)], and 24% were re-infections. General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) (42%) and Respiratory symptoms (cough, dyspnea, chest pain) (31%) predominated (TABLE 1, TABLE 2, TABLE 3).

VARIABLES	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE FROM OCTOBER 2022 OCTOBER 2023 N= 21
> = 65 years	14 (67)
= < 45 years	0
Women	13 (62)
Social-occupancy class of patients (people with some type of labor specialization)	7 (33)
Socio-Health Care Workers	5 (24)
Moderate-severe severity	2 (9) (hypoxia, pneumonia)
Chronic diseases	18 (86)
Complex family/ Problems in the family context	2 (9)
Low income household	0
Ethnic minority	0
Reinfection	5 (24)

( ): Denotes percentages

Table 1: Selected Variables of Covid-19 Infections in Vaccinated People with 4th Dose from October 2022 October 2023

SYMPTOMS COVID-19 INFECTION* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE FROM OCTOBER 2022 OCTOBER 2023 N= 21
General (discomfort, asthenia, myalgia, fever, artralgias)	30 (42)
Respiratory (cough, dyspnea, chest pain)	22 (31)
ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis, ear pain)	11 (15)
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	1 (1)
Neurological (headache, dizziness, mental confusion, dysarthria, disorientation, photopsia, syncope)	7 (10)
Psychiatric (aAnxiety, insomnia)	0
Skin (chilblains, flictenas, rash)	0
Urológico (dysuria, frequency)	1 (1)
Total symptoms*	72 (100)

( ): Denotes percentages; * Patients could have more than one symptom. The percentages are over the total of symptoms

Table 2: Symptoms Of Covid-19 Infections in Vaccinated People With 4th Dose from October 2022 to October 2023

CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 INFECTIONS IN VACCINATED PEOPLE WITH 4TH DOSE FROM OCTOBER 2022 OCTOBER 2023 N= 21
-I Infectious	0
-II Neoplasms	2 (3)
-III Diseases of the blood	3 (4)
-IV Endocrine	14 (20)
-V M/ental	9 (13)
-VI-VIII Nervous and Senses	5 (7)

-IX Circulatory system	16 (22)
-X Respiratory system	2 (3)
-XI Digestive system	7 (10)
-XII Diseases of the skin	2 (3)
-XIII Musculo-skeletal	5 (7)
-XIV Genitourinary	6 (8)
TOTAL chronic diseases*	71 (100)

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

Table 3: Chronic Diseases in Covid-19 Infections in Vaccinated People With 4th Dose in the Period from October 2022 To October 2023

Discussion

1. Main findings

The main results of our study were that the covid-19 infections in vaccinated people with 4th dose:

1. They predominated in people over 65 years of age, women, with chronic diseases of the Circulatory system and Endocrine, without psychosocial risk factors, and with a significant frequency in Socio-Health Care Workers.

2. The main symptoms were General (discomfort, asthenia, myalgia, fever, arthralgia) and Respiratory (cough, dyspnea, chest pain).

3. They mostly presented mild severity.

4. A quarter of these infections were re-infections.

From the first months of 2022, the Omicron variant was the dominant variant in Spain after having displaced the Delta variant (32). The predominant variants in Spain during 2023 were those of the XBB family. The XBB.1.5 lineage became dominant globally in February 2023 and in March in Spain. The “Eris” variant (EG.5), a descendant of the omicron, also of the XBB family, has spread rapidly since the end of July 2023 throughout the United States, Europe (including Spain) and Asia (5, 33-36).

On the other hand, covid-19 is at a tipping point, meaning that high levels of immunity to SARS-CoV-2 are beginning to limit its impact and reach. Currently, many countries do not test all symptomatic patients, nor do they systematically collect the number of cases or their clinical-epidemiological characteristics [16, 37]. In Spain, the surveillance and control strategy against covid-19 after the acute phase of the pandemic, in force since March 28, 2022, indicates the need to perform PCR or antigen testing only in specific situations that fundamentally include people with vulnerability criteria, of vulnerable areas, and those that require hospital admission. The reported cases therefore represent these groups and not the total number of SARS-CoV-2 infections, so the evolution of the pandemic monitoring indicators must be adapted to this circumstance and the data from these reports cannot be compared with those of prior reports [38]. In this situation, many people with symptoms in the community choose to perform individual tests at home [39]. But, frequently, people with a positive test at home do communicate this circumstance to their family doctor, to seek treatment and/or sick leave.

Taking into account these circumstances that contextualize our results, given the risk profile of the cases and the frequency of reinfections, and the infrequent severity of the infections, one can think about the usefulness of the fourth dose of vaccine; as well as the in its short duration. So it would seem reasonable to continue advising revaccination of vulnerable people (the elderly, women, Health Care Workers and chronically ill patients).

2. Comparison with other studies

Vaccination provides substantial protection against both symptomatic and severe covid-19. However, there has been continued and substantial evolution of SARS-CoV-2 variants since the virus emerged, such as Omicron and its sub-variants, posing challenges for the public health response, including ensuring that vaccines continue to provide protection, which have markedly reduced efficacy in regimens based on the ancestral Wuhan variant. Thus, booster vaccination for the prevention of covid-19 is required to overcome this loss of protection [40, 41].

Since September 2022, Moderna and Pfizer-BioNTech bivalent SARS-CoV-2 vaccines containing equal amounts of spiked mRNA from the ancestral BA.4-BA.5 and omicron subvariants replaced their monovalent counterparts as booster doses for people over 12 years old. It is strongly suggested that a bivalent booster may preserve the safety and serological efficacy of the original monovalent booster while broadening the spectrum of antibody response, helping to restore protection that might have diminished since the last previous dose [42-49]. This justifies the use of sequence-adapted vaccines [50-60] .Thus, it has been reported that benefits of mRNA covid-19 vaccines in protecting against the omicron variant outweigh the risks, regardless of age, sex, and comorbidity [61].

Immunological profiles are increasingly heterogeneous (individuals who have been previously infected, or previously vaccinated with a primary series and/or booster doses on different platforms, with various spike protein antigens; as well as individuals who have been infected and then vaccinated, and individuals who have been vaccinated and then infected), so the performance of an updated vaccine will vary depending on the nature and magnitude of the previously acquired immunity in each person (40). The continued circulation of SARS-CoV-2 in the current endemic period will manifest itself depending on reinfection rates, the availability and effectiveness of the vaccine, and the social, immune and innate factors that modulate the transmissibility of the virus [62]. We found 24% of covid-19 re-infections were in vaccinated people with 4th dose.

Bivalent vaccine, a previous infection, or timely access to screening and treatment can help prevent the seriously cases from Covid-19. However, some people are more likely than others to become seriously ill from Covid-19. This includes older people or those who are immunocompromised, certain disabilities or underlying conditions (57, 60, [63, 64]. We found that 67% of the covid-19 cases with the fourth dose of vaccine were >= 65 years, and 86% had chronic diseases, mainly of the Circulatory system (22%) and Endocrine (20%).

Finally, in relation to psychosocial factors, understood as the risks to physical, mental, mental and social health generated by socioeconomic determinants, the employment condition, the organization and content of work and the relational factors that intervene in the psychological functioning, it is admitted that they influence cognitive, emotional, behavioral processes and, with regard to risk perception of covid-19 and vaccination with the fourth dose [65]. In our study we did not find psychosocial risk factors in cases of covid-19 with the fourth dose.

Study limitations and strengths

1. The number of cases was small and thus the results may be subject to erroneous interpretations.

2. Asymptomatic patients were not included, since no screening intervention was performed

3. The great accessibility of patients to the family doctor, and the fact of the continuity of care that characterizes family medicine, suggest that the data presented correspond to the population reality.

4. It must be taken into account that case series studies only include "numerators" so they cannot be extrapolated to incidence rate values.

conclusion

In our series from October 2022 October 2023, in the context of a general medicine consultation in Toledo (Spain), covid-19 infections in vaccinated people with 4th dose predominated in older women with chronic diseases of the Circulatory system and Endocrine; without psychosocial risk; with a significant frequency in Socio-Health Care Workers; with General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) and Respiratory symptoms (cough, dyspnea, chest pain), with slight severity; and a quarter of these infections were re-infections. Given the risk profile of the cases, the frequency of reinfections, and the low frequency of severity, revaccination of vulnerable people (the elderly, women, Health Care Workers and chronically ill people) is still advisable.

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