



What are the Clinical-Epidemiological Differences between Initial Infection and Reinfection Covid-19 with Fourth Dose of Bivalent mRNA Vaccine? A Study in the Period from October 2022 to October 2023, In a General Medicine Office (Toledo, Spain)

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Abstract

Background: The clinical-epidemiological differences between primary infections versus reinfections of covid-19 with the 4th dose of bivalent mRNA vaccine are not known.

Objective: Compare primary infections versus reinfections of covid-19 with 4th dose of bivalent mRNA vaccine.

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: 16 people with fourth dose and with covid-19 infections and 5 people with fourth dose and with covid-19 reinfections from October 2022 to October 2023 were included. Reinfection versus primary infections were more frequent in women, social-health care workers, complex family, moderate-severe severity of infection, chronic diseases of the Neoplasms, Endocrine, Musculo-skeletal and Genitourinary groups, and presented more ENT and neurological symptoms. But, the only variable with statistically significant differences was the presence of Neoplasms (13% versus 0%; Fisher exact test = 0.0483).

Conclusion: In the context of a general medicine consultation in Toledo (Spain) from October 2022 to October 2023, in people with the fourth dose of bivalent mRNA vaccine against covid-19, covid-19 reinfections did not differ in their clinical-epidemiological characteristics except for being more frequent in presumably immunosuppressed patients (patients with Neoplasms) compared to covid-19 primary infections. In any case, our results, although consistent with the existing literature, should be taken with caution due to the small number of covid-19 cases included.

Keywords: COVID-19; SARS-CoV-2; Epidemiological Characteristic; Symptoms; Vaccine Effectiveness; Breakthrough Infection; Reinfection; General Practice

Introduction

Estimates suggest that more than 500 million people worldwide have been infected with severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) at least once [1]. For the large and growing number of people who have suffered a first infection, the question of whether a second infection carries additional risks is important [2]. The severity of

the SARS-CoV-2 disease has changed drastically in the last 4 years, causing, at least in people under 65 years of age who do not have comorbidities, little acute damage [3]. This change has a lot to do with the fact that in January 2020 the world population was immunologically surprised by the new infection; But possibly an evolutionary compensation has also weakened SARS-CoV-2: as the virus has spread to billions of people, it may have become less virulent in order to spread more easily [4].

As the virus evolves, new variants may emerge with the ability to evade a person's existing immunity. This could increase the risk of reinfection [5]. The problem of reinfections became significantly more frequent when Omicron emerged, and its more infectious subvariants became dominant in December 2022 [6,7].

In this scenario, reinfection with SARS-CoV-2 has brought new challenges to the global prevention and control of the coronavirus disease 2019 (covid-19) pandemic [8]. For reinfection to occur, there are two key elements, according to the studies published to date and the view of the immunologists: the time since the first infection occurred and the variant that was involved. In parallel, the time elapsed since the last dose of vaccine seems relevant to avoid reinfection [9]. Although prior SARS-CoV-2 infection can protect against reinfection for an average of seven months, immunity wanes afterward. Repeated outbreaks of covid-19 can be harmful (even if the episodes are mild) because the long-term consequences accumulate with each additional infection [2]. For those who have had a previous infection, vaccination often adds greater protection, especially against reinfections that lead to hospitalization [5].

In any case, the number of reinfections is expected to increase as the cumulative incidence of first infections increases, immunity induced by infections and vaccines decreases, and new variants with greater transmissibility and immune escape characteristics emerge [10]. But, the clinical impact of reinfection is not yet fully understood. In general, reinfections have been reported to be clinically less severe than initial SARS-CoV-2 infections [11,12] and clinical-epidemiological trends in reinfections have not been characterized [6] with the effects of vaccine boosters on reinfection risk unknown[7].

Due to differences in the definition of reinfection, epidemic period, follow-up time, and other factors used in different studies, there is still great uncertainty about the risk of covid-19. Furthermore, due to economic, political, cultural and geographical differences, the epidemic status, surveillance and level of testing of covid-19 may vary between different countries.

Omicron remains the dominant variant in the world today. Compared with the wild-type virus, some Omicron sub variants have significantly enhanced immune escape ability and increased risk of reinfection, which has posed new challenges for the global prevention and control of the covid-19 pandemic. Accurate assessment of the severity and outcomes of SARS-CoV-2 reinfection cases is essential for rational allocation of medical resources and optimization of vaccination strategies [8]. An accurate estimate of the clinical-epidemiological factors of SARS-CoV-2 reinfections would be essential to optimize restriction and vaccination policies for the hundreds of millions of previously infected subjects [13].

In this context, an important question is what are the clinical-epidemiological differences of reinfections in relation to initial infections? To better understand these differences we present a longitudinal and prospective study of cases of primary infection and reinfection of adult people with a fourth dose of bivalent mRNA vaccines, 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 was conducted from October 2022 to October 2023 in a general medicine office in the Santa Maria de Benquerencia Health Center, 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 dependent neighbourhood of the Health Center has a population of 20,000 inhabitants. 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 [14]. The descriptive results of the case series have already been published [15,16].

Outcome of Interest

Compare the clinical-epidemiological characteristics of the cases of primary infection versus covid-19 reinfection with the 4th dose of bivalent mRNA vaccine, to assess differences in health utility applicable to clinical work in general medicine.

Diagnosis of Covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction or pharyngeal swab tests or antigen testing [17] performed in health services or at home.

Definition of Reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection [18-20].

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 [21,22]. 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 centers with disabilities and those with risk conditions, including social-health personnel [23].

Collected Variables

- Age and sex
- Symptoms of covid-19 in reinfection 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" [24], both classified according to the International Statistical Classification of Diseases and Health-Related Problems, ICD-10 Version: 2019 [25].
- Social-occupancy class (according to the Registrar General's classification of occupations and social status code: professional occupations, intermediate occupations, non-manual skilled occupations, manual skilled occupations, partly skilled occupations, unskilled occupations, other -students, armed forces, and people whose occupation is inadequately described) [26,27].
- 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. In this way, "problems in the family context" was defined as families with "complex genogram". The definition of "low income household" was based on the opinion of the family doctor who performed the genogram at the past time, and who has remained in the same practice for over 30 years [28-31].

- Ethnic minority, defined as a human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group [32].
- Severity of the disease -primary infection and reinfection (mild cases: clinical symptoms are mild and no manifestation of pneumonia can 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 \geq 30 breaths / min; pulse oxygen saturation \leq 93% with room air at rest; arterial partial pressure of oxygen / oxygen concentration \leq 300 mmHg) [33]. To simplify comparison, moderate and severe cases were counted together.
- Vaccination status against covid-19 at the date of infection: vaccinated with fourth dose (second booster) for fall-winter 2022

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 classes that classify the age groups were made taking into account $>$ and $<$ de 65 years [34]. The age of 65 years was used as the beginning of old age [35]. Figures with decimals were rounded to facilitate a more intuitive comparison.

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X^2), X^2 with Yates correction or Fisher Exact Test.

Results

16 people with fourth dose and with covid-19 infections and 5 people with fourth dose and with covid-19 reinfections from October 2022 to October 2023 were included. Reinfection versus primary infections were more frequent in women, social-health care workers, complex family, moderate-severe severity of infection, chronic diseases of the Neoplasms, Endocrine, Musculo-skeletal and Genitourinary groups, and presented more ENT and neurological symptoms. The only variable with statistically significant differences was the presence of Neoplasms (13% versus 0%; Fisher exact test = 0.0483) (Tables 1-3).

Variables	People With Fourth Dose and With Covid-19 Infections from October 2022 To October 2023 N= 16	People With Fourth Dose And With Covid-19 Reinfections From October 2022 to October 2023 N=5	Statistical Significance
> = 65 years	11 (69)	3 (60)	Fisher exact test= 1. NS
= < 45 years	0	0	Fisher exact test= 1. NS
Women	9 (56)	4 (80)	Fisher exact test= 0.6065. NS
Socio-Health Care Workers	3 (19)	2 (40)	Fisher exact test= 0.5528. NS
Complex family/ Problems in the family context	1 (6)	1 (20)	Fisher exact test= 0.4286. NS
Low income household	0	0	Fisher exact test= 1. NS
Ethnic minority	0	0	Fisher exact test= 1. NS
Moderate-severe severity of infection	1 (6)	1 (20)	Fisher exact test= 0.4286. NS
Chronic diseases	13 (81)	5 (100)	Fisher exact test= 0.5489. NS

Table 1: Comparison of Infections with Reinfections of Covid-19 with Fourth Dose of Bivalent mRNA Vaccine in the Period from October 2022 to October 2023.

(): Denotes percentages; NS: Not significant.

Chronic Diseases* (Classified According To The ICD-10 Version: 2019)	People With Fourth Dose and with Covid-19 Infections from October 2022 To October 2023 N= 16	People With Fourth Dose And With Covid-19 Reinfections From October 2022 To October 2023 N=5	Statistical Significance
-II Neoplasms	0	2 (13)	Fisher exact test= 0.0483. Significant at $p < .05$.
-III Diseases of the blood	3 (5)	0	Fisher exact test= 1. NS
-IV Endocrine	10 (18)	4 (25)	X2 with Yates correction= 0.0607. $p = .805411$. NS
-V Mental	8 (14)	1 (6)	Fisher exact test= 0.673. NS
-VI-VIII Nervous and Senses	4 (7)	1 (6)	Fisher exact test= 1. NS
-IX Circulatory system	15 (27)	1 (6)	X2 with Yates correction=2.0492. $P = .15229$. NS
-X Respiratory system	2 (4)	0	Fisher exact test= 1. NS
-XI Digestive system	6 (11)	1 (6)	Fisher exact test= 1. NS
-XII Diseases of the skin	1 (2)	1 (6)	Fisher exact test= 1. NS
-XIII Musculo-skeletal	3 (6)	2 (13)	Fisher exact test= 0.3137. NS
-XIV Genitourinary	3 (6)	3 (19)	Fisher exact test= 0.1232. NS
TOTAL chronic diseases**	55 (100)	16 (100)	---

Table 2: Comparison of Chronic Diseases between Infections and Reinfections in People with Fourth Dose of Bivalent mRNA Vaccines from October 2022 to October 2023.

(): Denotes percentages; RR: Relative risk; NS: Not significant.

Symptoms Covid-19 Infection* According to WHO, ICD-10 Groups	People with Fourth Dose and with Covid-19 Infections from October 2022 to October 2023 N= 16	People with Fourth Dose and with Covid-19 Reinfections from October 2022 to October 2023 N=5	Statistical Significance
General (discomfort, asthenia, myalgia, fever, artralgiás)	23 (42)	7 (41)	X ² = 0.0022. p=.962588. NS
Respiratory (cough, dyspnea, chest pain)	17 (31)	5 (29)	X ² = 0.0137. p=.906752. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis, ear pain)	8 (14)	3 (18)	Fisher exact test= 0.7139. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	1 (2)	0	Fisher exact test= 1. NS
Neurological (headache, dizziness, mental confusion, disartria, photopsia, syncope and collapse)	5 (9)	2 (12)	Fisher exact test= 0.6655. NS
Psychiatric (Anxiety, insomnia)	0	0	Fisher exact test= 1. NS
Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Urological (dysuria, frequency)	1 (2)	0	Fisher exact test= 1. NS
Total symptoms*	55 (100)	17 (100)	---

Table 3: Comparison of Symptoms between Infections and Re-Infections in People with Fourth Dose of Bivalent mRNA Vaccines from October 2022 to October 2023.

(): Denotes percentages; NS: Not significant; * Patients could have more than one symptom. The percentages are over the total of symptoms.

Discussion

Main Findings

The main results of our study were:

- Reinfections versus primary infections were more frequent in women, Socio-Health Care Workers, Complex family/ Problems in the family context, Moderate-severe severity of infection, chronic diseases of the Neoplasms, Endocrine, Musculo-skeletal and Genitourinary groups, and presented more ENT and neurological symptoms.
- The only variable with statistically significant differences between reinfections versus primary infections was the presence of Neoplasms.

However, these results should be interpreted with caution. Firstly, because of the few cases included. 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 [36]. Furthermore, 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].

Comparison with Other Studies

Previous exposure to the virus can hypothetically be expected to reduce the risk of reinfection and its severity; However, SARS-CoV-2 is mutating rapidly and every few month's new variants and sub variants replace older ones. Evidence suggests that the risk of reinfection is especially higher with the Omicron variant, which has been shown to have a marked ability to evade immunity from previous infection. Any protection against reinfection and its severity also decreases over time. Furthermore, deterioration in health as a result of the first infection could lead to an increased risk of adverse health consequences following

reinfection [2].

The risk of reinfection may also vary individually based on demographic characteristics, vaccination history, and exposure risk, which are known to be interrelated [11,37]. So, significant disparities in morbidity and mortality from covid-19 infection have been associated with sociodemographics and geography [38]. However, there are a heterogeneity between studies may be due to a variety of factors, including differences in the definition of asymptomatic status, differences in age, vaccination status, extent of previous infections and antibody status, specific countermeasures of the society, mandatory testing regimes, different sub variants and parameters yet to be identified [39].

For an infection to result in a case a person must be infected, diagnosed, and meet the case reporting definition and the report must be transmitted. Asymptomatic infections, untested infections, or infections diagnosed by self-examination often do not meet reporting criteria. So, number of reinfections is likely underestimated because not all people infected with SARS-CoV-2 become sick enough to be tested. Since reinfection usually results in somewhat milder symptoms, it is even more difficult to fully assess the true count [8]. Furthermore, the proportion of asymptomatic cases in Omicron-infected populations is highly variable, but the proportion of asymptomatic cases among Omicron-infected persons has been reported to be very high [8,39]. Likewise, there is an underreporting of reinfections, because some infections can be taken as primary and are in fact reinfections; A Canadian study estimated that 40% of people who had antibodies in their blood (proof that they had been infected by SARS-CoV-2) had not experienced any symptoms in the previous six months and were unaware that they had contracted the disease [40].

Although routine case reports consistently show higher rates among women than men, it is more informative to state that the risk of infection is lower among women but that the risk of reporting due to infection is high [38].

Reinfections are often mild, but there may be cases of severe disease. The immune response can protect against reinfection for several months, but this protection wanes over time. A meta-analysis of 91 published studies showed that vaccination decreased the risk of reinfection, although the vaccines were less effective in preventing reinfection against Omicron variants [13]. On the other hand, people with weakened immune systems who get an infection may have a limited or no immune response. Protection against severe covid-19 usually lasts longer than protection against infections. This means that even if people become infected again, your immune response would help protect you and prevent you from becoming seriously ill and hospitalized

[5]. It has been reported that compared to cases of primary SARS-CoV-2 infection, reinfection cases were more likely to have mild disease [8].

A recent systematic review showed wide variations between the severities of primary infection compared to reinfection, with increases in asymptomatic cases. It has been suggested that most reinfections with a genetically different strain of SARS-CoV-2 were of similar severity; 19% had worse symptoms and 12% milder symptoms with the second episode [7]. The multiple variants that have emerged from those known as Alpha and Delta have made the symptoms slightly different as well. However, regardless of the variant or sub variant, the symptoms detected and suffered are usually the same: Cough and nasal congestion, difficulty breathing, sore throat, fever, fatigue and discomfort, muscle and joint pain, nausea and vomiting, and diarrhoea. In some cases, increasingly less frequent, you can also suffer a loss of smell and taste, something that was the clear sign of covid-19 at the beginning of the pandemic; with the primacy of Omicron and his lineages, these symptoms have been declining [41].

The four most common symptoms of reinfections during the circulation of BA.5 sub lineages were cough (63%), sore throat (54%), fatigue (49%), and fever (437%) [42]. Likewise, it has been reported that reinfections with BA.5 sub lineages had a significantly lower incidence and severity of fever, fatigue, sore throat and cough, compared to primary infections with BA.5 sub lineages. SARS-CoV-2 Omicron reinfections were less severe than primary Omicron infections during circulation of the same subvariant [42].

In short, our results indicate that reinfections versus primary infections were more frequent in women, Socio-Health Care Workers, Complex family/ Problems in the family context, Moderate-severe severity of infection, chronic diseases of the Neoplasms, Endocrine, Musculo-skeletal and Genitourinary groups, and presented more ENT and neurological symptoms; And these data generally coincide with what has been published.

Study Limitations and Strengths

The small number of covid-19 cases may mask the statistical significance between variables.

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

Our study offers evidence at the population level for one year, from October 2022 to October 2023 and in the context of a general medicine consultation in Toledo (Spain), that in people with the fourth dose of bivalent mRNA vaccine against covid-19, the reinfections did not differ in their clinical-epidemiological characteristics, except for being more frequent in presumably immunosuppressed patients (patients with Neoplasms) compared to covid-19 primary infections. It is suggested that in this population, in addition to having the vaccine boosters updated, non-pharmacological preventive measures should be taken to the extreme. In any case, our results, although consistent with the existing literature, should be taken with caution due to the small number of covid-19 cases included.

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