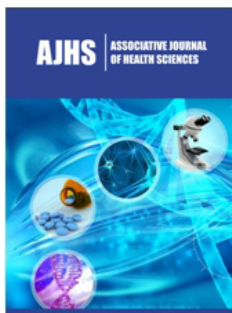


COVID-19 Reinfection without Vaccination Vs. with Vaccine: They are not Differentiated by Biological Factors, but by Psycho-Social Variables

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Abstract

Background: The clinical-epidemiological differences and their importance regarding public health between cases of COVID-19 reinfection without vaccination and cases of COVID-19 reinfection with 1, 2 or 3 doses of vaccine are not known.

Objectives: To compare the clinical-epidemiological characteristics of the cases of COVID-19 reinfection without vaccination with the cases of COVID-19 reinfection with 1, 2 or 3 doses of vaccine, to assess whether there are differences in health utility applicable to clinical work in general medicine.

Methodology: An observational, longitudinal and prospective study of COVID-19 re-infections was conducted from March 1, 2020, to July 1, 2022, in a general medicine office in Toledo, Spain.

Result: Eight cases of COVID-19 reinfection without vaccination and 35 with vaccine (1, 2 or 3 doses) were included. 2 cases presented 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of the vaccine, respectively. The unvaccinated COVID-19 reinfection cases were younger, male, of a lower social-occupancy class, and with more complex problems in the family context. There were no statistically significant differences between the cases of COVID-19 reinfection without vaccination and those vaccinated (1, 2 or 3 doses) by presence of health care workers, low-income household, ethnic minority, severity of primary infection symptoms, chronic diseases, days from primary infection (or first reinfection) to reinfection (or second re-infection), or year of reinfection (2020, 2021 or 2022).

Conclusion: The cases of COVID-19 reinfection without vaccination vs. cases of COVID-19 reinfection with vaccine (1, 2 or 3 doses) are not differentiated by biological factors, but by psychosocial variables, which probably associate other health behaviors with not being vaccinated against COVID-19.

Keywords: COVID-19; SARS-CoV-2; Reinfections; COVID-19 vaccine; General practice; Public health

Introduction

Currently, it is predicted that it will be normal to be infected with the severe acute respiratory syndrome coronavirus (SARS-CoV-2) several times throughout life; In other words, the behavior of SARS-CoV-2 will resemble that of the rest of the coronaviruses that coexist with humans [1-4]. A SARS-CoV-2 reinfection occurs when a person with COVID-19 recovers and gets SARS-CoV-2 again, although after having presented COVID-19, most individuals will have some degree of protection [5].

The SARS-CoV-2 infection control strategy, and in particular its vaccination, is at a crossroads. The following keys can be highlighted:

1. Currently high incidence of symptomatic infection, generally mild, including people

with a complete vaccination schedule and those who have had previous infections (re-infections).

2. Vaccine effectiveness against infection and symptomatic disease waning over time (humoral immunity). It is important to note that the three-dose vaccine regimen maintains a very notable protection against severe disease and death even with circulating omicron variants (protection based on cellular immunity).

3. Permanent and rapid evolution of the virus. Recently the subvariants of omicron BA.4 and BA.5 are the predominant ones (and new ones are already on the horizon), and they seem to show a very high transmissibility and greater ability to escape from natural immunity due to previous infections and from the vaccine. So, the evolution of the virus is uncertain and unpredictable [6-9].

Historically, vaccination has been one of the safest and most cost-effective public health interventions available. As of January 2022, 60.5% of the world's population has received at least one dose of a COVID-19 vaccine. Vaccination rates continue to lag in low-income countries, where only 10% of the population have received at least one dose of a vaccine, while in high- and upper-middle-income countries, 77% of the population have received at least one dose of a vaccine [10].

On the other hand, it is worrying that numerous reports suggest that people's willingness to be vaccinated against COVID-19 is far from universal. There is significant variation in vaccine acceptance, due to a variety of individual and vaccine-related factors. Varying rates of vaccine hesitancy have been reported in different countries: 26% in Europe, 11% in Japan, 35% in the United States, 8-35% in China, and 20% in low- and middle-income countries from Asia, Africa and South America [11]. Consequently, the factors associated with vaccination against covid-19 continue to be the subject of a variety of investigations around the world [10].

In this context, reinfections are increasingly common and will continue with the emergence of new variants that escape previous vaccination. Data are lacking to identify how these reinfections occur, who is most at risk, and the severity of reinfection episodes [5]. In this way, numerous questions are raised; one of them is what the differences between the clinical-epidemiological characteristics of the cases of COVID-19 reinfection without vaccination versus the cases of COVID-19 reinfection with are 1, 2 or 3 doses of vaccine, to assess whether there are differences which could be applicable to clinical work in general medicine.

Material and Methods

Design and emplacement

An observational, longitudinal and prospective study of COVID-19 re-infections was conducted from March 1, 2020 to July 1, 2022 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 centre 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 [12]. The descriptive results of the COVID-19 reinfections case series which are presented here, as well as the incidence and risk factors from the same case series, have already been published [13,14].

Outcome of interest

To compare the clinical-epidemiological characteristics of the cases of COVID-19 reinfection without vaccination with the cases of COVID-19 reinfection with 1, 2 or 3 doses of vaccine, to assess whether there are differences of utility applicable to clinical work in general medicine.

Definition of reinfection

SARS-CoV-2 reinfection was conventionally defined as a documented infection occurring at least 90 days after a previous infection, to avoid misclassification of prolonged PCR positivity as reinfection if a shorter time interval is used [15-17].

Diagnosis of COVID-19 and definition of doses of vaccine

The diagnostic criteria for COVID-19, the definitions of vaccination with 1, 2 or 3 doses (booster) have been previously published for this study [13,14].

Collected variables

- A. Age and sex
- B. Symptoms of COVID-19 in reinfection
- C. 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], classified according to the International Statistical Classification of Diseases and Health-Related Problems, ICD-10 Version: 2019 [19])
- D. Patients with the presence of at least one chronic disease
- E. Dates of COVID-19 infections and days from COVID-19 primary infection to COVID-19 reinfection
- F. 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) [20,21].
- G. If they were Health Care Workers
- H. 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 [22-25].

I. Ethnic minority, defined as a “human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group” [26].

J. 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 ≥ 30 breaths/min; pulse oxygen saturation $\leq 93\%$ 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.

K. Vaccinated with 1 dose, with 2 doses, with booster, and not vaccinated against COVID-19

Statistic analysis

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

Ethical aspects

Individual patient data is not used, but only aggregated statistical data.

Result

Table 1: Variables in COVID-19 reinfection without vaccination versus with vaccine (1, 2 or 3 doses).(): Denotes percentages; NS: Not significant.

Variables	COVID-19 Reinfection without Vaccination N=8	COVID-19 Reinfection with Vaccine (1, 2 or 3 doses) N=35	Statistical Significance
Mean age (Arithmetic mean +- Standard deviation; Range)	30.5+-4.24 (24-37 years)	43.82+-14.69 (17-70 years)	t= -2.51691. p=. .007922. Significant at p < .05.
> = 65 years	0	2 (6)	Fisher exact test= 1. NS
Women	4 (50)	29 (83)	X2= 3.9389. p=. .047182. Significant at p < .05.
Health Care Workers	0	7 (20)	Fisher exact test= 0.315. NS
Moderate-severe severity of primary infection	0	3 (9)	Fisher exact test= 1. NS
Chronic diseases presence	4 (50)	22 (63)	X2 with Yates correction= 0.0731. p=. .786946. NS
Social-occupancy class of patients (people with some type of labor specialization)	0	15 (43)	Fisher exact test= 0.0358. Significant at p < .05.
Complex family/ Problems in the family context	2 (25)	1 (3)	X2= 4.9194. p=. .026557. Significant at p < .05.
Low-income household	1 (12)	3 (9)	Fisher exact test= 1. NS
Ethnic minority	1 (12)	5 (14)	Fisher exact test= 1. NS

Table 2: Variables in COVID-19 reinfection without vaccination versus with vaccine (1, 2 or 3 doses).

(): Denotes percentages; NS: Not significant; *COVID-19 reinfection with vaccine (1, 2, or 3 doses) N=35 people; 2 cases presented 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of the vaccine, respectively. The number of infections is used as denominator: N=37.

Variables	COVID-19 Reinfection without Vaccination N=8	COVID-19 Reinfection with Vaccine (1, 2 or 3 Doses)* N=37	Statistical Significance
Symptomatic COVID-19 reinfection	8 (100)	35 (95)	Fisher exact test= 1. NS
Days of covid-19 from primary infection (or first reinfection) to reinfection (or second reinfection)) (Arithmetic mean +- Standard deviation)	326.5+-173.73 (152-668 days)	351.13+-177.45 (95-813 days)	t-value= -0.35725. p=. .361326. NS
Reinfection in 2020	0	1 (3)	Fisher exact test= 1. NS
Reinfection in 2021	4 (50)	10 (27)	Fisher exact test= 0.2315. NS
Reinfection in 2022	4 (50)	26 (70)	Fisher exact test= 0.41. NS

Table 3: Chronic diseases in COVID-19 reinfection without vaccination versus with vaccine (1, 2 or 3 doses).

(): Denotes percentages; NS: Not significant; *Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases of symptomatic and asymptomatic patients.

Chronic Diseases*	COVID-19 Reinfection without Vaccination N=8	COVID-19 Reinfection with Vaccine (1, 2 or 3 Doses) N=35	Statistical Significance
-I Infectious	0	0	Fisher exact test= 1. NS
-II Neoplasms	0	1 (2)	Fisher exact test= 1. NS
-III Diseases of the blood	0	0	Fisher exact test= 1. NS
-IV Endocrine	2 (18)	10 (17)	Fisher exact test= 1. NS
-V Mental	2 (18)	3 (5)	Fisher exact test= 0.177 NS
-VI-VIII Nervous and Senses	1 (9)	4 (7)	Fisher exact test= 1. NS
-IX Circulatory system	0	5 (9)	Fisher exact test= 0.3361. NS
-X Respiratory system	1 (9)	10 (17)	Fisher exact test= 0.6789. NS
-XI Digestive system	0	4 (7)	Fisher exact test= 1. NS
-XII Diseases of the skin	2 (18)	3 (5)	Fisher exact test= 0.177. NS
-XIII Musculo-skeletal	1 (9)	7 (12)	Fisher exact test= 1. NS
-XIV Genitourinary	2 (18)	11 (19)	Fisher exact test= 1. NS
TOTAL chronic diseases*	11	58	---

Table 4: Symptoms COVID-19 reinfection cases without vaccination versus with vaccine (1, 2 or 3 doses).

(): Denotes percentages; NS: Not significant; *Patients could have more than one symptom. The percentages are over the total of symptoms; ***COVID-19 reinfection with vaccine (1, 2, or 3 doses) N=35 people; 2 cases presented 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of the vaccine, respectively. The number of infections is used as denominator: N=37.

Symptoms COVID-19 Reinfection* According to WHO, ICD-10 Groups	COVID-19 Reinfection without Vaccination N=8	COVID-19 Reinfection with Vaccine (1, 2 or 3 Doses) N=37**	Statistical Significance
General (discomfort, asthenia, myalgia, fever, artralgiás)	7 (37)	37 (39)	$X^2 = 0.0296$. $p = .863377$. NS
Respiratory (cough, dyspnea, chest pain)	5 (26)	26 (27)	$X^2 = 0.0089$. $p = .925003$.
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistaxis)	6 (32)	23 (24)	X^2 with Yates correction= 0.148. $p = .700462$. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	0	3 (3)	Fisher exact test= 1. NS
Neurological (headache, dizziness, mental confusion -brain fog)	1 (5)	6 (6)	Fisher exact test= 1. NS
Psychiatric (Anxiety, insomnia)	0	0	Fisher exact test= 1. NS
Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Total symptoms*	19	95	---

Eight cases of COVID-19 reinfection without vaccination and 35 with vaccine (1, 2 or 3 doses) were included. 2 cases presented 2 reinfections: 2 women aged 17 and 19 with 2 and 1 dose of the vaccine, respectively. The unvaccinated COVID-19 reinfection cases were younger, male, of a lower social-occupancy class and with more complex problems in the family context. There were no statistically significant differences between the cases of COVID-19 reinfection without vaccination and those vaccinated (1, 2 or 3 doses) due to the presence of health care workers, low-income household, ethnic minority, severity of primary infection symptoms, chronic diseases,

days from primary infection (or first re-infection) to reinfection (or second re-infection), or year of reinfection (2020, 2021 or 2022) (Table 1-4).

Discussion

Main findings

The main results of our study are that the cases of COVID-19 reinfection without vaccination were younger, male, of a lower social-occupancy class, and with more complex problems in the family context. On the other hand, there were no statistically

significant differences between the cases of COVID-19 reinfection without vaccination and those vaccinated (1, 2 or 3 doses) due to the presence of low-income household, ethnic minority, severity of primary infection symptoms or chronic diseases. Taking into account that the three-dose vaccine regimen maintains a very remarkable protection against severe disease and death even with circulating omicron variants, these data may allow planning strategies to improve the vaccination rate [1-4].

Comparison with other studies

Immunity: SARS-CoV-2 infection offer a high level of sustained protection against reinfection, comparable to that offered by vaccines, but decrease with the introduction of new major variants of the virus; dramatically when Omicron appear. Decreases in protection against reinfection appeared to be primarily driven by viral evolution [28]. Vaccine-induced immunity after a primary vaccination series is modest against Omicron infection in the months following vaccination and declines significantly over time. Most studies have found that the protection conferred by hybrid immunity against infection and mild symptomatic disease is similar to or slightly better than immunity induced by infection or vaccine alone [29]. Therefore, previous infection or vaccination guarantees a certain degree of protection against SARS-CoV-2 reinfections. However, emerging variants could reinfect naturally to infected or vaccinated individuals [30].

Vaccine hesitancy: Vaccine hesitancy is not a clear issue, but rather represents a spectrum of beliefs and concerns [31]. Existing research reports that factors influencing COVID-19 vaccine acceptance may include gender, background knowledge, perceived risk of COVID-19, vaccine knowledge, vaccine confidence, etc., and vary between different populations [11]. The following factors were significantly associated with the decision to accept the COVID-19 vaccination (and to vaccinate their children): level of education, employment status, presence of chronic diseases, and consultation with a health professional from the beginning of the pandemic [10].

Socioeconomic level and family psychosocial problems: Most educated patients and those with high income levels are willing to be vaccinated [32-34]. The fact that a lower socio-economic level is associated with a lower COVID-19 vaccination rate highlights the problem of inequalities in the pandemic. Different possible pathways may include unhealthy lifestyles associated with lower socioeconomic position, such as smoking, physical inactivity, alcohol use, and cannabis use. Some of these behavioural factors have been associated with an increased risk of susceptibility to COVID-19. Low socioeconomic status can be a barrier to access health care services for COVID-19, but it does not occur in our context, where health care is universal and free, and each person is assigned a GP that is the door to the health system [12]. Family support and a herd mentality can help improve vaccination among the undecided [11]. Other family characteristics, such as living alone, without a partner or children, and being single, were negatively associated with the desire to be vaccinated [34-36]. People living alone with limited care may have less access, irregular preventive health visits, and less support from family members [37].

Sex and age: In general, greater acceptance is found among women [10]. In a study among college students who were hesitant to get vaccinated, 56% were men [11]. Patients older than 65 years are more willing to be vaccinated than younger patients [10,34], and these usually mention that “the situation is not serious enough” or that they are not at risk” [38] in order not to accept the vaccine. By against, those with chronic health conditions who perceive their health to be less than good and people who are considered at risk of contracting the disease are willing to be vaccinated [34]. Older adults, particularly those with chronic conditions, are in the most vulnerable categories for all phases of COVID-19, from contracting the virus to being at risk of severe illness or death. In addition, their vulnerability to COVID-19 is It is exacerbated in many cases by dependency on a caregiver who moves in and out of the home, thereby increasing the risk of contracting COVID-19 from the community. In short, vaccination reluctance is less or almost nil in older adults [39].

Comorbidities: No strong evidence has been found, and studies showing conflicting results, whether certain diseases (including diseases of the circulatory, digestive, nervous, respiratory, genitourinary, musculoskeletal, and connective tissue systems, metabolic diseases, and mental disorders) increase the risk of COVID-19 [36]. Like all infectious processes, the clinical severity depends on the virulence of the microorganism and the susceptibility of the host. Some people with comorbidities may be out of control or have associated complications; for example, in patients with underlying lung disease, having a new episode of COVID-19 can become a severe episode, and patients with immunocompromise can excrete the virus for weeks or months, having a persistent active infection [5].

Symptoms and severity in reinfection: Vaccines against COVID-19 help protect against severe illness, hospitalizations, and death. Additionally, COVID-19 vaccines help protect against infection. However, vaccinated people can still get COVID-19. When a vaccinated person contracts COVID-19, they are much less likely to have severe symptoms compared to people who are not vaccinated [40]. Among patients who became reinfected, hospitalization rates were similar for both vaccinated and unvaccinated patients, with approximately one in five reinfected patients admitted to hospital [41]. In a rapid systematic review of 17 cases of genetically confirmed COVID-19 reinfection, it was found that 69% of people had symptoms similar to those of their first episode, 19% had a more severe condition and 12% a milder one. The virus inoculum received the possible differences between SARS-CoV-2 variants and changes in a person’s health status can modify the symptoms of reinfection. The key point to know, and also for future vaccines, would be to resolve the role of immunological memory and whether it affects symptoms during the second infection [42,43].

Role of the GP: COVID-19 vaccines induce better long-term immunity than infection [44,45]. Regarding the action signals, one of the significant predictors that increase the intention to be vaccinated is the recommendation of the GP [10,34]. The situation is not calm enough for the vaccine boosters to be reduced. There

are still vulnerable people who can develop serious forms and die from them. It should not be forgotten that current vaccines prevent hospitalization, but the duration of protection is conditioned by the level of transmission. The more infections there are, the more the virus will replicate, and the more replication there is, the more opportunities there are for mutations and, therefore, for the appearance of new variants" [46].

Study limitations:

- a) Infections were not genetically sequenced; thus, reactivations of the strain involved in the first episode cannot be completely ruled out.
- b) The number of cases was small.
- c) The study may have missed asymptomatic cases who did not attend GP consultation, as no systematic surveillance or screening was performed.
- d) Preventive behaviours associated with transmission were not analyzed.

Conclusion

The cases of COVID-19 reinfection without vaccination vs. cases of COVID-19 reinfection with vaccine (1, 2 or 3 doses) are not differentiated by biological factors, but by psychosocial variables, which probably associate other health behaviours with not being vaccinated against COVID-19. GPs should recognize these psychosocial variables in their patients and recommend vaccination.

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