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# Relative COVID-19 Vaccine Booster Effectiveness and Clinical-Epidemiological Characteristics Before and After 29 Days of Shot

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## Abstract

**Background:** When the highest vaccine COVID-19 booster effectiveness (VBE) is obtained is not clearly known.

**Objective:** To compare the cases of COVID-19 in booster vaccinated people with a time of <29 days vs. ≥ 29 days from booster to infection diagnosis and assess their relative VBE.

**Methodology:** An observational, longitudinal and prospective case series study of adult patients with COVID-19 breakthrough infections in booster vaccinated people, in general medicine and for the period December 2021 to February 2022, during the omicron variant contagion wave.

**Results:** Forty-six cases were included, 28 cases of COVID-19 breakthrough infections with booster shot <29 days (61%), with a mean time from booster to COVID-19 of 12 days (1-25 days), and 18 cases with booster ≥ 29 days (39%), with a mean time from booster to COVID-19 of 50 days (29-84 days). Relative VBE ≥ 29 days before infection [1 - (Cases with vaccine booster shot ≥ 29 days) / (Cases with vaccine booster shot <29 days) x 100] was 36%. No VBE found with shot <29 days vs. booster shot ≥ 29 days. COVID-19 cases with booster shot ≥ 29 days had shorter duration of symptoms, were more socio-health workers, and had more sick leave. COVID-19 cases with booster shot ≥ 29 days had been more vaccinated with 2 doses of Pfizer-BioNTech plus booster of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna).

**Conclusion:** In the general practice setting in Toledo, Spain, from December 1, 2021 to February 28, 2022, at the peak of omicron infections, booster after a period of <29 days had relative VBE of 36% against symptomatic disease vs. <29 days; but, our cohort was too small and the follow-up time was too short to allow precise determination of vaccine effectiveness.

**Keywords:** COVID-19, SARS-CoV-2, Vaccine effectiveness, Breakthrough infection, General practice

## Introduction

Vaccines have saved more lives than any other health intervention in the last century. The World Health Organization estimated that more than two million deaths a year are averted by immunization programs around the world, but there may have been many more during the time of the coronavirus disease (COVID-19) pandemic [1].

The theoretical efficacy of a vaccine is measured in a controlled clinical trial. No vaccine is approved if its theoretical efficacy rate is not greater than 50%. Vaccine effectiveness (VE) measures how well vaccination protects people from infection, symptomatic disease, hospitalizations, and deaths. VE is generally measured through observational studies specially designed to estimate the protection of vaccination under "real world" conditions [2]. Actual effectiveness may differ from theoretical efficacy measured in a trial [3].

Until December 20, 2021, the European Commission (EC) had authorized four vaccines: Comirnaty, from Pfizer/BioNTech, Modern vaccine, AstraZeneca vaccine, and Janssen/Johnson &

Johnson vaccine. Evidence from vaccine deployment programs has shown that COVID-19 vaccines are highly effective against serious illness, hospitalization, and death. Therefore, COVID-19 infection can be prevented with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines [4-7]. However, the ways of reporting the effectiveness of COVID-19 vaccines vary widely depending on the date of application of the last dose, the variant in question, the type of patients in which it is applied (for example, immunocompromised vs. immunocompetent ), according to age or the type of effect to be measured, be it infections, hospitalizations or mortality [1].

On the other hand, although COVID-19 vaccines offer great protection, it takes some time to develop. It is necessary to receive all the necessary vaccine doses to obtain total immunity. With the two-dose regimens, the first dose confers only partial protection and it is the second dose that increases protection. The maximum level of immunity is reached a few weeks after the second dose. It is recognized that the vaccines only confer maximum protection of 1 to 4 weeks after the last necessary dose [8-13]; therefore, there is a diversity of opinion regarding how many days it takes to achieve immunity with each COVID-19 vaccine.

Each of four vaccines approved by the EC, AstraZeneca, Pfizer, Moderna and Janssen, have their necessary period to achieve complete immunity. Pfizer's is the fastest of all the vaccines that require two doses, since 7 days after receiving the second dose (21 days after the first) patient will already be immunized; in total 28 days to achieve complete immunity. That of AstraZeneca with an interval between doses of 10-12 weeks, from 15 days after the second dose is around 80%, the greater effectiveness of the vaccine; that is, immunity with AstraZeneca would be achieved around 111 days after the first dose. With the Moderna vaccine, immunity would be achieved 14 days after the second dose. The interval between the first and the second dose of Moderna is 28 days, so 42 days after the first dose one would be immunized. Regarding the Jansen vaccine, which is the only one of all the vaccines that only requires a single dose, immunity would be achieved 14 days after administration [14].

Furthermore, although SARS-CoV-2 vaccines provide protection against hospitalization and death from COVID-19 for at least six months, breakthrough infections have increased with decreased immunity and the spread of the delta and omicron variants in the summer and winter of 2021 [15,16]. Studies clearly established that vaccine efficacy against infection and symptomatic disease declines over time, so additional doses of vaccine (boosters) may be beneficial [17].

Booster vaccinations enhance immunity against SARS-CoV-2 variants of concern [18]. But, the effectiveness of the booster also tends to decrease over time. For the two-dose regimens of the messenger RNA (mRNA) vaccines BNT162b2 (30 µg per dose) and mRNA-1273 (100 µg per dose), the vaccine effectiveness against COVID-19 was 94.5% and 95.9%, respectively, at 2 months from the first dose and decreased to 66.6% and 80.3%, respectively, at 7 months. For the one-dose regimen of Ad26.COV2.S (5×10 10 viral particles), the efficacy against COVID-19 was 74.8% at 1 month and decreased to 59.4% at 5 months [19-22]. All this makes continuous monitoring of the effectiveness of the vaccines necessary; Real-world data is needed to guide appropriate health policies [13,23-26].

In this context, we present this study, where we estimate the relative effectiveness of the COVID-19 vaccine against symptomatic disease, presumably caused, based on the time period studied, by delta and especially omicron variants, after two doses (primary immunization) of the vaccine, plus homologous or heterologous booster doses < 29 vs. >29 days.

## Material and Methods

An observational, longitudinal and prospective study of COVID-19 breakthrough infections in vaccinated people with Vaccine Booster 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 [27].

### Objective of the study

A. To evaluate the relative vaccine booster effectiveness (VBE) between <29 days and >29 days.

B. To compare the cases of COVID-19 breakthrough infections in vaccinated people with vaccine booster with a time of <29 days vs. ≥ 29 days days from booster to infection diagnosis.

### Criteria for inclusion and exclusion of participants

The methodology of the study has already been published previously [28]. Only cases of patients fully vaccinated with two doses, plus booster, were included.

**1. To consider a person as fully vaccinated (primary vaccination), it was required** [29]:

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.

**2. Definition of homologous or heterologous booster**

Currently, the EC has authorized four vaccines: Comirnaty, from Pfizer/BioNTech, authorized December 21, 2020; Moderna vaccine, authorized on January 6, 2021; AstraZeneca vaccine, authorized on January 29 and Janssen/Johnson & Johnson vaccine, authorized on March 11, 2021. These four vaccines are currently available in Spain; all of them have been approved by the European Medicines Agency. These vaccines have been shown to be highly effective in preventing mild to severe COVID-19 [29]. The original BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), mRNA-1273, and ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca) regimens were homologous induction and booster regimens, whereas the original Ad26. COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine) was a single injection regimen [30].

As of November 23, 2021, in Castilla La Mancha, the region where the study was carried out, booster doses against COVID-19 with mRNA vaccines began 6 months after completion of the vaccination schedule and after 3 months in case of having received a dose of the Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson 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 Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine) as primary vaccination and those with a homologous schedule of Vaxzevria as primary vaccination (first and second dose of Vaxzevria, from AstraZeneca), followed by people aged between 79 to 70 years old, from 69 to 65 years old, 64 to 60 years old, 59 to 50 and 49 to 40 years old, etc. The booster dose was administered with mRNA vaccines (0.3 ml of Comirnaty or 0.25 ml of Spikevax – half the usual dose in primary vaccination) [31,32].

-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 incomplete regimen (in vaccines that require two doses as primary vaccination) the regimen was completed first with mRNA vaccine (0.3 ml of BNT162b2 mRNA vaccine [Comirnaty, Pfizer / BioNTech] or 0.5 ml of mRNA- 1273 vaccine [Spikevax, formerly COVID-19 Vaccine Moderna]). The booster dose (0.3 ml Comirnaty or 0.25 ml Spikevax) 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 Comirnaty or 0. 25 ml of Spikevax) 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 (Comirnaty or Spikevax), and from 3 months if it was an adenovirus vector vaccine (ChAdOx1 nCoV-19 vaccine [Vaxzevria, Oxford / AstraZeneca] or Ad26.COV2.S vaccine [Janssen vaccine; Johnson & Johnson vaccine]) [31,32].

3. To consider a person completely vaccinated with the booster, it was required:

For the data in this study, all COVID-19 cases in people fully vaccinated with the booster were included, regardless of time to COVID-19 diagnosis.

All possibilities of reinforcement were considered:

-Full homologous booster dose:

A. 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with Pfizer-BioNTech booster

B. 2 doses of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) with Moderna booster

-The 6 possible combinations of heterologous booster doses:

A. 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with mRNA-1273 vaccine booster (Spikevax, formerly COVID-19 Vaccine Moderna)

B. 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with booster of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna)

C. 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

D. 1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with mRNA-1273 vaccine booster (Spikevax, formerly COVID-19 Vaccine Moderna)

E. 1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

F. 2 doses of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

**3. 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 in the consultation. 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 [29]. The onset date of a confirmed case was defined as the date of the first appearance of self-reported clinical symptoms [31]. The onset date for an asymptomatic carrier was defined as the date a positive COVID-19 PCR test was obtained [33]. 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 [34].

**Calculation of VBE** [35-37]

We calculated the VBE, which was estimated as a percentage, as follows:

1-[Cases with vaccine booster shot ≥ 29 days / Cases with vaccine booster shot <29 days] × 100

**Collected variables**

The following variables were collected:

-Primary case or secondary case

-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" [38], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [39]

-Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [40,41]

-If they were Health Care Workers

-Problems in the family context and low-income household based on the genogram and in the experience of the GP for their continuity of care and knowledge of the family (genogram is a schematic model of the structure and processes of a family, which included the family structure, life cycle and family relational patterns. It was understood that "complex" genograms present families with psychosocial problems) [42-45]

-Number of family members

-Ethnic minority

-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 29 December and the Janssen / Johnson & Johnson vaccine, authorized on March 11. In Spain, these four vaccines are currently available, all of which have been approved by the European Medicines Agency) [30]

**Sample size**

The sample size was calculated for two unpaired groups, with a Two-sided Confidence Level (1-alpha) of 95%, Power (% probability of detection) of 80%, Ratio of controls per case of 2:1, Proportion of COVID-19 with exposure to 2 doses of Pfizer-BioNTech plus mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster >29 days of 70%, and proportion of COVID-19 with exposure to 2 doses of Pfizer-BioNTech plus mRNA- 1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster <29 days of 40%, shows a total sample size (Fleiss) of 95 people (32 and 63, respectively) [46].

**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

Forty-six cases were included, 28 cases of COVID-19 breakthrough infections with booster shot <29 days (61%), with a mean time from booster to COVID-19 of 12 days (1-25 days) and 18 cases with booster ≥29 days (39%), with a mean time from booster to COVID-19 of 50 days (29-84 days).

COVID-19 cases with booster shot ≥ 29 days differed statistically from those with vaccine booster shot <29 days in that they had shorter duration of symptoms, were more socio-health workers, and had more sick leave. No statistically significant differences were found in symptoms and chronic diseases in COVID-19 breakthrough infections

≥ 29 vs. <29 days after booster. There were no differences in the proportions of cases with homologous or heterologous booster doses. COVID-19 cases with booster shot ≥ 29 days had been more vaccinated with 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) plus booster of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), and less vaccinated with 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) plus mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster, but in both cases without statistical significance **(Table 1, Table 2, Table 3, Table 4)**.

Relative VBE ≥29 days before infection [1 - (Cases with vaccine Booster shot ≥ 29 days) / (Cases with vaccine Booster shot <29 days) x 100] was 36%. No VBE found with shot <29 days vs. booster shot ≥29 days **(Table 5)**.

**Table 1:** COVID-19 breakthrough infections < 29 vs. ≥ 29 days after booster.

| VARIABLES | COVID-19 BREAKTHROUGH INFECTIONS <29 DAYS AFTER BOOSTER N=28 | COVID-19 BREAKTHROUGH INFECTIONS ≥ 29 DAYS AFTER BOOSTER N=18 | TOTAL COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PEOPLE WITH VACCINE BOOSTER N=46 | STATISTICAL SIGNIFICANCE VACCINE BOOSTER < 29 vs. ≥ 29 DAYS |
|---|---|---|---|---|
| Age in years (Arithmetic mean ± Standard deviation; Range) | 54.14 ± 11.90 (32-72) | 53.16 ± 16.26 (26-90 years) | 53.76 ± 13.61 (26-90 years) | t=0.2349. p=.407688. |
| ≥ 65 years | 9 (32) | 4 (22) | 13 (28) | X2=0.5319. p=.465819. NS |
| ≤ 45 years | 7 (25) | 5 (28) | 12 (26) | X2 with Yates correction=0.0181. p=.892921. NS |
| Women | 14 (50) | 13 (72) | 27 (59) | X2=2.2318. p=.1352. NS |
| Previous symptomatic COVID-19 | 3 (11) | 4 (22) | 7 (15) | Fisher exact test =0.4069. NS |
| Time in days from Booster to COVID-19 (Arithmetic mean ± Standard deviation; Range) | 12.67 ± 7.57 (1-25 days) | 50.16 ± 15.10 (29-84 days) | 27.34 ± 21.51 (1-84 days) | NR |
| Symptomatic COVID-19 in breakthrough infections in vaccinated booster people | 26 (93) | 15 (83) | 41 (89) | Fisher exact test=0.3655. NS |
| Duration of symptoms in days of COVID-19 in breakthrough infections in vaccinated people (Arithmetic mean ± Standard deviation; Range) | Symptomatic N=26 6.42 ± 3.31 (3-15 days) | Symptomatic N=15 4.80 ± 2.04 (2-10 days) | Symptomatic N= 41 5.82 ± 2.99 (2-15 days) | t=1.71378. p=.047254. The result is significant at p<.05. |
| COVID-19 breakthrough infections in vaccinated people with severity moderate and severe | 1 (Pneumonia) (4) | 0 | 1 (2) | Fisher exact test=1. NS |
| Social-occupancy class of patients (people with some type of labor specialization) | 14 (50) | 11 (61) | 25 (53) | X2=0.5452. p=.460292. NS |
| Health Care Workers with COVID-19 breakthrough infections in vaccinated people | 4 (14) | 9 (50) | 13 (28) | X2=6.8931. p=.008653. Significant at p<.05. |
| Sick leave for COVID-19 breakthrough infections in vaccinated people | 8 (29) | 12 (67) | 20 (43) | X2=6.4703. p=.010969. Significant at p<.05. |

| | | | | |
|---|---|---|---|---|
| Ethnic minority with COVID-19 breakthrough infections in vaccinated people | 1 (4) | 2 (11) | 3 (6) | Fisher exact test=0.5518. NS |
| Complex family with COVID-19 breakthrough infections in vaccinated people | 4 (14) | 0 | 4 (9) | Fisher exact test=0.1442. NS |
| Chronic diseases presence in COVID-19 breakthrough infections in vaccinated people | 22 (79) | 13 (72) | 35 (76) | X2 with Yates correction=0.0192. p=.889788. NS |
| ( ): Denotes percentages; NS: Not significant; NR: Not Relevant | | | | |

**Table 2:** Symptoms in COVID-19 breakthrough infections < 29 vs. ≥ 29 days after booster.

| **SYMPTOMS * ACCORDING TO WHO, ICD-10 GROUPS** | **COVID-19 BREAKTHROUGH INFECTIONS <29 DAYS AFTER BOOSTER N=28** | **COVID-19 BREAKTHROUGH INFECTIONS ≤ 29 DAYS AFTER BOOSTER N=18** | **TOTAL COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PEOPLE WITH VACCINE BOOSTER N=46** | **STATISTICAL SIGNIFICANCE VACCINE BOOSTER < 29 vs. ≥ 29 DAYS** |
|---|---|---|---|---|
| General (discomfort, asthenia, myalgia, fever, arthralgias) | 20 (30) | 14 (32) | 34 (31) | X2=0.0284. p=.866219. NS |
| Respiratory (cough, dyspnea, chest pain) | 15 (23) | 9 (20) | 24 (22) | X2=0.0799. p=.777376. NS |
| ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis) | 24 (36) | 17 (39) | 41 (37) | X2=0.0583. p=.809164. NS |
| Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain) | 3 (4) | 0 | 3 (3) | Fisher exact test=0.2734. NS |
| Neurological (headache, dizziness, mental confusion -brain fog) | 4 (6) | 4 (9) | 8 (7) | X2 with Yates correction is 0.0506. p=.822106. NS |
| Total symptoms* | 66 (100) | 44 (100) | 110 (100) | --- |
| ( ): Denotes percentages; NS: Not Significant; *Patients could have more than one symptom. The percentages are over the total of symptoms | | | | |

**Table 3:** Chronic diseases in COVID-19 breakthrough infections < 29 vs. ≥ 29 days after booster.

| **CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS** | **COVID-19 BREAKTHROUGH INFECTIONS <29 DAYS AFTER BOOSTER N=28** | **COVID-19 BREAKTHROUGH INFECTIONS ≤ 29 DAYS AFTER BOOSTER N=18** | **TOTAL COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PEOPLE WITH VACCINE BOOSTER N=46** | **STATISTICAL SIGNIFICANCE VACCINE BOOSTER < 29 vs. ≥ 29 DAYS** |
|---|---|---|---|---|
| -II Neoplasms | 3 (3) | 2 (4) | 5 (3) | Fisher exact test=1. NS |
| -III Diseases of the blood | 0 | 1 (2) | 1 (1) | Fisher exact test =0.3542. NS |
| -IV Endocrine | 14 (15) | 10 (19) | 24 (16) | X2=0.4918. p=.483107. NS |
| -V Mental | 8 (9) | 0 | 8 (6) | Fisher exact test=0.0506. NS |

| | | | | |
|---|---|---|---|---|
| -VI-VIII Nervous and Senses | 11 (12) | 3 (6) | 14 (10) | X2=1.3266. p=.249413. NS |
| -IX Circulatory system | 9 (10) | 9 (18) | 18 (12) | X2=1.9127. p=.166662. NS |
| -X Respiratory system | 6 (6) | 2 (4) | 8 (6) | Fisher exact test=0.7123. NS |
| -XI Digestive system | 13 (14) | 5 (10) | 18 (12) | X2=0.5248. p=.4688. NS |
| -XII Diseases of the skin | 6 (6) | 2 (4) | 8 (6) | Fisher exact test=0.7429. NS |
| -XIII Musculo-skeletal | 10 (11) | 7 (14) | 17 (12) | X2=0.2796. p=.596981. NS |
| -XIV Genitourinary | 13 (14) | 10 (19) | 23 (16) | X2=0.7777. p=.377842. NS |
| TOTAL chronic diseases* | 93 (100) | 51 (100) | 144 (100) | --- |
| ( ): Denotes percentages; * Patients could have more than one chronic disease. The percentages are over the total of chronic diseases. | | | | |

**Table 4:** Vaccine type in COVID-19 breakthrough infections <29 vs. ≥ 29 days after booster.

| **VACCINE TYPE** | **COVID-19 BREAKTHROUGH INFECTIONS <29 DAYS AFTER BOOSTER N=28** | **COVID-19 BREAKTHROUGH INFECTIONS ≤ 29 DAYS AFTER BOOSTER N=18** | **TOTAL COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PEOPLE WITH VACCINE BOOSTER N=46** | **STATISTICAL SIGNIFICANCE VACCINE BOOSTER < 29 vs. ≥ 29 DAYS** |
|---|---|---|---|---|
| HOMOLOGOUS booster dose | 4 (14) | 3 (17) | 7 (15) | Fisher exact test=1. NS |
| 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) booster | 3 (11) | 2 (11) | 5 (11) | Fisher exact test=1. NS |
| 2 doses of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster | 1 (4) | 1 (5) | 2 (4) | Fisher exact test=1. NS |
| HETEROLOGOUS booster dose | 24 (86) | 15 (84) | 39 (85) | Fisher exact test=1. NS |
| 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster | 12 (43) | 13 (72) | 25 (54) | X2=3.808. p=.05101. NS |
| 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster | 9 (32) | 1 (6) | 10 (22) | X2 with Yates correction=3.1237. p=.077161. NS |
| 1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster | 2 (7) | 1 (6) | 3 (7) | Fisher exact test=1. NS |

| | | | | |
|---|---|---|---|---|
| 2 doses of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) with BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) booster | 1 (4) | 0 | 1 (2) | Fisher exact test=1. NS |
| TOTAL | 28 (100) | 18 (100) | 46 (100) | --- |
| ( ): Denotes percentages | | | | |

**Table 5:** Relative vaccine booster effectiveness > 29 vs. <29 days.

| Cases with vaccine booster shot <29 days | Gross incidence rate | Cases with vaccine booster shot ≥ 29 days | Gross incidence rate |
|---|---|---|---|
| 28/46 | 61% | 18/46 | 39% |
| Vaccine booster effectiveness ≥ 29 days = 1 - [COVID-19 cases incidence with vaccine Booster ≥ 29 days / COVID-19 cases incidence with vaccine Booster <29 days] × 100 = 36% | | | |

## Discussion

Assessing EV in the real world for any disease is challenging, but even more so with COVID-19 because deployment of vaccines has occurred at unprecedented speed in divergent geographic and social settings. Furthermore, these vaccines were developed during the early period of the pandemic, when SARS-CoV-2 variants were not well understood [7]. On the other hand, what does it mean that a vaccine is, for example, 90% effective in preventing COVID-19? This value does not mean that 90% of people are protected and 10% can get sick; it also does not mean that out of every 10 vaccinated, 1 will contract the disease. It means that the probability of developing COVID-19 in vaccinated people decreases by 90% compared to unvaccinated people [12,47]. In simple terms, "efficacy" and "effectiveness" are synonymous, but when used in a medical context, a distinction is often made between the efficacy of an intervention and its effectiveness, the former interpreted under 'ideal' conditions and the latter under 'real' world conditions. However, the distinction is based on having to define "ideal" and "real world" conditions if, in fact, a satisfactory definition can be made for both [48,49].

Vaccines have shown moderate to no effectiveness in reducing symptomatic infections. And in addition, humoral immunity is lost over time, so those who still receive a third dose in November and December 2021, could find themselves without "quality antibodies" to face a new wave. Initial protection, for symptomatic infection after vaccination, is low. Six months after the second dose, it is estimated between 0 and 10%; And probably between 30 to 50%, after the third dose, or even less in some countries. But fortunately, immunity has been maintained for severe effects and mortality [50].

Although considerations for boosting COVID-19 vaccine immune responses are surprisingly controversial, several existing non-COVID-19 vaccines have routine three-dose regimens to provide maximum efficacy [1,51]. The omicron variant of SARS-CoV-2 swept the world in the last months of 2021. This new wave occurred despite very high levels of vaccination coverage in some countries and the prevalence of the variant highly transmissible delta. However, studies indicate that people who receive a booster dose of the mRNA vaccine have greater neutralization of the omicron variant [20,52-57].

Therefore, the importance of a third dose of vaccine is clear, due to the greater neutralization efficacy against the omicron variant after the third dose than after the second dose; however, even with three doses of vaccine, neutralization against the omicron variant was less than against the delta variant, and the durability of the effect of the third dose of the COVID-19 vaccine remains to be determined [58,59]. In other words, the evidence available today confirms that the effectiveness of the vaccine in reducing symptomatic infection in times of the omicron variant has fallen below 50%, but is partially recovered with an additional dose. The effectiveness in reducing hospitalizations and deaths has fallen less steeply for two doses of any vaccine, but an additional dose can restore sustained immunity [23]. Different studies report the EV for symptomatic infection of different vaccines approximately between 45% and 60%, a drop in efficacy of around 10%, to recover effectiveness between 60-75% with an additional dose. However, these studies failed to identify how long after the last dose they measured effectiveness. And on the other hand, they report that it later drops to 40-65% [15,23,60-62]. As the omicron outbreaks spread, boosters were used to increase levels of neutralizing antibodies, curbing cases and easing strain on hospitals. But the concern is that the boosters do not block infections for long [63] and in assessing their results, the target population, the preparation interval, the durability of the booster, the level of circulation of SARS CoV-2 and global inequality in access to vaccines [4].

Regarding VBE, it has been reported that it was 93% for people vaccinated 6 months earlier [64]. A trial, prior to the sequencing of the omicron variant, detected an increase in immunity after the third injection in those treated with AstraZeneca or Pfizer,

although the results are very different depending on the dose combination [65]. Heterologous boosting resulted in more robust immune responses than homologous boosting and might enhance protection [18,57,66]. Six different COVID-19 vaccines have been reported to be safe and effective to use as booster doses in people who previously received the Oxford AstraZeneca or Pfizer BioNTech vaccines, but the antibody boost they provide varies substantially: the Moderna vaccine produced the largest antibody response [67,68]. At 29 days after the booster immunization, each of nine possible booster combinations increased binding and neutralizing antibody titers to comparable levels [18].

But, for VBE studies only data collected over a relatively short period of time after the booster dose are available, thus providing no information on the durability of response. A recent analysis of the durability of antibody responses after primary and booster immunizations of mRNA-1273 suggests greater durability after the boost; however, the response against Omicron decreased 6.3-fold during the same 6-month time period after the boost [69]. Our study has this same limitation of a relatively short period of time after the booster dose, given that the first boosters were placed in healthcare personnel from November 2021.

In our study, VBE ≥ 29 days for symptomatic infection in relation to <29 days was 36% in a period where the omicron variant predominated. This result is lower than previously published. It has been reported that among those who received two doses of AstraZeneca vaccine, a Pfizer or Moderna vaccine booster was 60% effective in preventing symptomatic disease 2 to 4 weeks after injection. But after 10 weeks, the Pfizer booster was 35% effective and the Moderna booster was 45% effective. Among those given three doses of Pfizer, the effectiveness of the vaccine was 70% about a week after the booster, but fell to 45% after 10 weeks. At the same time, those who received an initial two-dose series of the Pfizer vaccine and then a Moderna booster appeared to be 75% effective up to 9 weeks [70,71]. In our study, the heterologous booster predominated in both groups (85%; 86% in booster <29 days and 84% in booster ≥ 29 days).

## Limitations and Strengths of the Study

1. Non-randomized design is a limitation for the generalization of the results, 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.

2. Sample was small, and did not get adequate power; so, the statistical significance of some variables could be hidden, and an imprecise determination of vaccine effectiveness may be obtained.

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 people

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

5. Estimates of omicron variant VE were based on infections that occurred during periods when the omicron variant was in the majority, but genomic surveillance and classification were not performed.

6. VBE was studied only for 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.

## Conclusion

COVID-19 vaccines showed excellent efficacy until the end of December 2021 when the world registered the highest number of infections related to the Omicron variant. On the other hand, it is not clearly known how long after the vaccine booster shot can it be considered protective, nor since when the highest VBE is obtained. In the context of the general medicine clinic in Toledo, Spain, from December 1, 2021 to February 28, 2022, in the peak period of omicron infections, the relative homologous or heterologous VBE after a period of ≥ 29 days, was 36% against symptomatic disease. No relative VBE was found <29 days after booster, although our cohort was too small and the follow-up time too short to allow precise determination of vaccine effectiveness.

## References

1. Roa R. [Is it useful to report the number needed to vaccinate?] La biblioteca de Springfield; 30 de marzo. 2022. https://rubenroa.blogspot.com/2022/03/es-util-reportar-el-numero-necesario.html

2. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. COVID-19 Vaccines are Effective. 2021. Last Updated Dec. 23, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/index.html

3. WHO Vaccine efficacy, effectiveness and protection. 2022. https://www.who.int/es/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection

4. Sablerolles RS, Rietdijk WJ, Goorhuis A, Postma DF, Visser LG, Geers D, et al. Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming. N Engl J Med. 2022.

5. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med. 2021;27:2032-40.

6. Rearte A, Castelli JM, Rearte R, Fuentes N, Pennini V, Pesce M, et al. Effectiveness of rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines for risk of infection with SARS-CoV-2 and death due to COVID-19 in people older than 60 years in Argentina: a test-

negative, case-control, and retrospective longitudinal study. Lancet. 2022;399(10331):1254-64.

7. Mills EJ, Reis G. Evaluating COVID-19 vaccines in the real world. Lancet. 2022;399(10331):1205-6.

8. Demonbreun AR, Sancillo A, Vaught LA, Reiser NL, Pesce L, McNally EM, et al. Antibody titers before and after booster doses of SARS-CoV-2 mRNA vaccines in healthy adults. medRxiv2021.11.19.21266555.

9. MUSC Health. COVID-19 Vaccine Frequently Asked Questions (FAQ). 2022. https://muschealth.org/vaccine-faq

10. Andrews N, Stowe J, Kirsebom F, Gower C, Ramsay M, Lopez Bernal J. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against COVID-19 related symptoms in England: test negative case-control study. MedRxiv 2021.11.15.21266341.

11. Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. Lancet. 2021;2(7): 279-80.

12. Anonymous. What does it really mean for a vaccine to be 90% effective? the conversation: March 20. 2021. https://theconversation.com/que-significa-realmente-que-una-vacuna-tenga-una-eficacia-del-90-156710

13. Pérez-Then E, Lucas C, Monteiro VS, Miric M, Brache V, Cochon L, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. Nat Med. 2022;28:481–5.

14. Anonymous. [How many days are needed to achieve immunity with each vaccine?]. El Mundo; Miércoles, 14 julio. 2021. https://www.elmundo.es/ciencia-y-salud/salud/2021/07/08/60e6c4a721efa0d1458b469b.html

15. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. COVID-19 vaccine effectiveness against the Omicron (B. 1.1. 529) variant. N Eng J Med. 2022;386(16):1532-46.

16. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, et al. Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. Clin Infect Dis. 2021;73(9):e2946-e51.

17. Koelle K, Martin MA, Antia R, Lopman B, Dean NE. The changing epidemiology of SARS-CoV-2. Science. 2022;375(6585): 1116-21.

18. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and Heterologous COVID-19 Booster Vaccinations. N Engl J Med. 2022.

19. Rössler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron Variant Neutralization in Serum from Vaccinated and Convalescent Persons. N Eng J Med. 2022.

20. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against COVID-19 by BNT162b2 booster across age groups. N Engl J Med. 2021;385(26):2421-30.

21. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to COVID-19. N Engl J Med. 2021;385:2413-20.

22. Roa R. [Is an additional dose effective?]. La biblioteca de Sprinfield. 2021. https://rubenroa.blogspot.com/2021/12/es-efectiva-una-dosis-adicional.html

23. Roa R. [Three doses with the omicron variant]. La biblioteca de Springfield; 23 de marzo. 2022. https://rubenroa.blogspot.com/2022/03/tres-dosis-con-la-variante-omicron.html

24. Vanshylla K, Tober-Lau P, Gruell H, Münn F, Eggeling R, Pfeifer N, et al. Durability of omicron-neutralising serum activity after mRNA booster immunisation in older adults. The Lancet Infectious Diseases. 2022 Apr 1;22(4):445-6.

25. Wu M, Wall EC, Carr EJ, Harvey R, Townsley H, Mears HV, et al. Three-dose vaccination elicits neutralising antibodies against omicron. Lancet. 2022; 399(10326): 715-7.

26. Castagnoli R, Marseglia GL. Tracing and vaccinating: how to REACT to COVID-19 pandemic. Lancet Resp Med. 2022;10(4):317-18.

27. Turabian JL. [Notebooks of Family and Community Medicine. An introduction to the principles of Family Medicine]. Madrid: Díaz de Santos. 1995. http://www.amazon.co.uk/Cuadernos-medicina-familia-y-comunitaria/dp/8479781920

28.-Turabian JL. Case series of 46 COVID-19 breakthrough infections in vaccinated people with vaccine booster shot. J Community Prev Med. 2022;5(1).

29.-Ministerio de Sanidad. [COVID-19 early detection, surveillance and control strategy. 2021. Updated December 1, 2021]. https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Estrategia_vigilancia_y_control_e_indicadores.pdf

30. Consejería de Sanidad Castilla La Mancha. 2021. https://sanidad.castillalamancha.es/ciudadanos/enfermedades-infecciosas/coronavirus/preguntas-frecuentes-sobre-el-coronavirus-covid-19/campa%C3%B1a-vacunacion

31. [Update 10 Vaccination strategy against COVID-19 in Spain. Recommendations agreed upon in the Public Health Commission after review and proposal made by the Vaccination Program and Registry Report together with the COVID-19 Vaccination Technical Working Group and the COVID-19 Vaccination Working Group in the Child Population December 2021]. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Actualizaciones_Estrategia_Vacunacion/docs/COVID-19_Actualizacion10_EstrategiaVacunacion.pdf

32.-Sistema Nacional de Salud. [Vaccination strategy against COVID-19 in Spain (2021) COVID-19 Vaccination Technical Working Group, of the Presentation of the Vaccination Program and Registry November 2, 2021]. 2021. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Actualizaciones_Estrategia_Vacunacion/docs/COVID-19_Actualizacion9_Modificada_EstrategiaVacunacion.pdf

33. Mao S, Huang T, Yuan H, Li M, Huang X, Yang C, et al. Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. BMC Public Health. 2020;20:1525.

34. Ayoub HH, Tomy M, Chemaitelly H, Altarawneh HN, Coyle P, Tang

P, et al. Estimating protection afforded by prior infection in preventing reinfection: Applying the test-negative study design. medRxiv. 2022 Jan 1.

35. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Guevara M, Fernández-Huerta M, Burgui C, et al. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. Euro Surveill. 2021;26(39):pii=2100894.

36. Snijders BE, van Lier A, van de Kassteele J, Fanoy EB, Ruijs WL, Hulshof F, et al. Mumps vaccine effectiveness in primary schools and households, the Netherlands, 2008. Vaccine. 2012;30(19):2999-3002.

37. de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kassteele J, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Eurosurveillance. 2021;26(31):2100640.

38. Strauss AL. Chronic illness and the quality of life. St Louis: The C.V. Mosby Company. 1984.

39. WHO. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version: 2019. https://icd.who.int/browse10/2019/en

40. Royal Collage of General Practitioners. The Classification and Analysis of General Practice Data. Occasional Paper 26, 1986.

41. Donaldson RJ, Donaldson LJ. Essential Community Medicine. Lancaster: MTP Press. 1983.

42. Turabian JL. Family Genogram in General Medicine: A Soft Technology that can be Strong. An Update. Res Med Eng Sci. 2017;3(1):RMES.000551.

43. Russell LT. Capturing Family Complexity in Family Nursing Research and Practice. J Fam Nurs. 2020;26(4):287-93.

44. Watts C, Shrader E. How to do (or not to do)… The genogram: a new research tool to document patterns of decision-making, conflict and vulnerability within households. Health Policy Plan. 1998;13:459-64.

45. McIlvain H, Crabtree B, Medder J, Stange KC, Miller WL. Using practice genograms to understand and describe practice configurations. Fam Med. 1998;30:490-6.

46. Open Source Epidemiologic Statistics for Public Health. http://www.openepi.com/SampleSize/SSCC.htm

47. Zimmer C, Collins K. What Do Vaccine Efficacy Numbers Actually Mean? The New York Times; 2021 March 3. https://www.nytimes.com/interactive/2021/03/03/science/vaccine-efficacy-coronavirus.html?utm_source=Nature+Briefing&utm_campaign=7de7a692f7-briefing-dy-20210305&utm_medium=email&utm_term=0_c9dfd39373-7de7a692f7-42937943

48. Wald N. Efficacy and effectiveness. J Med Screen. 2021.

49. Olliaro P. What does 95% COVID-19 vaccine efficacy really mean? Lancet. 2021; 21(6): 769.

50. Roa R. La biblioteca de Sprinfield; 1 de abril. 2022. https://rubenroa.blogspot.com/2022/04/otra-ola-con-la-variante-omicron.html

51. Nixon DF, Schwartz RE, Ndhlovu LC. Booster vaccines for COVID-19 vaccine breakthrough cases?. The Lancet. 2022 Mar 26;399(10331):1224.

52. Elliott P, Bodinier B, Eales O, Wang H, Haw D, Elliott J, Whitaker M, Jonnerby J, Tang D, Walters CE, Atchison C. Rapid increase in Omicron infections in England during December 2021: REACT-1 study. Science. 2022 Mar 25;375(6587):1406-11.

53. Dolgin E. Omicron thwarts some of the world's most-used COVID vaccines. Inactivated-virus vaccines elicit few, if any, infection-blocking antibodies — but might still protect against severe disease. Nature. 2022.

54. Richterman A, Scott J, Cevik M COVID-19 vaccines, immunity, and boosters. BMJ. 2021;375:n3105.

55. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. COVID-19 Vaccine Effectiveness in New York State. N Eng J Med. 2022;386:116-27.

56. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of Protection against Mild and Severe Disease by COVID-19 Vaccines. N Engl J Med. 2022.

57. Garcia-Beltran WF, Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. Cell. 2021;185(3):457-66.

58. Nemet I, Kliker L, Lustig Y, Zuckerman N, Erster O, Cohen C, et al. Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. N Engl J Med. 2022;386:492-4.

59. Pajon R, Doria-Rose NA, Shen X, Schmidt SD, O'Dell S, McDanal C, et al. SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination. N Engl J Med. 2022.

60. Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Schommers P, Lehmann C, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. Nature Medicine. 2022;19:1-4.

61. Baum U, Poukka E, Leino T, Kilpi T, Nohynek H, Palmu AA. High vaccine effectiveness against severe COVID-19 in the elderly in Finland before and after the emergence of Omicron. medRxiv2022.03.11.22272140.

62. Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, et al. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA. 2022;327(7):639–651.

63. Watson C. Three, four or more: what's the magic number for booster shots? COVID vaccine boosters are proving a useful tool against Omicron, but scientists say that endless boosting might not be a practical or sustainable strategy. Nature. 2022;602:17-18.

64. Saciuk Y, Kertes J, Stein NS, Zohar AE. Effectiveness of a Third

Dose of BNT162b2 mRNA Vaccine. J Infect Dis. 2022;225(1):30-3.

65. Limón R. [COVID booster shots are safe, but offer variable efficacy]. El País; 03 DIC. 2021. https://elpais.com/ciencia/2021-12-02/las-vacunas-de-refuerzo-contra-la-covid-son-seguras-pero-ofrecen-una-eficacia-variable.html#?rel=mas

66. Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MB, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet. 2022;399(10324):521-9.

67. Mahase E. COVID-19: Antibody boost after third dose varies greatly by vaccine, study finds. BMJ. 2021;375:n3011.

68. Munro AP, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. The Lancet. 2021 Dec 18;398(10318):2258-76.

69.-Shen X. Boosting immunity to Omicron. Nat Med. 2022; 28: 445–6.

70. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing. 2021 December. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf

71. Anthes E Booster protection wanes against symptomatic Omicron infections, British data suggests. The New York Times; 2021 Dec. 23. https://www.nytimes.com/2021/12/23/health/booster-protection-omicron.html