Original Research

SECONDARY INFECTIONS IN THE FAMILY FROM PRIMARY CASES OF COVID-19 BREAKTHROUGH INFECTIONS IN FULLY VACCINATED OR NOT FULLY VACCINATED PEOPLE. TWO DOSES MODESTLY REDUCE FAMILY TRANSMISSION BUT DOES NOT ELIMINATE IT

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Keywords: COVID-19, SARS-CoV-2, Epidemiological characteristic, Household contact, Secondary attack rate.

Abstract: ***Introduction.*** It is unclear whether vaccination of individuals against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protects members of their households.

Objective. Epidemiological evaluation of SARS-CoV-2 transmissibility from fully and incompletely vaccinated index cases with COVID-19 breakthrough infection to initially uninfected family members (secondary attack rate).

***Material and methods*.** An observational, longitudinal, and prospective study of all families with a primary case of COVID-19 breakthrough infection in fully vaccinated or not fully vaccinated people and at least one COVID-19 secondary case in family members was conducted from February to November 2021 in a general medicine office in Toledo, Spain. Clinical and epidemiological variables were compared between secondary cases of primary cases of COVID-19 breakthrough infection in fully vaccinated people versus secondary cases of primary cases of COVID-19 breakthrough infection in not fully vaccinated people.

Results. Twenty-five index cases (25 families; 84 people) were included, 13 fully vaccinated, which gave rise to 20 secondary cases, and 12 not fully vaccinated, which gave rise to 21 secondary cases. The secondary attack rate of exposed family members to fully vaccinated primary cases were 61% (20/33), and the secondary attack rate of exposed family members to not fully vaccinated primaries was 81% (21/26).

Conclusion. In the context of general medicine in Toledo (Spain), from February to November 2021 (before micron), two doses of COVID-19 vaccine vs. only one modestly reduce family transmission but do not eliminate it.

INTRODUCTION

COVID-19 infection can be prevented with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. Scientists produced safe and effective SARS-CoV-2 vaccines in record time, and the vaccination program began in December 2020 [1]. Reports of historical successes in vaccine development during the COVID-19 pandemic have highlighted two critical measures of vaccine performance: vaccine efficacy as determined by randomized controlled trials and estimated from post-introduction observational studies. Both statistics describe an individual's risk reduction after vaccination [2].

Real-world evidence from vaccine deployment programs has shown that COVID-19 vaccines are highly effective against serious illness, hospitalization, and death and reduce both asymptomatic infection and intra-household transmission [3]. Antibody levels predict the vaccine's efficacy: the higher the level of antibodies, the greater the protection provided by the messenger RNA (mRNA) vaccine [4]. However, it has been published that those vaccinated who subsequently become infected have the same probability of infecting those around them as unvaccinated people who develop COVID-19 [5].

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As immunization programs expand globally, more estimates are needed of the third measure of vaccine performance: vaccine impact. Vaccine impact studies estimate the reduction in disease in a community. Reductions in disease outcomes are achieved through direct effects of vaccination on vaccinated persons and indirect effects due to reduced transmission within a community [2].

Homes are ideal settings to assess the transmissibility of a pathogen and the associated determinants of susceptibility and infectivity [6]. Additionally, households are the site of most SARS-CoV-2 transmission globally [5]. However, less attention has been paid to family members and others who care for people with COVID-19 in the community.

Assessing the effect of COVID-19 vaccination on the trajectory of the pandemic is important to verify that vaccines are working as expected at the population level. It will be important to assess public health outcomes in various settings, given differences in the circulation and occurrence of viral variants, the heterogeneity of vaccines and vaccination schedules, and the diversity of target populations [2, 7].

Randomized trials and post-marketing studies have shown that SARS-CoV-2 vaccines dramatically reduce symptomatic, and possibly asymptomatic, COVID-19; however, less is known about its effects on transmission between individuals [8]. Since vaccination reduces SARS-CoV-2 infection, it is plausible that the vaccine reduces transmission; however, data from clinical trials and observational studies are lacking. It is unclear whether vaccination of individuals against SARS-CoV-2 protects members of their households [9].

On the other hand, epidemiological evaluation studies of transmissibility (the probability that a pathogen spreads from an infected individual to an uninfected individual) and household heterogeneity in the family are not frequent, so the risk of transmission at home, given a primary case of COVID-19 in fully vaccinated or not fully vaccinated people, is not clear. In addition, attention has been drawn to the fact that vaccinated people infected with Delta could, unlike other variants, easily transmit it. Some initial findings indicate that virus levels in those who become infected with Delta after being vaccinated may be similar to levels found in unvaccinated people. This may have implications for the infectiousness of people, whether or not they have been vaccinated [10].

Efficacy of the COVID-19 vaccine (VE) has been reported to be 40% against symptomatic infections 4 to 6 months after the second dose, which represents a substantial decrease from that reported at one month after the second dose. Although it was initially unclear whether this was due to decreased immunity overtime or the more transmissible Delta variant, it became clear that time itself was a key factor: waning immunity has occurred, to a variable degree, after all, vaccines studied to date, and the loss of protection was likely amplified by a higher prevalence of Delta [11]. A report of nearly 140,000 people who were in contact with infected individuals with reverse transcriptase-polymerase chain reaction (PCR)-confirmed COVID-19 showed that the AstraZeneca and Pfizer/BioNTech vaccines suppressed transmission. Still, their ability to do so was markedly lower for Delta in compared to Alpha and lower in people vaccinated with AstraZeneca compared to the Pfizer/BioNTech vaccine [12].

In this context, the present study aimed at the epidemiological evaluation of the transmissibility of SARS-CoV-2 from fully and incompletely vaccinated index cases with COVID-19 breakthrough infection to initially uninfected family members (secondary attack rate).

MATERIAL AND METHODS

An observational, longitudinal, and prospective study of all families with one case of COVID-19 breakthrough infection in fully vaccinated or not fully vaccinated people (index or primary case) and at least one family member with COVID-19 (secondary case) was conducted from February 1 to November 30, 2021, 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, and are the gateway for all patients to the system, and each person is assigned a GP [13].

Outcome of interest

The outcomes of interest were:

1. Assess the secondary transmission of SARS-CoV-2 from people vaccinated with the complete schedule versus the non-complete schedule to other family members. In this sense, the secondary attack rate of COVID-19 breakthrough infections in the family was calculated. This secondary attack rate of COVID-19 in families was calculated at the GP's office by dividing the number of infection events by a person's follow-up time [14].

2. Describe the clinical and epidemiological variables. In this sense, the clinical and epidemiological variables were compared between secondary cases of primary cases of COVID-19 breakthrough infection in fully vaccinated people versus secondary cases of primary cases of COVID-19 breakthrough infection in not fully vaccinated people.

Diagnosis of COVID-19 breakthrough infections in vaccinated people

Because the vaccines require about two weeks to reach their maximum effectiveness, a person is not considered fully vaccinated until two weeks after completing 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 PCR or antigen) for COVID-19 being fully vaccinated [15].

To consider a person as fully vaccinated, it was required [16]:

1. That they have received two 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 the Janssen vaccine (Johnson & Johnson vaccine) more than 14 days ago were also considered fully vaccinated.

2. Or, having passed the disease, they have received a dose of any vaccines after the minimum period equal to that established for the second dose.

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 seven days if the second dose was with Comirnaty, or after 14 days if it was with the Moderna vaccine

Diagnosis of COVID-19

The diagnosis was performed by 1) Reverse transcriptase-polymerase chain reaction (PCR) oropharyngeal swab tests, or 2) Antigen testing. Rapid antigen tests were carried out for symptomatic patients with less than five 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 in the consultation. A symptomatic confirmed case with active infection was considered in any person with a clinical picture of sudden-onset acute respiratory infection of any severity, such as fever, cough, or 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 positive PCR or rapid antigen test positive [16].

Secondary attack rate

Secondary attack rate was defined as the number of new cases divided by the number of people exposed to a primary case. The existence of second or third-generation cases was not assessed. The cases for determining the attack rate included confirmed symptomatic cases and asymptomatic cases.

Household contacts

Household contacts were defined as people who shared a residence with the COVID-19 index case. We defined family members as those who had lived with primary cases in a house at least four days before and for more than 24 hours after the primary cases developed illness related to COVID-19. Presumed household transmission through an index case in households was cataloged using the definition of secondary transmission from 1 to 14 days [17]. The onset date of a confirmed case was defined as the date of the first appearance of self-reported clinical symptoms. The onset date for an asymptomatic carrier was defined as the date a positive COVID-19 PCR test was obtained (18).

Collected variables

- Primary case or secondary case
- Age and sex
- Symptoms
- 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" [19], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [20].

- Duration of symptoms in days
- Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [21, 22].
- 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 based on 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) [23-26].
- Number of family members
- Ethnic minority
- Symptomatic/asymptomatic COVID
- Time in days since last vaccine dose
- Severity of the disease (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 ≤ 93% with room air at rest; arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg) [18]. To simplify the comparison, moderate and severe cases were counted together.
- Vaccine type: Comirnaty (Pfizer-BioNTech-BNT162b2 mRNA; Pfizer / BioNTech), Moderna-mRNA-1273 mRNA, Vaxzevria (AstraZeneca), and Janssen / Johnson & Johnson vaccine (Currently, the European Commission has licensed four vaccines: Comirnaty, Pfizer / BioNTech, licensed December 21, 2020; Moderna vaccine, licensed January 6; AstraZeneca vaccine, licensed December 29 and the Janssen / Johnson & Johnson vaccine, authorized on March 11. These four vaccines are currently available in Spain, all approved by the European Medicines Agency) [27].

Sample

All families in which a case of COVID-19 was diagnosed, at the consultation, in fully or not fully vaccinated people, during the study period, were included. The families participating in the study were chosen because they had their members in the same consultation, and/or all medical information was available.

Sample size

The sample size was calculated, from data on mean age in women in secondary cases, for Comparing Two Means, for a Two-sided Confidence Level (1-alpha) of 95, a Power (% probability of detection) of 80%, a ratio of 1: 1, a hypothetical mean age of women in secondary cases of fully vaccinated primary cases of 52 years and hypothetical mean age of women in secondary cases of not fully vaccinated primaries of 36 years. Thus total Sample Size should be 36; 18 secondary cases of primary cases fully vaccinated and 18 secondary cases of primary cases not fully vaccinated [28].

Statistical 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 the expected cell totals) for percentages, and the Student test for the mean.

RESULTS

Twenty-five index cases (25 families; 84 people) were included, 13 were fully vaccinated, and 12 were not fully vaccinated. The 13 primary cases of COVID-19 breakthrough infections in fully vaccinated people gave rise to 20 secondary cases: 9 cases of COVID-19 breakthrough infections in fully vaccinated people, 6 cases of COVID-19 breakthrough infections in not fully vaccinated people, and 5 cases in not vaccinated people. The 12 primary cases of COVID-19 breakthrough infections in not fully vaccinated people gave rise to 21 secondary cases: 4 cases of COVID-19 breakthrough infections in fully vaccinated people, 8 cases of COVID-19 breakthrough infections in not fully vaccinated people, and 9 cases in not vaccinated people (**FIGURE 1**). The secondary attack rate of exposed family members to fully vaccinated primary cases was 61% (20/33), and the secondary attack rate of exposed family members to not fully vaccinated primary cases was 81% (21 /26). Thus, the observed reduction in secondary cases was 20% in those exposed to fully vaccinated primary cases vs. exposed to primary cases not fully vaccinated.

Secondary cases of COVID-19 after a primary case of COVID-19 breakthrough infections in fully vaccinated people vs. secondary cases of COVID-19 after a primary case of COVID-19 breakthrough infections in not fully vaccinated people within the family were older, with more males, with older females ($p < 0.05$), more socio-health workers, with more symptomatic cases, with fewer general symptoms (discomfort, asthenia, myalgia, fever, arthralgia) ($p < 0.05$), with more cases presenting chronic diseases ($p < 0.05$), but less in the group, and with a longer time between the last dose of vaccine and the diagnosis of COVID-19. There were not statistically significant

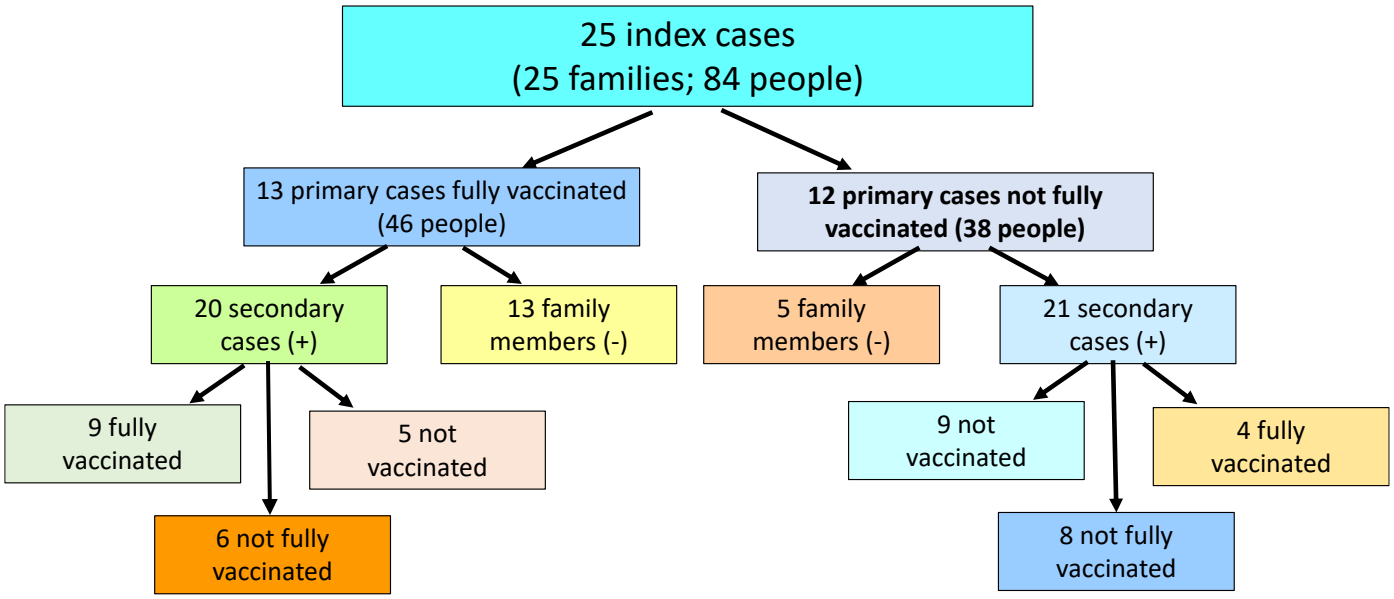

FIGURE 1. STUDY FLOWCHART. SECONDARY CONTAGES IN THE FAMILY FROM PRIMARY CASES OF COVID-19 BREAKTHROUGH INFECTIONS IN FULLY VACCINATED OR NOT FULLY VACCINATED PEOPLE

differences according to their vaccination status (fully or not fully vaccinated, and not vaccinated), but with a longer time in days from last vaccine dose to positive COVID-19 test ($p < 0.05$). There were no statistically significant differences according to vaccine types in secondary cases, although the number of individuals was small (**TABLE 1, TABLE 2, TABLE 3, and TABLE 4**).

DISCUSSION

Communicability from COVID-19 breakthrough infections in fully vaccinated people and not fully vaccinated people (Secondary attack rates and symptomatic cases)

It has been reported that fully vaccinated people are less contagious by reducing their infectiousness than those who are not vaccinated, and those who are vaccinated would eliminate the virus from their bodies much faster than those who are not vaccinated; this even in the presence of the Delta variant [29-33]. Since vaccination reduces symptomatic and asymptomatic SARS-CoV-2 infection, it is plausible that the vaccine reduces transmission [3, 9]. And, since antibody levels predict vaccine efficacy, the higher the antibody level, the greater the protection provided by the vaccine [4]. The most potent vaccines seem to impede viral replication drastically and thus transmission [34, 35].

It could be reasonably assumed that the level of efficacy of the vaccine in preventing disease in a person correlates with the level of efficacy of that vaccine in preventing transmission or contagion from that person to others. The level of efficacy to prevent disease also suggests the level of prevention of contagion. Thus, in the test-negative case-control analysis, the estimated vaccine effectiveness against symptomatic disease with the Delta variant was approximately 36% with a single dose of the BNT162b2 vaccine and approximately 30% with a single dose of the ChAdOx1 nCoV-19 vaccine; the effectiveness was approximately 88% with two doses of the BNT162b2 vaccine and approximately 67% with two doses of the ChAdOx1 nCoV-19 vaccine [36].

According to Pfizer data published in December 2020, the Pfizer-BioNTech vaccine is approximately 52% effective after the first dose (avoiding developing symptoms, and protection does not kick in until at least day 12). Two doses are 95% effective in preventing the disease after one week. For the Oxford-AstraZeneca vaccine, it has been published that the vaccine offers 64% protection after at least one standard dose and 70% if they have received two full doses. The Moderna vaccine has been reported to provide 80% protection after one dose, compared to 96% after the second [37-39].

In any case, SARS-CoV-2 has used the plasticity of its genome with an obvious advantage, increasing its transmissibility with the appearance of mutation or

VARIABLES	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH COMPLETE VACCINATION N=20	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH INCOMPLETE VACCINATION N=21	STATISTICAL SIGNIFICANCE
Men	10 (50)	5 (24)	X2=3.0287. P= .081804. NS
Men-Age (Arithmetic mean and standard deviation; Range)	36.1 +- 25.6 (Range: 11-78 years)	24.2+-24.4 (Range: 8-63 years)	t= 0.57014. p= .289151. NS
Women	10 (50)	16 (76)	X2= 3.0287. p= .081804. NS
Women-Age (Arithmetic mean and standard deviation; Range)	52.7 +- 13.3 (Range: 30-65 years)	36.6+-19.9 (Range: 7-70 years)	t= 2.23579. p= .017464. The result is significant at p < .05.
>= 65 years	4 (20)	2 (9)	X2 with Yates correction= 0.2567. p= .612386. NS
Children and adolescents <= 22 years	4 (20)	4 (19)	X2 with Yates correction= 0.1007. p= .751028. NS
Total Age in years (Arithmetic mean and standard deviation; Range)	44.4 +- 21.6 (Range: 11-78 years)	34.6+-20.7 (Range: 3-70 years)	t= 1.46865. p= .074974. NS.
Socio-health workers	4 (20)	1 (5)	Fisher exact test= 0.1836. N
Social-occupancy class of patients (people with some type of labor specialization)	1 (5)	1 (5)	Fisher exact test= 1. NS.
Complex family	0	2 (10)	Fisher exact test= 0.4878. NS
Ethnic minority	4 (20)	4 (19)	X2 with Yates correction= 0.1007. p= .751028. NS
Low income household	0	2 (10)	Fisher exact test= 0.4878. NS
Symptomatic	16 (80)	12 (57)	X2= 2.4716. p= .115921. NS
Moderate-severe severity	0	0	Fisher exact test= 1. NS
Symptom duration in days (Arithmetic mean and standard deviation; Range)	(N=16 Symptomatic) 5.1 +- 2.1 (Range: 2-9 days)	(N=12 Symptomatic) 4.4+-3.7 (Range: 1-15 days)	t= 0.63959. p= .264016. NS.
Incubation period in days (Arithmetic mean and standard deviation; Range)	(N=16) 2.8 +- 1.4 (Range: 1-7 days)	(N=12) 4.4+-3.5 (Range: 1-12 days)	t= -1.5945. p= .061455. NS
-Chronic diseases presence	12 (60)	4 (19)	X2= 7.2199. p= .00721. Significant at p < .05.

N: Number of individuals; ( ): Denotes percentages; NS: Not significant

TABLE 1. COMPARISON BETWEEN SECONDARY CASES OF COMPLETE AND INCOMPLETE VACCINATED PRIMARY CASES

SYMPTOMS * ACCORDING TO WHO, ICD-10 GROUPS	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH COMPLETE VACCINATION N=20	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH INCOMPLETE VACCINATION N=21	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, artralgias)	14 (32)	15 (68)	X2= 7.8733. p= .005017. Significant at p < .05.
Respiratory (cough, dyspnea, chest pain)	8 (18)	4 (18)	X2= 0. p= 1. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis)	15 (34)	3 (14)	X2= 3.0938. p= .078593. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	0	0	Fisher exact test= 1. NS
Neurological (headache, dizziness, mental confusion -brain fog)	6 (14)	0	Fisher exact test= 0.1674. NS
Psychiatric (Anxiety, insomnia)	1 (2)	0	Fisher exact test= 1. NS
Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Total symptoms*	44 (100)	22 (100)	---

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

TABLE 2. COMPARISON OF SYMPTOMS BETWEEN SECONDARY CASES OF COMPLETE AND INCOMPLETE VACCINATED PRIMARY CASES.

variants [35]. In addition, on the one hand, the figures reported for a single dose of EV are confusing and variable depending on the definition of effectiveness (number of people who tested positive for the virus, prevention of symptomatic disease, prevention of severe disease, hospitalization), population, type of vaccine and the predominant variant of the virus, etc. Still, in general, they are between 36% and 80% [40]. On the other hand, it has been reported that the proportion of infected contacts from community households in a real-life setting was similar regardless of the vaccination status of the index cases. Vaccination was found to be effective in reducing transmission of the alpha variant in households (B.1.1.7) by between 40% and 50%; and the Delta variant (B.1.617.2), which is more transmissible than the alpha variant [5].

Although vaccines remain highly effective in preventing severe illness and deaths from COVID-19, our findings suggest that vaccination is not sufficient to prevent transmission of the Delta variant in household settings. We found, from February to November 2021 (before Omicron), a secondary attack rate of exposed family members to fully vaccinated primary cases of 61% (20/33), and a secondary attack rate of family members family exposed to primary cases not fully vaccinated of 81% (21/26). That is an observed reduction of secondary cases of 20% in those exposed to primary cases fully vaccinated versus exposed to primary cases not fully vaccinated, which can be framed in the lower area of the published figures when comparing the transmission of vaccinated and not vaccinated. The reduction in cases in household contacts has been reported to range between 25% and 63% in various studies [41].

Partially vaccinated populations enter a new era in controlling the SARS-CoV-2 epidemic. However, given the high transmissibility and severity of the Delta variant and the reduced efficacy of vaccines against infection with this variant, SARS-CoV-2 may continue to generate substantial stress on healthcare in the absence of mitigation

CHRONIC DISEASES ACCORDING TO WHO, ICD-10 GROUPS*	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH COMPLETE VACCINATION N=20	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH INCOMPLETE VACCINATION N=21	STATISTICAL SIGNIFICANCE
-I Infectious	0	0	Fisher exact test= 1. NS
-II Neoplasms	0	0	Fisher exact test= 1. NS
-III Diseases of the blood	1 (4)	0	Fisher exact test= 1. NS
-IV Endocrine	7 (27)	1 (11)	Fisher exact test= 0.6478. NS
-V Mental	2 (8)	1 (11)	Fisher exact test= 1. NS
-VI-VIII Nervous and Senses	2 (8)	1 (11)	Fisher exact test= 1. NS
-IX Circulatory system	5 (19)	0	Fisher exact test= 0.2972. NS
-X Respiratory system	0	0	Fisher exact test= 1. NS
-XI Digestive system	3 (11)	1 (11)	Fisher exact test= 1. NS
-XII Diseases of the skin	0	0	Fisher exact test= 1. NS
-XIII Musculo-skeletal	6 (23)	2 (22)	Fisher exact test= 1. NS
-XIV Genitourinary	0	3 (34)	Fisher exact test= 0.0128. The result is significant at $p < .05$
Total chronic diseases*	26 (100)	9 (100)	---

N: Number of individuals; ( ): Denotes percentages; NS: Not significant; * Patients could have more than one chronic disease. The percentages are over the total of chronic diseases

TABLE 3. COMPARISON OF PREVALENCE OF CHRONIC DISEASES BETWEEN SECONDARY CASES OF COMPLETE AND INCOMPLETE VACCINATED PRIMARY CASES.

measures, even with high vaccination coverage. Under-vaccinated people contribute disproportionately to transmission, so targeting measures can help maximize epidemic control and minimize costs to society [42].

On the other hand, vaccines can further reduce the degree of transmissibility by reducing symptoms (e.g., coughing and sneezing) and increasing the threshold for host-to-host spread [8]. The most surprising result of the SARS-CoV-2 vaccine trials was its efficacy in preventing symptomatic infection and severe to fatal COVID-19, including particularly vulnerable and high-risk populations and the delta variant [43-51]. However, we found more symptomatic infections in secondary cases of exposed family members than fully vaccinated primary cases vs. exposed to primary cases not fully vaccinated (80% vs. 57%), although this difference was not statistically significant.

Time appears to be the key factor in reducing post-vaccination effectiveness.

A pattern of decreased immunity against multiple variants has been reported two months after the second dose. Although many studies have confirmed a reduction in serum neutralizing antibody concentrations 4 to 6 weeks after vaccination, the picture is less clear for T cell responses. Studies show small changes consistent with memory development immunological. The clinical decline in immunity after the first two months is particularly notable in people older than 60 years, whose susceptibility increased for both symptomatic infections and hospitalizations [11]. We found that secondary cases of COVID-19 after a primary case of COVID-19 breakthrough infections in fully vaccinated people vs. secondary cases of COVID-19 after a primary case of COVID-19 breakthrough infections in not fully vaccinated people within the family had a longer time in days from the last vaccine dose to positive COVID-19 test (and were older people).

VARIABLES RELATED TO COVID-19 VACCINATION	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH COMPLETE VACCINATION N=20	POSITIVE SECONDARY CASES OF PRIMARY CASES WITH INCOMPLETE VACCINATION N=21	STATISTICAL SIGNIFICANCE
Fully vaccinated	9/20 (45)	4/21 (19)	X2= 3.1863. p= .074258. NS.
Vaccinated one dose or without fulfilling adequate time from last dose to positive test	6/20 (30)	8/21 (38)	X2= 0.2985. p= .5848. NS
Completely vaccinated, or with a dose or without complying with adequate time from last dose to positive test	15/20 (75)	12/21 (57)	X2= 1.4527. p= .228101. NS
Not vaccinated	5/20 (25)	9/21 (43)	X2= 1.4527. p= .228101. NS.
Time in days from last vaccine dose to positive COVID-19 test (Arithmetic mean and standard deviation; Range)	(N=15 Fully vaccinated + vaccinated one dose or without meeting adequate time from last dose to positive test) 94.4 +- 59.4 (Range: 11-180 days)	(N=12 positive vaccinated) 20,120,30,10,52,26,60,6,1,1,52,107 40.4 +- 38.0 (Range: 1-120 days)	t-value= 2.69817. p= .006155.
VACCINE TYPES	N=15 Fully vaccinated + vaccinated one dose or without meeting adequate time from last dose to positive test	(N=12 positive vaccinated)	
BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)	11 (73)	6 (50)	X2 with Yates correction= 0.7167. p= .397231. NS
mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna)	0	1 (8)	Fisher exact test= 1. NS
2ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford /AstraZeneca)	4 (27)	4 (33)	Fisher exact test= 1. NS
Janssen (Johnson & Johnson vaccine)	0	1 (8)	Fisher exact test= 1. NS
TOTAL	15 (100)	12 (100)	---

( ): Denotes percentages; No pertinente; No pertinente; NS: Not significant

TABLE 4. COMPARISON OF VARIABLES RELATED TO COVID-19 VACCINATION BETWEEN SECONDARY CASES OF COMPLETE AND INCOMPLETE VACCINATED PRIMARY CASES.

Limitations and strengths of the study

1. The sample was not random, although by including all families with a primary case of COVID-19 in fully and not fully vaccinated people and the long duration of follow-up, it can be assumed that the data is not far from real life.
2. The sample was small, so the statistical significance of some variables could be hidden.
3. 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 of the cautious behaviors and personal protection in the family
4. May have been overlooked asymptomatic primary cases that did not attend GP consultation, as no surveillance or systematic screening was done.
5. There is potential for misclassification of household transmission if the secondary case infection was acquired outside the household or if the true household index case was not assessed.
6. Epidemiological data from contact tracing has not been combined with genomic data to estimate secondary attack rates.

Conclusion

In the context of general medicine in Toledo (Spain), from February to November 2021 (before omicron), the secondary attack rate within the family was clearly higher from primary cases not fully vaccinated vs. fully vaccinated primary cases. The observed reduction in secondary cases was 20% in those exposed to fully vaccinate vs. primary cases exposed to primary cases not fully vaccinated. These secondary cases of not fully vaccinated primaries had fewer chronic diseases, more general symptoms, and less time between the last dose of vaccine and the diagnosis of COVID-19. Our conclusion is that two doses of a COVID-19 vaccine modestly reduce family transmission (in a period when the delta variant predominated, and before omicron), but does not eliminate it.

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