



## Research Article

DOI: 10.36959/577/504

# Risk Factors and Incidence Rates of Covid-19 Breakthrough Infections in Vaccinated People in General Medicine Practice in Toledo (Spain)

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## Abstract

**Background:** COVID-19 vaccines show excellent efficacy, but some people still become infected after vaccination.

**Objective:** To determine incidence rates (IR) and risk factors of COVID-19 breakthrough infections in vaccinated people.

**Methodology:** A longitudinal and prospective case-control study of COVID-19 breakthrough infections in vaccinated people was carried out from February 1, 2021 to September 30, 2021, in a general practitioner (GP) office in Toledo (Spain).

**Results:** IR of COVID-19 breakthrough infections in vaccinated people > 14 years in GP consultation was 1.5% cases × 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%). IR according to the type of vaccine ranged from 0.4% cases with mRNA-1273 vaccine, to 5% cases with Janssen vaccine. The statistically significant protective factors were: complex family and chronic illnesses of the mental group; and statistically significant risk factors: chronic diseases of the digestive and musculoskeletal groups. Vaccination with BNT162-2 mRNA and mRNA-1273 were protective factors; and with ChAdOx1 nCoV-19 shown a moderate risk. Vaccination with Janssen was a statistically significant strong risk.

**Conclusion:** COVID-19 breakthrough infections in vaccinated people were rare, with higher rates in women and old people. Chronic diseases and social factors behaved mixed. Each of the vaccines has associated COVID-19 breakthrough infections, but the Janssen vaccine posed a strong risk; however, the small numbers prevent definitive conclusions.

## Keywords

COVID-19, SARS-CoV-2, Vaccination, Breakthrough Infection, General Practice, Cohort Studies, Risk Factors

## Introduction

The coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has had a great impact on public health worldwide, due to its rapid spread with pandemic behavior, its difficult control and few therapeutic alternatives [1]. Vaccines for COVID-19 have been developed at unprecedented speed, and phase III clinical efficacy trials reported results for some vaccines less than a year after the World Health Organization (WHO) declared the pandemic. Since December 2020, various vaccines have been licensed by regulators such as the European Medicines Agency, the US Food and Drug Administration, and the UK Medicines and Health Products Regulatory Agency [2-6]. Currently, the European Commission has licensed four vaccines: BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), mRNA-1273 vaccine Spikevax (formerly COVID-19 Moderna vaccine), ChAdOx1 nCoV-19 vaccine (AstraZeneca vaccine), and the Janssen/Johnson & Johnson vaccine. In

Spain, these four vaccines are currently available [7].

The benefits of these vaccines are substantial, and their rapid implementation is an important public health achievement [8]. Existing vaccine-effectiveness estimates have focused on these 4 vaccines. Data presented in different

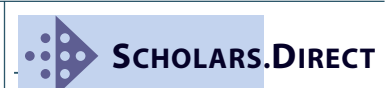
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**Accepted:** March 11, 2022

**Published online:** March 13, 2022

**Citation:** Turabian JL (2022) Risk Factors and Incidence Rates of Covid-19 Breakthrough Infections in Vaccinated People in General Medicine Practice in Toledo (Spain). Arch Fam Med Gen Pract 7(1):183-192

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studies and other phase 3 clinical trials have demonstrated a robust efficacy of these vaccines (> 85%) in preventing severe symptomatic disease [9-16]. Ambitious COVID-19 vaccination campaigns are underway around the world, but knowledge is still scant about the real-world effectiveness of COVID-19 vaccines. Some people still become infected with SARS-CoV-2 after vaccination [17]. This could be a reflection of numerous factors, including the appearance of SARS-CoV-2 variants and the presence of comorbidities, for example, advanced age, overweight, and use of immunosuppressive agents [18].

No vaccine provides 100 percent protection against infection, so breakthrough cases are not new, and not unique, to COVID-19. And little is known about the real-world conditions risk factors for COVID-19 breakthrough infections in vaccinated people [19-22]. Characterizing those most at risk is essential to promote specific interventions aimed at improving the protection of vulnerable populations [23].

In this scenario, observational studies are emerging as fundamental sources of information on the effectiveness of the vaccine outside the controlled environment of randomized trials [24]. Thus, in our context, after initial anecdotal reports of breakthrough infections among fully vaccinated people [25], a study is presented that aimed to determine the incidence rates (IR) and risk factors related to COVID-19 breakthrough infections in vaccinated people.

## Material and Methods

In part, the methodology has already been exposed in a previous descriptive article on this series of cases [25].

## Design and emplacement

An observational, longitudinal and prospective case-control study of COVID-19 breakthrough infections in vaccinated people, based on a prospective cohort of patients was carried out from February 1, 2021 to September 30, 2021, in a general medicine office in the Health Center Santa Maria de Benquerencia, 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 [26]. The number of residents of the neighbourhood that is treated at the Health Center, by 2020, was 22,553 people [27].

## Outcome of interest

The outcomes of interest were:

1. Determine IR of COVID-19 breakthrough infections in vaccinated people. COVID-19 breakthrough infections in vaccinated people IR in GP consultation were calculated by dividing the number of infection events by the person follow-up time [28].

2. To study some of the possible risk factors for COVID-19 breakthrough infections in vaccinated people. In this sense, the variables collected were compared by calculating the relative risk (RR) as the Incidence among the vaccinated population

with COVID-19 breakthrough infections/Incidence among the vaccinated population without COVID-19 breakthrough infections. 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 [29]:

- 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

## Diagnosis of COVID-19 breakthrough infections in vaccinated people

Because the vaccines require about two weeks reaching their maximum effectiveness, a person is not considered fully vaccinated until two weeks after they completed the recommended number of doses for the vaccine they received. Therefore, for public health surveillance purposes, a case of COVID-19 vaccine breakthrough is defined as someone who tests positive (reverse transcriptase polymerase chain reaction -PCR- or antigen) for COVID-19 being fully vaccinated [19].

## To consider a person as fully vaccinated, it was required [30]

1. That they have received 2 doses of vaccine separated by a minimum of 19 days if the first dose was BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), 21 days in the case of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca) or 25 days in the case of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), and that a minimum period of 7 days has elapsed since the last dose if the last dose was with BNT162b2 mRNA vaccine (Comirnaty), or 14 days if it was with ChAdOx1 nCoV-19 vaccine (Vaxzevria) or mRNA-1273 vaccine (Spikevax). People who received a dose of Janssen vaccine (Johnson & Johnson vaccine) more than 14 days ago were also considered fully vaccinated.
2. Or, that having passed the disease they have received a dose of any of the vaccines, after the minimum period equal to that established for the second doses.
3. In the heterologous regimen in which Vaxzevria (Oxford/AstraZeneca) is used in the first dose and mRNA vaccines in the second, it was considered fully vaccinated after 7 days if the second dose was with Comirnaty, or after 14 days if it was with the Moderna vaccine.

## Definition of cases and controls

Patients with full COVID-19 vaccination 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 vaccinated for COVID-19, from the GP's list of patients, who did not go to medical attention or were diagnosed at another level of the health system with COVID-19 positive. As explained below, 100% of the consultation's patient list (2,000 people) were considered to have been fully vaccinated or had passed COVID-19, as of the date of data analysis (September 30, 2021). It can be said that a negative symptoms or no-consultation design was used for COVID-19 breakthrough infections in vaccinated people [24].

### Calculation of rate denominators

The total number of patients assigned to the consultation (2000 people) was used as an approximation to the denominator of rates. Spain began its mass immunization program on December 27, 2020, shortly after the first COVID-19 vaccine (BNT162b2 mRNA vaccine; Comirnaty, Pfizer/BioNTech) was approved earlier that month. With data of September 30, 2021, in Castilla La Mancha, (Spain), 85% of the population has a complete COVID-19 vaccination schedule [7]. These data, in the consultation object of the study suppose 1700 people vaccinated completely. To this figure must be added the patients who have passed COVID-19 (and who consequently were not vaccinated with a full schedule, but with a single dose, and are not counted in the official data of vaccinated with a full schedule), than in the consultation object of the study were, 295 since May 15, 2020 (date from which the consultation has records, since they begin to perform PCR on suspected COVID-19 cases, and as of December 22, 2020 they also begin to perform rapid antigen tests for symptoms of less than 5 days of evolution) until September 30, 2021. Consequently, that number of patients who passed COVID-19 is a minimum figure that does not count the cases of the first wave. In total, 1700 fully vaccinated plus 295 who have overcome the disease, that's 1995, so we used the denominator of 2000 people in the study.

The population for the neighbourhood that depends on the consultation object of the study and Toledo (Castilla La Mancha) was considered based on official statistical data [27] to obtain approximations of the data of the age groups attended in the consultation. Thus, COVID-19 breakthrough infections in vaccinated people (cases) were compared with the total population attended in the consultation (controls) (2,000 people minus the cases of COVID-19 breakthrough infections in vaccinated people) whose data regarding some variables of interest (as complex family, and chronic diseases) were previously published [31,32]. For the denominators of the types of vaccines applied in the total population, official vaccination data were used [33].

### COVID-19 diagnosis

Diagnosis was performed with PCR oropharyngeal swab

test or antigen test for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. A symptomatic 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 [34].

### Collected variables

Data were extracted from the medical records of the general medicine practice under study. The following variables were collected:

1. Age and sex.
2. 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" [35], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [36].
3. Social-occupancy class de COVID-19 breakthrough infections in vaccinated people (according to the Registrar General's classification of occupations and social status code) [37,38].
4. Complex family based on the genogram and in the experience of the general practitioner about continuity of care and knowledge of the family (genogram was 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" genogram identified complex families with psychosocial problems) [39-42].
5. Vaccine type: BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), and Janssen (Johnson & Johnson vaccine). In Spain, these four vaccines are currently available, all of which have been approved by the European Medicines Agency) [7].

### Sample

All patients who consulted for COVID-19 breakthrough infections in vaccinated people from February 1, 2021 to September 30, 2021 were included, and that they were seen in the consultation object of the study and their medical documentation was available.

### Statistic analysis

The bivariate comparisons were performed using the Chi

Square test (X2) with Yates correction or Fisher Exact Test when necessary, (according to the number the expected cell totals) for percentages, and the Student t test for the mean.

## Results

IR of COVID-19 breakthrough infections in vaccinated people > 14 years in GP consultation was 1.5% cases × 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%). IR of COVID-19 breakthrough infections in vaccinated people by type of vaccine ranged from 0.4 cases in mRNA of Moderna-mRNA-1273 vaccine, to 5 cases per 100 vaccinated × 8 months with Janssen vaccine (Table 1). Being > = 65-years-old was a Moderate risk, = < 18-years-old, having some type of labor specialization, and having a complex family were protective factors, but only the latter was statistically significant (Table 2).

**Table 1:** Incidence rates of Covid-19 Breakthrough infections in vaccinated people in general medicine and estimated for the city of Toledo (Spain) for the Period February-September 2021.

Variables	Covid-19 breakthrough infections in vaccinated people N = 30	Estimated population of gp office N = 2.000	Incidence rates of covid-19 breakthrough infections in vaccinated people x 8 months
= < 14-years	30 (100)	2.000 (100)	1.5 cases per 100 people = < 14-years × 8 months
> = 65-years	8 (27)	349 (17)	2.3 cases per 100 people > = 65- years × 8 months
14-65 years	22 (73)	1651 (83)	1.3 cases per 100 people 14-65 years × 8 months
= < 18-years	0	120 (6)	0
Women	16 (53)	1020 (51)	1.6 cases per 100 women × 8 months
Men	14 (47)	980 (49)	1.4 cases per 100 men × 8 months
BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech)	18 (60)	1380 (69)	1.3 cases per 100 vaccinated × 8 months
mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna)	1 (3)	260 (13)	0.4 cases per 100 vaccinated × 8 months
ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca)	6 (20)	260 (13)	2.3 cases per 100 vaccinated × 8 months
Janssen vaccine (Johnson & Johnson vaccine)	5 (17)	100 (5)	5% cases per 100 vaccinated × 8 months

( ): Denotes percentages

**Table 2:** Comparison of the variables studied between Covid-19 breakthrough infections and no Covid-19 breakthrough infections in vaccinated people and calculation of relative risks.

Risk factors	COVID-19 breakthrough infections in vaccinated people N = 30	No COVID-19 breakthrough infections in vaccinated people N = 1970	Statistical significance	Relative risk (RR)
= < 65-years	8 (27)	341 (17)	X <sup>2</sup> = 1.7961 P = 0.18019. NS	RR = 1.72 (CI 95%: 0.65, 4.52). Moderate risk
= < 18-years	0	120 (6)	Fisher exact test = 0.2552. NS	RR = 0 (CI 95% Infinity, 0). Protection factor effectively
Women	16 (53)	1004 (51)	X <sup>2</sup> = 0.0664 P = 0.79672. NS	RR = 1.1 (CI 95%: 0.08, 15.86) Not significant
Social-occupancy class of patients (people with some type of labor specialization)	10 (33)	900 (45)	X <sup>2</sup> = 1.675 P = 0.195596. NS	RR= 0.61 (CI 95%: 1.46, 0.25) True benefits
Complex family	1 (3)	600 (30)	X <sup>2</sup> = 10.3134 P = 0.001321 Significant at p < 0.05	RR = 0.08 (CI 95%: 0.41, 0.02). Protection factor effectively

( ): Denotes percentages; NS: Not significant at p < 0.05; RR: Relative risk

**Table 3:** Comparison of chronic diseases between Covid-19 breakthrough infections and no Covid-19 breakthrough infections in vaccinated people and calculation of relative risks.

Risk factors chronic diseases* according to who, ICD-10 groups	Covid-19 breakthrough infections in vaccinated people N =30	No Covid-19 breakthrough infections in vaccinated people N =1970	Statistical significance	Relative risk (RR)
-I Infectious	0	20 (0.5)	Fisher exact test = 1. NS	RR = 0 (CI 95%: Infinity, 0) Protection factor effectively
-II Neoplasms	0	153(3)	Fisher exact test = 0.1834. NS	RR = 0 (CI 95%: Infinity, 0) Protection factor effectively
-III Diseases of the blood	2 (3)	87 (2)	Fisher exact test = 0.6561. NS	RR =1.39 (CI 95%: 0, 561299.91). Weak risk
-IV Endocrine	13 (16)	553 (12)	$X^2 = 1.8161$ $p = 0.177783$ . NS	RR =1.5 (CI 95%: 0.76, 2.96). Weak risk
-V Mental	4 (5)	627 (13)	$X^2 = 4.635$ $p = 0.031326$ Significant at $p < 0.05$	RR = 0.35 (CI 95%: 0.98, 0.12). Protection factor effectively
-VI-VIII Nervous and Senses	10 (13)	367 (8)	$X^2 = 2.7479$ $p = 0.097384$ . NS	RR = 1.73 (CI 95%: 0.82, 3.63). Moderate risk
-IX Circulatory system	10 (13)	867 (18)	$X^2 = 1.6789$ $p = 0.195064$ . NS	RR= 0.65 (CI 95%: 1.35, 0.31). True benefits
-X Respiratory system	3 (4)	393 (8)	$X^2 = 2.1172$ $p = 0.145648$ . NS	RR = 0.44 (CI 95%: 1.59, 0.12). Protection factor effectively
-XI Digestive system	12 (15)	387 (8)	$X^2 = 5.335$ $p = 0.020901$ Significant at $p < 0.05$	RR = 2.03 (CI 95%: 1.05, 3.93). Moderate risk
-XII Diseases of the skin	0	120 (2)	Fisher exact test = 0.2684. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XIII Musculo-skeletal	19 (24)	720 (15)	$X^2 = 4.9532$ $p = 0.026042$ . Significant at $p < 0.05$	RR= 1.77 (CI 95%: 1.03, 3.04). Moderate risk
-XIV Genitourinary	6 (7)	406 (9)	$X^2 = 0.0962$ . $p = 0.756492$ . NS	RR= 0.88 (CI 95%: 8.58, 0.09). Not significant
-XVII Congenital malformations	0	20 (0.5)	Fisher exact test = 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XIX Injury, poisoning and certain other consequences of external causes	0	20 (0.5)	Fisher exact test = 1. NS	RR= 0 (CI 95%: Infinity, 0). Protection factor effectively
-XXI Factors influencing health status	0	13 (0.5)	Fisher exact test = 1. NS	RR = 0 (CI 95%: Infinity, 0). Protection factor effectively
Total chronic diseases**	79 (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  $p < 0.05$ ; RR: Relative risk

The presence of chronic diseases of Infectious, Neoplasms, Circulatory system, Respiratory system, Diseases of the skin, Congenital malformations, and Mental were protective factors for COVID-19 breakthrough infections in vaccinated people, but only the latter group was statistically significant. Chronic diseases

of blood, Endocrine, Nervous and Senses, Injury, poisoning and certain other consequences of external causes, digestive system and Musculo-skeletal, were risks for COVID-19 breakthrough infections in vaccinated people, only in the last two groups the association it was statistically significant (Table 3).



**Table 4:** Comparison of vaccine types between Covid-19 breakthrough infections and no Covid-19 breakthrough infections in vaccinated people and calculation of relative risks.

Vaccine types	Covid-19 breakthrough infections in vaccinated people n=30	No Covid-19 breakthrough infections in vaccinated people n=1970	Statistical significance	Relative risk (RR)
BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech)	18 (60)	1362 (69)	X <sup>2</sup> = 1.1533 P = 0.28285. NS	RR = 0.67 (CI 95%: 1.63, 0.27). True benefits
mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna)	1 (3)	259 (13)	X <sup>2</sup> with Yates correction = 1.7235. p = 0.189248. NS	RR = 0.23 (CI 95%: 2.07, 0.03). Protection factor effectively
ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca)	6 (20)	254 (13)	X <sup>2</sup> = with Yates correction = 0.766. p = 0.381462. NS	RR = 1.67 (CI 95%: 0.53, 5.23). Moderate risk
Janssen vaccine (Johnson & Johnson vaccine)	5 (17)	95 (5)	Fisher exact test = 0.0148. Significant at p < 0.05.	RR = 3.79 (CI 95%: 1.35, 10.64). Strong risk
TOTAL	30 (100)	2000 (100)	-	-

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

Vaccination with Pfizer-BioNTech-BNT162b2 (Pfizer/BioNTech) mRNA and Moderna-mRNA-1273 mRNA were protective factors for COVID-19 breakthrough infections in vaccinated people factor, but not statistically significant. Vaccination with AstraZeneca - ChAdOx1 nCoV-19 (AZD1222) was a moderate risk and that of Johnson & Johnson. COVID-19 Vaccine Janssen shown a strong risk, statistically significant, of COVID-19 breakthrough infections in vaccinated people (Table 4).

## Discussion

Based on published results from vaccine trials and other data sources, it has been estimated that people immunized against COVID-19 would lose about half of their defensive antibodies every 108 days. As a result, vaccines that initially offered 90% protection against mild cases of the disease may be only 70% effective after 6 to 7 months [43,44]. Although more than 97% of people hospitalized for COVID-19 are not vaccinated, vaccinated people can contract infections, overwhelmingly asymptomatic or mild [45]. One study found that during a period that included the impact of the Delta variant, unvaccinated people were approximately 4.5 times more likely to contract COVID-19, 10 times more likely to be hospitalized, and 11 times more likely to die from it than those who were fully vaccinated [46]. Thus, these vaccines are highly effective (90%-95%), but at least 5% to 10% of the fully vaccinated population is unprotected, for unclear reasons [47].

## Vaccine efficacy

National surveillance data from the first 4 months of Israel's vaccination campaign showed that two doses of BNT162b2 reduced symptomatic and asymptomatic infections, COVID-19-related hospitalizations, severe illness, and death [48]. A recent study with Scottish data at the national population level showed

that by the fourth week after the first dose, the BNT162b2 and ChAdOx1 vaccines reduced the risk of hospital admission by 85% and 94%, respectively [11]. A prospective cohort study of hospital staff in England reported that the effectiveness of the vaccine was 72% within 21 days of the first dose of the BNT162-2 mRNA vaccine [49]. A cohort study of healthcare workers in Israel reported a 75% reduction in SARS-CoV-2 infection and an 85% reduction in symptomatic COVID-19 during the 15-28 days after the first dose of BNT162b2 [50].

## IR of COVID-19 breakthrough infections in vaccinated people

Based on the reported vaccine efficacy data, as worrisome as breakthrough infections may seem, they are still relatively rare [51]. The reported rates range from 0.01% to 57% (in an outbreak): 0.01%, 0.05% (although later, in an outbreak they reported a rate of 57%, 0.09%, 0.2%, 0.3% 0.4%, 0.55%,1.5% and 5.5%, according to geographic location, type of people vaccinated (nursing homes, health workers, general population), time since vaccination, predominance of new variants of SARS.Cov-2, data on an outbreak, inclusion or not of asymptomatic patients, etc. [17,51-58]. It must be taken into account that where vaccination rates are high, breakthrough cases already represent one third of all cases A situation can be envisaged in which, in the absence of third doses, breakthrough cases represent a higher number of COVID cases and the disease they cause in most cases remains relatively mild. The decrease in Immunity or further evolution of the virus could also mean that breakthrough cases are aggravated, making booster injections essential cials [17,59-62]. In our study, the rate found of 1.5 cases per 100 people aged 14-65 years × 8 months is in the high range of those reported, but within the accepted pattern that COVID-19 breakthrough infections in vaccinated people are rare or very rare events.

## Sex/gender

Of the COVID-19 breakthrough infections in vaccinated people, 63% were reported to be women (but proportional to the vaccinated) [47]. We found a slightly higher IR in women vs. men (1.6 cases per 100 women vs. 1.4 cases per 100 men × 8 months), but the RR of being a woman for COVID-19 breakthrough infections in vaccinated people was 1.1 (CI 95%: 0.08, 15.86), not significant.

## Age

Anti-COVID-19 vaccines offer strong protection against hospitalization and death, even against the delta variant, but the protection of the vaccine appears to decrease among older populations (> 75 years) [46,63-65]. Our results (with a IR of 2.3 cases per 100 people in > = 65 years × 8 months, a figure higher than in the population aged 14-65 years with 1.3 cases per 100 people 18-65 years × 8 months, and the fact that age > = 65 years was a risk factor, and age = < 18-years is a protective factor for COVID-19 breakthrough infections in vaccinated people) are in line with what was previously published. A median age of 58-years has been reported for COVID-19 breakthrough infections in vaccinated people [47]. Likewise, it was communicated increasing age was strongly and independently associated with an increased risk of serious illness or death in people with breakthrough infection, although this association has been well described in people with primary infection [22,66].

## Frailty and comorbidity

Poor immune responses in older age groups and general frailty or the presence of risk factors such as diabetes, obesity, or asthma may be potential explanations for increased risk among older people [67]. Our study finds mixed results of the risk or protection of the different chronic diseases with respect to COVID-19 breakthrough infections in vaccinated people, which has also occurred in other studies [55], this fact, cannot be clearly explained. Probably, it is the behavior regarding infection control guidelines (that is, the use or not of masks, distancing, etc.) associated with certain chronic diseases, and not the disease itself, that is the risk or protective factor; furthermore, associations of marginal importance should be interpreted with caution [55].

It has been reported in one study that the burden of comorbidities was not associated with an increased risk of severe illness or death [66]. However, researchers from the University of Oxford, UK, who used the Qcovid tool [68] to examine the risk of severe COVID-19 leading to hospitalization or death 14 days after a full vaccination schedule, when expected substantial immunity, identified as risk factors: Down syndrome, kidney transplant, sickle cell anemia, chemotherapy, nursing home residence, HIV/AIDS, liver cirrhosis, neurological conditions, recent bone marrow transplant or organ transplant ever solid, dementia, and Parkinson's disease [69]. In any event, mortality appears to remain high for high-risk or frail vaccinated individuals admitted to hospital with SARS-CoV-2 infection [55,60].

## Social factors

Greater social deprivation (higher population density and greater ethnic diversity) has been associated with higher odds of SARS-CoV-2 infection after a single dose of vaccine, consistent with findings from the pre-vaccination era [55]. We found that having some type of labor specialization, and having a complex family were protective factors, but only the latter was statistically significant. Again, we think these mixed results may not persist after further adjustment for adherence to infection control and healthcare seeking behavior guidelines.

## Vaccines

It has been reported in a cohort with 2,551 nucleic acid amplification tests from samples of fully vaccinated individuals had 14 breakthrough infections, which six received BNT162b2 mRNA vaccine, five received mRNA-1273 vaccine and three received Janssen vaccine [61]. An analysis after full vaccination with mRNA-1273 vaccine, BNT162b2 mRNA vaccine or Janssen vaccine, showed greater efficacy against COVID-19 hospitalizations for mRNA-1273 vaccine (93%) than for BNT162b2 mRNA vaccine (88%); The efficacy of both mRNA vaccines was higher than that of the Janssen vaccine (71%). The protection of BNT162b2 mRNA vaccine decreased 4 months after vaccination. Post-vaccination levels of anti-spike IgG and anti-RBD IgG were significantly lower in people vaccinated with the Janssen vaccine than in mRNA-1273 vaccine or BNT162b2 mRNA vaccine [70]. Likewise, it has been reported that both of the mRNA vaccines available are highly effective against severe COVID-19, but recent studies suggest that mRNA-1273 vaccine elicits a stronger immune response and might be better at preventing breakthrough infections.

In multiple independent studies, significantly lower antibody levels and more vaccine breakthrough infections have been detected in BNT162b2 mRNA vaccine [71]. For example, in an observational study in healthcare workers, mRNA-1273 vaccine elicited a greater antibody response against SARS-CoV-2 than BNT162b2 mRNA vaccine [72]. On the other hand, the Agence Nationale de Sécurité du Médicament et des Produits de Santé in France, has communicated new doubts about the real effectiveness of the Janssen single-dose vaccine: since the start of vaccination with this formula on April 24, there have been observed 32 post-vaccination COVID-19 episodes, including 29 severe cases, of which 4 were fatal. In addition, regional pharmacovigilance centers in Marseille and Tours have observed an overrepresentation in intensive care units of patients vaccinated with one dose of that vaccine, compared to those who received full schedules of other products [73]. However, Johnson & Johnson has reported that a single dose of its vaccine induces a strong immune response and long-lasting immune memory, even though it suggests that applying a second dose two months after the first increases efficacy against COVID-19 moderately to severe. At the beginning of the 2021 the company had reported that the single-dose vaccine was 66% effective for moderate forms of the disease and 85% for severe forms [74]. Finally, it has also been published that among vaccinated

patients with systemic autoimmune rheumatic disease, 16 intercurrent infections were identified: seven (44%) received BNT162b2 mRNA vaccine, five (31%) received mRNA-1273 vaccine, and four (25%) received Janssen vaccine [75].

Our results are again along the same lines: IR of COVID-19 breakthrough infections in vaccinated people by type of vaccine ranged from 0.4 cases in mRNA-1273 vaccine, to 5 cases per 100 vaccinated × 8 months with Janssen vaccine. Vaccination with BNT162b2 mRNA vaccine and mRNA-1273 vaccine were protective factors for COVID-19 breakthrough infections in vaccinated people, but not statistically significant. Vaccination with ChAdOx1 nCoV-19 vaccine shown a moderate risk and Janssen vaccine a strong risk of COVID-19 breakthrough infections in vaccinated people, in the latter statistically significant.

### Limitations of the study

Our study has several limitations:

1. The number of cases was relatively small.
2. It is possible that we have overlooked asymptomatic cases, since patients who consulted with symptoms (and this case their contacts, who could be asymptomatic) were counted. It is recognized that more than a quarter of COVID-19 breakthrough infections in vaccinated people may be asymptomatic [47]. Unfortunately, given that a proportion of COVID-19 patients after vaccination are asymptomatic, it is challenging to know the true prevalence of the disease after vaccination. Therefore our results should be understood as “minimal” IR.

### Conclusion

In the context of general medicine in Toledo (Spain), during the first 8 months of COVID-19 vaccination, these vaccines were extremely effective, and COVID-19 breakthrough infections in vaccinated people were rare, with higher rates in women and old people. Although it must be taken into account that asymptomatic infections did not consult the GP and are not counted, except that they were found when tracing contacts. Chronic digestive and musculoskeletal diseases were a risk factor, and the complex family, and chronic mental diseases protective factors. These mixed results are possibly linked to the preventive behavior of COVID-19 and the use of medical services. Each of the vaccines has associated breakthrough infections, but the Janssen vaccine represented a statistically significant strong risk of COVID-19 breakthrough infections in vaccinated people. However, with these small numbers we cannot report that one is more or less effective in our population.

Our findings could support the cautious relaxation of physical distancing and other personal protection measures in the post-vaccination era, but particular care should be taken around frail older adults and people vaccinated with the Janssen vaccine, and this could have implications for strategies such as booster vaccinations.

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**DOI: 10.36959/577/505**