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Research Article

Risk factors and incidence rates of COVID-19 breakthrough infections in vaccinated people with vaccine booster in general medicine, Toledo (Spain), for the period December 2021 to February 2022

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Abstract

Background: The effectiveness of vaccines against COVID-19 has been demonstrated, but because new variants appear and immunity fades over time, continuous monitoring is necessary.

Objectives: To determine incidence rates (IR) and risk factors of COVID-19 breakthrough infections in vaccinated people with vaccine booster (VB).

Methodology: An observational, longitudinal, and prospective study of patients with COVID-19 breakthrough infections in vaccinated people with VB in a general practice setting in Toledo, Spain, for the period December 2021 to February 2022, during the wave of infections by omicron variant.

Results: Forty-six cases of COVID-19 breakthrough infections with booster shot were included. The IR was 3.1 cases per 100 people with booster. The IR was higher in < 45 years (4.7%) vs. > 65 years (4.2%), and in women (3.6%) vs. man (2.6%). The only statistically significant risk/prevention factors were the presence of diseases of the skin [RR = 2.74 (95% CI: 1.3, 5.79)], Genitourinary chronic diseases [RR = 1.87 (95% CI: 1.19, 2.95)], complex family [RR = 0.22 (CI 95%: 0.58, 0.08)] and chronic diseases of the mental group [RR = 0.4 (95% CI: 0.82, 0.2)].

Conclusion: The IR of COVID-19 breakthrough infections with a booster shot, at the peak of omicron infections (December 2021-February 2022), in the general medicine clinic, Toledo, Spain, was high, suggesting modest VB protection effectiveness against symptomatic infection. Statistically significant risk and protective factors show mixed results; so, it is hypothesized that they are related to other main variables such as gender and age, and/or with risk/preventive behaviors. However, the small numbers of COVID-19 breakthrough infections with booster shots prevent definitive conclusions.

Introduction

The widespread availability of coronavirus disease (COVID-19) vaccines was the most exciting medical event in healthcare in 2021 [1]. The effectiveness of vaccines against COVID-19 has been demonstrated for two and three doses. However, most of the studies that exist so far focus on the delta variant. Because new variants appear and immunity wanes over time, continuous monitoring of vaccine effectiveness is necessary [2-4].

In December 2021, the severe acute respiratory syndrome (SARS-CoV-2) omicron variant rapidly overtook the delta variant to become globally dominant in the COVID-19 pandemic. Understanding the extent of Omicron's resistance to vaccine-evoked immune responses, especially after a COVID-19 vaccine booster, is crucial for future vaccine development and public health policy. Because neutralizing antibody levels have tended to correlate with COVID-19 vaccine-mediated protection, it is reasonable to expect similar levels of protection against

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Omicron after an mRNA boost to those seen against previous variants after two doses of vaccine [5].

Although vaccines against coronavirus disease 2019 (COVID-19) are highly effective, breakthrough infections are taking place. It must be taken into account that in view of the increase in vaccination rates, where these are high, the breakthrough cases progressively represent the majority of all COVID-19 cases [6]. This situation has triggered calls to intensify vaccination programs, including the provision of booster doses of the vaccine [7]. It is plausible that the broader and increased antibody titers generated by a third or booster dose may overcome the reduced neutralization associated with the omicron variant. Further research evaluating the effectiveness of primary and additional vaccine doses against omicron is clearly a priority [8]. In any event, data on the serial use of homologous boosters (same as a primary vaccine) and heterologous boosters (other than primary vaccine) in fully vaccinated recipients are needed to guide appropriate health policies [9,10].

In short, this is an important topic on which currently available data is sparse, and needs to be addressed. In this context, we present this study with the objective of determining the incidence rates (IR) and risk factors related to COVID-19 breakthrough infections in vaccinated people with a booster shot.

Materials and methods

An observational, longitudinal, and prospective study of COVID-19 breakthrough infections in vaccinated people with vaccine boosters was conducted from December 1, 2021, to February 28, 2022, 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 [11].

Outcome of interest

1. Determine the incidence rate (IR) of COVID-19 breakthrough infections in vaccinated people with a booster in GP consultation. IR was calculated by dividing the number of infection events by the person's follow-up time [12].

2. Assess the risk and protective factors to present COVID-19 breakthrough infections in vaccinated people with a vaccine booster (VB). In this sense, the variables collected were compared by calculating the relative risk (RR) as the Incidence among the exposed population / Incidence among the population not exposed to possible risk factors. The RR expresses to the clinician the excess risk that a patient has for being exposed to the risk factor, and also serves to identify people at high risk, but does not measure the probability that someone with the risk factors will acquire the disease. The RR was interpreted as follows [13]:

-From 0 to 0.5: protection factor effectively

-From 0.6 to 0.8: true benefits

-From 0.9 to 1.1: not significant

-From 1.2 to 1.6: weak risk

-From 1.7 to 2.5: moderate risk

-More than 2.5: strong risk

Definition of cases and controls

Patients with full COVID-19 vaccination plus VB who had accessed medical care for a disease similar to COVID-19 and had undergone diagnostic tests for SARS-CoV-2 were considered cases, these being positive. It must be taken into account that asymptomatic infections that did not consult the GP were not counted, except when they were found when tracing contacts of positive cases.

The control patients were the rest of the people full vaccinated plus VB for COVID-19, from the GP's list of patients, who did not go to medical attention NI were diagnosed at another level of the health system with COVID-19 positive. As explained below, 73% of the consultation's patient list (2,000 people) were considered to have been fully vaccinated plus VB, as of the date of data analysis (February 2022). It can be said that a negative symptom or no-consultation design was used for COVID-19 breakthrough infections in vaccinated people.

Calculation of rate denominators

To calculate the RR we used a "test-negative design". Official data on the frequency of vaccine boosters in Castilla La Mancha (Spain) in the period from December 27, 2021, to February 24, 2022, were used, and these figures were used as the value of the midpoint of the study period (from December 1, 2021, to February 28, 2022).

In the period from December 27, 2021, to February 24, 2022, the VB in Castilla La Mancha (Spain) [14] were:

20-29 years old: 51,702 (31%)

30-39 years old: 83,078 (41%)

40-49 years old: 171,208 (60%)

50-59 years old: 219,452 (77%)

From 60-69 years old: 204,407 (93%)

> 70 years old: 269,374 (91%)

These data give a crude prevalence of VB of 65%. On the other hand, given that in the analysis of the data collected there was only 1 case under 30 years of age, the prevalence of BV in this population over 30 years old (according to previous data) was considered to be 73%. Consequently, it was estimated that

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for the population seen in the clinic (N = 2,000), 73% had BV (N = 1,460). From this data, the population with BV without COVID-19 in the study period, which constituted the controls, was calculated. Variables were then compared between cases and controls.

The data of the variables of interest in the controls (population attended in the consultation), such as complex family, and chronic diseases, were previously published [15,16].

Criteria for inclusion and exclusion of participants

The methodology of the study has already been published previously [17,18]. All cases of patients fully vaccinated with two doses, plus a booster were included.

Definition of homologous or heterologous booster

At the time of the study, the European Commission had authorized four vaccines: Pfizer authorized on December 21, 2020; Moderna vaccine, authorized on January 6, 2021; AstraZeneca vaccine, authorized on January 29 and Janssen vaccine, authorized on March 11, 2021. From November 23, 2021, in Castilla La Mancha, a region where the study was carried out, doses began to be given booster against COVID-19 with mRNA vaccines from 6 months after completing the vaccination schedule and 3 months in case of having received a dose of Janssen vaccine. Recruitment was carried out actively by age cohorts in a descending manner, beginning with those over 80 years of age and people inpatients in centers for the elderly and in other socio-health and health centers (including day centers and occupational centers), regardless of age, people who received a dose of Janssen vaccine as primary vaccination and those with a homologous AstraZeneca schedule as primary vaccination (first and second dose of AstraZeneca), followed by people aged between 79 to 70 years, 69 to 65 years, 64 to 60, 59 to 50 and 49 to 40 years old, etc. The booster dose was administered with mRNA vaccines (0.3 ml of Pfizer or 0.25 ml of Moderna –half the usual dose in primary vaccination).

-Homologous or heterologous booster

Any mRNA vaccine was used to administer the booster dose, regardless of the vaccine used in the primary vaccination. In people with an incomplete regimen (in vaccines that require two doses as primary vaccination) the regimen was completed first with mRNA vaccine (0.3 ml of Pfizer or 0.5 ml of Moderna). The booster dose (0.3 ml Pfizer or 0.25 ml Moderna) was given 6 months later. In people for whom a booster dose was recommended who had a history of symptomatic or asymptomatic SARS-CoV-2 infection, a booster dose with mRNA (0.3 ml of Pfizer or 0. 25 ml of Moderna) at least 4 weeks after the diagnosis of the infection and from 6 months (subsequently modified on January 13, 2022, to 5 months) if the last dose administered in the primary vaccination was with mRNA vaccine (Pfizer or Moderna), and from 3 months if it was an adenovirus vector vaccine (AstraZeneca] or Janssen vaccine) [19,20]. For the data in this study, all COVID-19 cases in people fully vaccinated with the booster were included, regardless of the time to COVID-19 diagnosis.

All possibilities of booster were considered:

-Full homologous booster dose:

A. 2 doses of Pfizer with Pfizer booster

B. 2 doses of Moderna with Moderna booster

-The 6 possible combinations of heterologous booster doses:

A. 2 doses of Pfizer with Moderna

B. 2 doses of AstraZeneca with a booster of Moderna

C. 2 doses of AstraZeneca with a booster of Pfizer

D. 1 dose of Janssen vaccine with Moderna vaccine booster

E. 1 dose of Janssen vaccine with a booster of Pfizer

F. 2 doses of Moderna with a booster of Pfizer

Diagnosis of COVID-19

The diagnosis was performed with reverse transcriptase-polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing. Rapid antigen tests began to be carried out for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. The cases included confirmed cases and asymptomatic carriers. Information on COVID-19 patients and their contacts was obtained from the registry systems used by general medical services during the consultation. Asymptomatic confirmed case with active infection was considered to be any person with a clinical picture of sudden-onset acute respiratory infection of any severity that occurs, among others, with fever, cough, or feeling of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain, or headache, among others, were also considered symptoms of suspected SARS-CoV-2 infection according to clinical criteria; and a positive PCR or rapid antigen test positive [21]. The onset date of a confirmed case was defined as the date of the first appearance of self-reported clinical symptoms [22]. The onset date for an asymptomatic carrier was defined as the date a positive COVID-19 PCR test was obtained [23]. Previous SARS-CoV-2 infection was defined as a positive result in the PCR assay or antigen test at least 90 days before a new positive result [24].

Collected variables

- 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” [25], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [26].

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- Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [27, 28].

- Problems in the family context (complex families) 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) [29-32].

Statistic analysis

The bivariate comparisons were performed using the Chi-Square test (X2), X2 with Yates correction or Fisher Exact Test when necessary, (according to the number of the expected cell totals) for percentages, and the Student test for the mean.

Results

The population of the consultation with VB was estimated at 1,460 people. Forty-six cases of COVID-19 breakthrough infections with VB shot in the population attended in the consultation object of the study were included. The population of the consultation with BV and without COVID-19 in the study period was estimated at 1414 people. The crude incidence rate (IR) was 3.1 cases per 100 people with BV (December 2021-February 2022). By age groups, it was higher (4.7%) for = < 45 years vs. for > = 65 years (4.2%). IR was higher in women (3.6%) vs. men (2.6%) (Table 1).

The risk factors were:

- Weak risk: > = 65 years, women, people with some type of labor specialization, endocrine, nervous and senses, and digestive system chronic diseases

- Moderate risk: = < 45 years and chronic diseases of the genitourinary group

- Strong risk: Diseases of the skin ($p < 0.05$)

The protective factors were:

- Protection factor effectively: Complex family ($p < 0.05$), chronic diseases of the mental group ($p < 0.05$), infectious, and diseases of the blood

- True benefits: men, chronic diseases of the circulatory system, respiratory system, and musculoskeletal group (Tables 2,3).

Discussion

The unprecedented increase in SARS-CoV-2 infections during December 2021 coincided with the rapid spread of the Omicron variant worldwide. The antibody titer required for neutralization of omicron is estimated to be 20 to 40 times higher than for delta. However, in vitro studies indicate that people who receive a booster dose of the mRNA vaccine have greater neutralization of the Omicron variant [33].

A third dose of the vaccine improves both humoral and cellular immunity against SARS-CoV-2, with greater neutralizing activity against different variants [34]. Despite the decrease in vaccine efficacy, it stays against clinically severe outcomes [35]. What is certain is that the virus has mutated enough to escape first-line immune defenses, specific antibodies. This is why a high incidence of breakthrough infections was to be expected even in highly vaccinated populations [36,37]. This situation occurred in Spain, where although eligibility for booster vaccination was initially restricted to older adults, immunocompromised people, and people with severe or multiple chronic diseases, it was later extended, depending on the age group, to the rest of the population. But, as booster vaccination was expanded, the omicron variant was introduced into the population, causing the largest epidemic wave of SARS-CoV-2 infections [6], despite the fact that as of January 21, 2022, the Ministry of Health of Spain reported that 90.7% of the population over 70 years of age, 88.9% of those over 60, 78.8 % of those over 50 and 66.7% of those over 40, had already received the third dose of the vaccine [38].

What is the efficacy and risk factor of the COVID-19 vaccination booster?

To measure the efficacy and risks factor of COVID-19 vaccination booster is need to calculate the RR, which is the risk of something happening (getting sick with COVID-19 having been vaccinated with a booster shot) [13]. We found an IR of 3.1

Table 1: Incidence rates of COVID-19 breakthrough infections in vaccinated people with vaccine booster in general medicine (Toledo, Spain) for the period december 2021 to february 2022.

Variables	COVID-19 Breakthrough infections in vaccinated people with vaccine booster N = 46	Estimated population of GP office con VB and without COVID-19 N = 1.414	Incidence rates of COVID-19 breakthrough infections in vaccinated people with VB December 2021-February 2022 N = 1.460
TOTAL	46 (100)	1414 (100)	N = 1460 3.1 cases per 100 people con booster x December 2021-February 2022
> = 65 years	13 (28)	299 (21)	N = 312 4.2 cases per 100 people > = 65 years x December 2021-February 2022
= < 45 years	12 (26)	242 (17)	N = 254 4.7 cases per 100 people = < 45 years x December 2021-February 2022
Women	27 (59)	717 (51)	N = 744 3.6 cases per 100 women x December 2021-February 2022
Men	19 (41)	697 (49)	N = 716 2.6 cases per 100 men x December 2021-February 2022

( ): Denotes percentages

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Table 2: Comparison of selected variables.

Risk factors	COVID-19 breakthrough infections in vaccinated people with vaccine booster N = 46	Estimated population of GP office and without COVID-19 N = 1.414	Statistical Significance	Relative Risk (RR)
> = 65 years	13 (28)	299 (21)	X2 = 1.3423. *p* = .246636. NS	RR = 1.45 (CI 95%: 0.69, 3.05). Weak risk
= < 45 years	12 (26)	242 (17)	X2 = 2.4957. *p* = .114156. NS	RR = 1.67 (CI 95%: 0.81, 3.46). Moderate risk
Women	27 (59)	717 (51)	X2 = 1.1376. *p* = .286155. NS	RR = 1.37 (CI 95%: 0.7, 2.68). Weak risk
Men	19 (41)	697 (49)	X2 = 1.1376. *p* = .286155. NS	RR = 0.73 (CI 95%: 1.43, 0.37). True benefits
Social-occupancy class of patients (people with some type of labor specialization)	25 (53)	636 (45)	X2 = 1.5783. *p* = .208999. NS	RR = 1.44 (CI 95%: 0.76, 2.74). Weak risk
Complex family	4 (9)	437 (31)	X2 = 10.4238. *p* = .001244. Significant at p < .05.	RR = 0.22 (CI 95%: 0.58, 0.08). Protection factor effectively

( ): Denotes percentages; NS: Not significant at *p* < .05; RR: Relative Risk

Table 3: Comparison of chronic diseases.

Chronic diseases* according to who, ICD-10 groups	COVID-19 with vaccine booster N = 46	Estimated population of GP office con vb and without COVID-19 N = 1.414	statistical significance	Relative Risk (RR)
-I Infectious	0	47 (1)	Fisher exact test statistic = 0.4034. NS	RR = 0 (CI 95%: Infinity, 0). Protection factor effectively
-II Neoplasms	5 (3)	190(4)	X2 = 0.1009. *p* = .750811. NS	RR = 0.86 (CI 95%: 16.53, 0.04). Not significant
-III Diseases of the blood	1 (1)	95 (2)	Fisher exact test = 0.5318. NS	RR = 0.35 (CI 95%: 4.44, 0.03). Protection factor effectively
-IV Endocrine	24 (16)	570 (12)	X2 = 2.865. *p* = .090526. NS	RR = 1.45 (CI 95%: 0.91, 2.31). Weak risk
-V Mental	8 (6)	618 (13)	X2 = 6.9517. *p* = .008374. Significant at p < .05.	RR = 0.4 (CI 95%: 0.82, 0.2). Protection factor effectively
-VI-VIII Nervous and Senses	14 (10)	380 (8)	X2 = 0.5636. *p* = .452807. NS	RR = 1.23 (CI 95%: 0.63, 2.42). Weak risk
-IX Circulatory system	18 (12)	856 (18)	X2 = 2.8937. *p* = .088927. NS	RR = 0.66 (CI 95%: 1.1, 0.4). True benefits
-X Respiratory system	8 (6)	380 (8)	X2 = 1.14. *p* = .285648. NS	RR = 0.68 (CI 95%: 1.56, 0.3). True benefits
-XI Digestive system	18 (12)	380 (8)	X2 = 3.7989. *p* = .051286. NS	RR = 1.61 (CI 95%: 0.96, 2.71). Weak risk
-XII Diseases of the skin	8 (6)	95(2)	X2 with Yates correction = 6.9466. *p* = .008398. Significant at p < .05.	RR = 2.74 (CI 95%: 1.3, 5.79). Strong risk
-XIII Musculo-skeletal	17 (12)	713 (15)	X2 = 1.1251. *p* = .288823. NS	RR = 0.76 (CI 95%: 1.35, 0.43). True benefits
-XIV Genitourinary	23 (16)	428 (9)	X2 = 8.1144. *p* = .004392. Significant at p < .05.	RR = 1.87 (CI 95%: 1.19, 2.95). Moderate risk
TOTAL chronic diseases**	144 (100)	4753 (100)	---	---

( ): Denotes percentages; * Patients could have more than one chronic disease. The percentages are over the total of chronic diseases; NS: Not significant at p < .05; RR: Relative risk

cases per 100 people with VB (December 2021-February 2022). By age groups, it was higher (4.7%) for = < 45 years vs. for > = 65 years (4.2%). IR was higher in women (3.6%) vs. men (2.6%). In a study on the same population of the consultation in vaccinated people (2 doses) that was carried out from February 1, 2021, to September 30, 2021, the IR of COVID-19 was 1.5% cases x 8 months; higher in people > = 65 years vs. 14-65 years (2.3% vs. 1.3%), and higher in women vs. men (1.6% vs. 1.4%) [38].

On the other hand, the data from the current study show an IR of COVID-19 in vaccinated with three doses during the period from December 2021 to February 2022 (3 months) at the time of the "wave" of omicron infections, in the general medicine consultation, which was almost as high as that calculated for the first wave of the pandemic in March 2020 in the same population attended in the same consultation, where an IR of 3%-5% of COVID-19 infections was estimated in March-April 2020 [39]. For example, in another study, a SARS-CoV-2 prevalence of 0.83% has been reported in England in September 2021, higher than that estimated in July 2021 (0.63%) (Before vaccine booster) [40]. Taken together, all these data suggest relatively low vaccine booster effectiveness for our study.

Regarding the risk/protective factors of COVID-19 breakthrough infections with a vaccine booster shot, we found mixed results that can hardly be explained directly. In the study on the same population of the consultation in vaccinated people (2 doses) that was carried out from February 1, 2021, to September 30, 2021, similar results were found [38]. These

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mixed results may be associated with other main variables such as gender and age, and/or may not persist after further adjustment for adherence to infection control, for example regarding fear of contagion that modulates the use of masks, and social distancing.

Regarding age, older age is a key risk factor for morbidity and mortality associated with SARS-CoV-2 infection. Therefore, older adults have generally been prioritized for COVID-19 vaccination. In addition, the lower immunogenicity of the vaccine and the more pronounced decline in humoral immunity in older people than in younger people have prompted earlier booster campaigns [41,42]. Along the same lines, we found that being > = 65 years of age was a risk factor (Weak risk); but so was having = < 45 years (Moderate risk), probably related to risk behaviors in young people.

Finally, remember that it has been proposed that the most disappointing error surrounding the use of COVID-19 vaccines was the labeling of mild illnesses or asymptomatic infections after vaccination as "breakthroughs." As is true for all mucosal vaccines, the goal is to protect against serious illness — to keep people out of the hospital, intensive care unit, and morgue. The term "breakthrough," which implies failure, created unrealistic expectations and led to the adoption of a zero-tolerance strategy for this virus. If we are to move from pandemic to endemic, at some point we are going to have to accept that vaccination or natural infection, or a combination of the two will not offer long-term protection against mild illness [43].

Limitations and strengths of the study

1. Non-randomized design; although by including all cases that were consulted with the GP, and taking into account the structure of the health system, the vast majority of cases were probably included. In addition, in this analysis, our comparison group was people with BV without having consulted with the GP or having been diagnosed with COVID-19. These people are unlikely to differ from the general population based on characteristics that could confound our IR estimates and risk factors.

2. The fact of carrying out the study in the same population for which data on COVID-19 cases are available in 2020 (without vaccination) and 2021 (with two doses of vaccine), gives greater value to the results and reduces data interpretation error. One must keep in mind that the probability that a person with pre-existing immunity will develop an infection is probably a function of both viral and host properties [44].

3. Sample was small (the number of COVID-19 cases), so the statistical significance of some variables could be hidden, and an imprecise determination of sRR may be obtained. In the future, it is necessary to have a larger sample size to increase the precision of the result.

4. It must be taken into account that the changes in community transmission during the study period may also imply changes in one direction or another in the cautious behaviors and personal protection in people.

5. May have been overlooked asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done.

6. Estimates of IR and risk factors were based on infections that occurred during periods when the omicron variant was in the majority, but genomic surveillance and classification were not performed. Consequently, this approach has the potential for variant misclassification.

7. The study included a short period after the booster vaccination (December 2021 to February 2022), and there is no information on the duration of protection after a booster dose beyond this follow-up time.

8. Data by type of vaccine administered were not available. Immunity after the third dose has been reported to be highly dependent on the combination of vaccines received [45-47].

Conclusions

1. The IR of COVID-19 breakthrough infections with booster shot, during peak of omicron infections (December 2021-February 2022), in the general medicine clinic, Toledo, Spain, was high, presenting figures similar to those calculated for the first wave of the pandemic in the same consultation, and lower figures than those found from February 1, 2021 to September 30, 2021 in the same consultation in vaccinated people (2 doses).

2. This result suggests modest VB protection effectiveness against symptomatic infection.

3. The statistically significant risk/protective factors do not show a plausible direct relationship with the infection, so it is hypothesized that these variables are probably intermediate variables of risk/preventive behaviors.

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