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Research Article

Incidence Rate of Covid-19 Infection in People with Fourth Dose of Vaccines Bivalent Mrna from October 2022 to October 2023 in A General Medicine Office in Toledo (Spain)

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Abstract

Background

Incidence rate of covid-19 infection in people vaccinated with 4th dose of RNA covid-19 vaccine remain subject of debate and is not clearly known

Objective

Estimate the incidence rate of covid-19 in vaccinated 4th dose people in general practitioner care level.

Methodology

An incidence rates epidemiological analysis of covid-19 infection in people with 4th dose of bivalent mRNA vaccines based in a longitudinal study from October, 2022 to October, 2023, in a general practice setting in Toledo, Spain.

Results

21 cases of covid-19 infection in vaccinated people with 4th dose were included. Incidence rate of covid-19 infection in total vaccinated people with 4th dose from October 2022 to October 2023 was 2%; it was greater in > = 65 years vs. < 65 years (3% vs. 1%), and in women vs. men (2% vs. 1%). Regarding incidence rate of covid-19 infection in vaccinated people with 4th dose in general population of the office was 1%; It was again older at > = 65 years vs. < 65 years (1% vs. 0.5%), but without differences between women and men (1% vs. 1%).

Conclusion

In general practice setting in Toledo, Spain, crude incidence rate of covid-19 infection in vaccinated people with 4th dose and in general population of the office was low. However, the population segments of >= 65 years and women, even with fourth vaccine dose, have a higher risk of covid-19 infection, and consequently should continue receiving booster vaccine. But these results should be interpreted with caution since the number of tests carried out in the community was low.

Kew Words: covid-19; sars-cov-2; vaccine effectiveness; breakthrough infection; population surveillance/methods; public health practice; general practice

Introduction

Since the original virus emerged, successive variants of coronavirus syndrome 2 (SARS-CoV-2) have appeared such as omicron and its subvariants. The Omicron variant is by far the most dangerous strain, with greater transmissibility and immune escape than previous variants that cause coronavirus disease 2019 (covid-19), such as Alpha, Beta, Gamma and Delta. It has been shown that the effective reproduction number of the Omicron variant is 3.19 times higher than that of Delta under the same epidemiological conditions [1].

These mutations endow the virus with greater infective capacity, increasing transmissibility rates, or may allow it the ability to avoid the recognition of antibodies that should protect against its infection, resulting in a lower protective effect of existing vaccines. Thus, a booster vaccination for the prevention of covid-19 is required to overcome this loss of protection [2-4].

Since September 2022, the bivalent SARS-CoV-2 vaccines from Moderna and Pfizer-BioNTech containing equal amounts of enriched mRNA from the ancestral subvariants BA.4-BA.5 and omicrons replaced their monovalent counterparts as booster doses for people over 12 years old [5-10]. These bivalent mRNA vaccines against covid-19 trigger a stronger immune

response than a fourth dose of the original monovalent vaccine, quadrupling the antibody titer against the BA.4 and BA.5 omicron subvariants in people over 55 years of age [11]. But there is a lack of data on how these events translate into significant clinical outcomes at the population level in the sense of preventing any infection [5, 11, 12].

In this scenario, it must be added that since the disappearance of the health alarm in many countries, cases of covid-19 are not counted and tests are carried out in health services only in certain situations, such as in people over 60 years, pregnant women or hospitalized patients and health personnel; In this way, people with symptoms in the community, who do not meet these criteria, frequently choose to perform specific tests at home [13-15]. On the other hand, in the long term, most infections will occur in previously vaccinated people. Data on incidence rates in vaccinated persons, based on sustained surveillance, may have important implications for guiding rational vaccination policies and decisions [6].

Consequently, the incidence rate of covid-19 infection in people vaccinated with 4th dose of RNA covid-19 vaccine is not clear. In these circumstances, novel approaches for sustained surveillance are needed, which could include longitudinal cohort studies at the general medicine consultation level. In this context, we present a longitudinal and prospective study of adult patients with covid-19 infection in vaccinated people with fourth dose of bivalent mRNA vaccines, in general medicine from October 1, 2022 to October 1, 2023, whose objective was to identify covid-19 incidence rate.

Material And Methods

A longitudinal and prospective study of cases and controls of adult patients with covid-19 infections in vaccinated people with fourth dose of bivalent mRNA vaccines, 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) was carried out. The GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and each person is assigned a GP. The descriptive data of the case series with covid-19 infections in vaccinated people with fourth dose of bivalent mRNA vaccines in this population have already been published [16-18]; This study will focus on describing the incidence rates in this at-risk population.

Objective of the study: To estimate incidence rate of covid-19 infections in vaccinated people with fourth dose of bivalent mRNA vaccines in GP consultation. Different outcome measures can be considered for Moderna and Pfizer-BioNTech bivalent SARS-CoV-2 vaccines: infection, severe infection leading to hospitalization, and severe infection leading to death [7]. In our study based on the general medicine consultation, covid-19 infection was the chosen outcome measure.

Calculation of incidence rates

Cumulative incidence rates were calculated at the GP's office by dividing the number of infection events during the study period divided by the individuals that could develop the event at the start of the study (population at risk) [19]. That is, for people with fourth dose, the incidence rate was calculated by dividing the number of cases of covid-19 infections in vaccinated people with fourth dose by the vaccinated people with fourth dose in the follow-up time (from October 1, 2022 to October 1, 2023) [20]. Similarly, the data on the incidence were extrapolated to the entire population attended in the consultation (N=2,000 people) [21].

Calculation of rate denominators

Data of number of people vaccinated with the 4th dose in the clinic object of the study were obtained by extrapolating the vaccination data at the national level to the population of the clinic and the neighbourhood served by the health centre [22-26]. In Spain, in November 2022, more than 60% of people over 80 years of age, and 37% of people over 60 years of age, already had the second booster (4th dose) dose of the covid-19 vaccine [27, 28].

Fourth booster dose for fall-winter 2022

In the patients included in the study Moderna and Pfizer-BioNTech's bivalent Covid-19 vaccines were used [29]. The vaccination campaign began in Spain on September 26, 2022. The administration of a booster dose against covid-19 was recommended to the population aged 60 and over, to people admitted to nursing homes and other centres with disabilities and those with risk conditions, including socio-health personnel [23].

Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing [30] performed in health services or at home subsequently communicated to the GP.

Epidemiological analysis

The calculation of the incidence rates as explained above (subsection “Calculation of incidence rates”) was made by dividing the number of infection events by the person follow-up time (from October, 2022 to October, 2023) [19, 20]. Data on the incidence were extrapolated to the entire population attended in the consultation (N=2,000 people) [21]. The classes that classify the age groups were made taking into account > and < 65 years [31]. The age of 65 years was used as the beginning of old age [32]. Figures with decimals were rounded to whole numbers to facilitate a more intuitive comparison.

Results

21 cases of covid-19 infection in vaccinated people with 4th dose were included. Incidence rate of covid-19 infection in total vaccinated people with 4th dose from October 2022 to October 2023 was 2%; It was greater in > = 65 vs. < 65 years (3% vs. 1%), and in women vs. men (2% vs. 1%). Regarding incidence rate of covid-19 infection in vaccinated people with 4th dose in general population of the office was 1%; being again greater in > = 65 vs. < 65 years (1% vs. 0.5%), but without differences between women and men (1% vs. 1%) (**TABLE 1**).

Variables	Population of the general medicine office N=2.000 (total population at risk)	Population vaccinated with fourth dose at the general medicine office from October 2022 to October 2023 N=1133 (population vaccinated with fourth dose at risk)	Covid-19 infections in vaccinated people with 4th dose from October 2022 October 2023 N= 21	Incidence rates of covid-19 infection in vaccinated people with fourth dose from October 2022 to October 2023	Incidence rates of covid-19 infection in vaccinated people with fourth dose in general population of the office from October 2022 to October 2023
Total = > 14 years	2.000	1.133 (100)	21 (100)	2%	1%
> = 65 years	480 (24)	455 (95)	14 (67)	3%	3%
< 65 years	1520 (76)	678 (45)	7 (33)	1%	0.5%
Women	1020 (51)	580 (57)	13 (62)	2%	1%
Men	980 (49)	555 (57)	8 (38)	1%	1%

Table 1: Incidence Rates of Covid-19 Infection with 4ª DOSE vaccines bivalent Mrna in general medicine (toledo, spain) from october 2022 to october 2023

Discussion

1. Main findings

The main results of our study were:

1. Crude incidence rate of covid-19 infection in vaccinated people with 4th dose was 2%.

2. Incidence rate of covid-19 infection was higher in > = 65 years vs. < 65 years (3% vs. 1%).

3. In vaccinated people with 4th dose, incidence rate of covid-19 infection was higher in women vs. men (2% vs. 1%).

However, these results should be interpreted with caution. It must be taken into account that in Spain, since April 28, 2022 there was a new "Surveillance and Control Strategy Against Covid-19" that included the non-performance of diagnostic tests, which were focused only on those over 60 years of age [14]. And on the other hand, 4th dose began to be given to older people [23]. This meant in practice that in many cases of symptoms of viral infections in the community no diagnostic tests were carried out, and that those that were carried out were more likely in older patients. Therefore, it can be thought that 1) there were more covid-19 cases; 2) the cases of covid-19 in older people are probably closer to reality than the cases in younger people.

On the other hand, it should be mentioned that in the study period, the omicron variant was the dominant one in Spain (in the week of November 21 to 27, 2022), the omicron percentage stood at 100% [23].

2. Comparison with other studies

The incidence (the new cases in a certain unit of time as the numerator, and the estimated population at the centre of the period as the denomination) is a way of expressing the morbidity rate [33]. Analysis of epidemiological data, such as Incidence Rates, for small areas is suitable for investigating differences in clinical decision-making as well as differences in the organization of services [34]. It is in this context where our study and its usefulness are inscribed.

On the other hand, vaccines are known to protect very well against serious disease, but much less well against infection [24]. In this way, severe cases have been studied more. Our study aims to provide data about infection in cases of relatively mild disease.

One of the first sources of empirical evidence on the possible public health impact of a 4th dose of mRNA vaccines as a second booster in immunocompetent people came from data from Israel. These data indicated that a 4th dose of an mRNA vaccine administered to immunocompetent persons at least 4 months after the third dose can restore humoral immunity to the level observed after the third dose without raising new safety concerns [35]. Other studies have also reported that bivalent boosts provide substantial additional protection against severe omicron infection in previously vaccinated or boosted people, although efficacy declined over time [36-43].

Regarding the incidence rate of covid-19 infection in people vaccinated with 4th dose of RNA covid-19 vaccine, different figures have been reported. Thus, a rate of severe covid-19 cases per 100,000 person-days of 1.5 has been reported in people with four doses (44); Another study showed an infection rate among Health Care Workers in Israel who received 4 doses of 6.9% [45].

Finally, we should mention that in a study on the same population as the current study, but limited to the period from October 2022 to February 2023, it showed similar but smaller results: An incidence rate of covid-19 infection in people vaccinated with the 4th dose of RNA covid-19 vaccine of 0.45%, with no difference between > and < 60 years, and with incidence rate was higher in women (0.53%) than in men (0.37%). And incidence Rate with respect to the total general population was 0.25%, being higher in >60 years (0.42%) than in <60 years (0.19%), and higher in women (0.29%) than in men (0.20%) [46].

Study limitations and strengths

1. The sample was small, so some data may cause misinterpretation.

2. Asymptomatic cases were missing because they did not attend in GP consultation, as no surveillance or systematic screening was done.

3. There may be an underreporting of infections to GP of patients with a positive test at home. But given the situation of the GP as the gateway to the health system, the vast majority of positive covid-19 tests at home, is likely to be reported in GP office.

4. The great accessibility of patients to the GP, and the fact of the continuity of care that characterizes family medicine, have important epidemiological connotations, presenting a unique opportunity to study incidence rates of diseases in small geographical bases.

Conclusion

Crude incidence rates of covid-19 infection in vaccinated people with 4th dose, as well as in general population of the office was low (2% and 1%, respectively). Incidence rate of covid-19 infection in vaccinated people with 4th dose, as well as in general population of the office was higher in > = 65 years vs. < 65 years, but with higher figures for vaccinated people with 4th dose (3% vs. 1%; and 1% vs. 0.5%, respectively). Incidence rate of covid-19 infection in vaccinated people with 4th dose was higher in women vs. men, but without differences in the general population of the office (2% vs. 1%, 1% vs. 1%, respectively). However, given that the number of tests carried out in the community was low, these results should be interpreted with caution.

In any case, despite finding a relatively low figure of the crude incidence rate of covid-19 infection in vaccinated people with 4th dose and in general population of the office (2% and 1%), and that people > = 65 years vs. < 65 years had a higher frequency of vaccination with 4th dose (95% vs. 45%) and despite this they showed a higher incidence rate of covid-19 infection; and that in vaccinated people with 4th dose incidence rate of covid-19 infection was higher in women vs. men, it can be concluded that these population segments (> = 65 years and especially women) have a higher risk, and consequetly should contnue receiving booster vaccine.

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