



Relative and Temporal Efficacy of the First and Second Covid-19 Booster Vaccine (3rd And 4th Dose) to Prevent Symptomatic Infection from December 2021 to October 2023 in a General Medicine Office in Toledo (Spain)

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Abstract

Background: The effectiveness of COVID-19 vaccines in preventing serious infection and death is established, but their protection against infection is less certain. Additionally, their effectiveness diminishes over time. Furthermore, the evolution of the effectiveness of different booster doses of the vaccine against COVID-19, to prevent symptomatic infection in real life during the pandemic and the subsequent endemic, is not clearly documented.

Objective: To compare the effectiveness of the 3rd and 4th vaccine boosters against COVID-19 in preventing symptomatic COVID-19 infection during both the pandemic and the subsequent endemic phase.

Methodology: A comparative secondary analysis of the vaccine's effectiveness against symptomatic COVID-19 infection (calculated as: $1 - (\text{COVID-19 cases with vaccine doses} / \text{COVID-19 cases without vaccine dose}) \times 100$) based on a prospective study from December 2021 to October 2023 in a general medicine office was conducted. The first booster dose was administered with monovalent mRNA vaccines, and the second booster with bivalent mRNA vaccines.

Results: From December 2021 to February 2022, the effectiveness of the primer vaccine booster was 60% when administered ≥ 15 days versus < 15 days before infection, and 36% when administered ≥ 29 days versus < 29 days before infection. From October 2022 to February 2023, the effectiveness of the vaccine's 4th dose was 84%. From October 2022 to October 2023, the effectiveness of the 4th dose of bivalent mRNA vaccine in preventing reinfections was 30%.

Conclusion: In the general practice setting in Toledo, Spain, the effectiveness of the first booster with mRNA vaccines against SARS-CoV-2 primary infection and symptomatic COVID-19 waned over time, but protection remained high with the second bivalent booster. However, the booster vaccine's effectiveness is more modest in preventing symptomatic reinfections. Overall, completing the booster vaccination is worthwhile.

Keywords

COVID-19, SARS-CoV-2, Vaccine Effectiveness, General Practice, Secondary Analysis

Introduction

The objective of evaluating vaccine effectiveness (VE) against coronavirus disease 2019 (COVID-19) is to generate solid and timely evidence through observational studies in real conditions that support vaccination policy. VE can measure the degree of protection that vaccination provides to prevent infections, symptomatic diseases, hospitalizations, and deaths. The theoretical VE is measured in a controlled clinical trial [1]. No vaccine is approved if its theoretical efficacy rate is not greater than 50%. However, actual effectiveness may differ from theoretical efficacy measured in a trial [2]. Several concepts of VE measurement can be distinguished: comparing the frequency of health outcomes in vaccinated and unvaccinated people (absolute efficacy), comparing people who have received one schedule or type of vaccine with those who received another schedule or type of vaccine (relative effectiveness), or comparing people who received more doses with those who received fewer doses (incremental effectiveness) [3].

Regarding the incremental effectiveness of vaccines, it is necessary to take into account that all viruses change over time, and so does severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. Most changes have little effect on the properties of the virus. However, some changes may influence its ease of spread, the severity of the associated disease, or the effectiveness of vaccines, treatment medications, diagnostic means, or other public and social health measures. In the beginning, it was the Wuhan virus. Forecasts about the mutation of the virus began to materialize when it was reported that since February 2020, a variant called D614G had begun to spread in Europe that contained a point mutation in the Spike protein of the virus, responsible for recognizing human cells and infecting them. Numerous more strongly mutated variants began to derive from this variant. Thus, there were the Alpha, Beta, Gamma, Delta, and Omicron variants. Beta and Gamma were in the minority, but they already suggested immune evasion by escaping the action of neutralizing antibodies. Alpha was explosive, 50% more transmissible, and the same thing happened with Delta, which also seemed to have surpassed the

previous ones in virulence. And finally, Omicron arrived, which has swept away all the others and presented several subvariants, which have been less dangerous as they more easily infect the upper respiratory tract but less the lung tissue [4,5].

The main objective of vaccination is to reduce the severity and mortality from COVID-19, especially protecting those most vulnerable groups [6]. And the effectiveness of COVID-19 vaccines in preventing serious infection and saving lives, including mRNA vaccines, booster vaccines, and bivalent vaccines, is well established [2,7-14]. However, marked decreases over time in VE have been found for SARS-CoV-2 infections for both the primary and booster series [15]. Furthermore, there is less data on VE regarding the prevention of infections [16]. In any case, it is important to measure the relative and incremental VE, since this data can help those responsible for formulating vaccination policies in decision-making [1-3].

In this scenario, a secondary analysis of previously published data is presented, to compare the relative and gradual VE of the first and second booster vaccines against COVID-19 to prevent symptomatic infection during the pandemic and the subsequent endemic, based on a prospective study from December 2021 to October 2023, in a general medicine office.

Material and Methods

Study Design, Methodology, Location, and Duration:

A secondary analysis was conducted on previously published data obtained from an observational, longitudinal, and prospective study of adult patients with COVID-19 infections from December 2021 to October 2023, in a general medicine office in Toledo, Spain, to compare the effectiveness of the first and second vaccine boosters against symptomatic COVID-19 infection. VE was calculated as a percentage using the formula: $1 - [(Covid-19 \text{ cases with vaccine dose} / Covid-19 \text{ cases without vaccine dose}) \times 100]$ [17-20].

The GP office serves a list of 2,000 patients aged > 14 years. In Spain, general practitioners (GPs) provide care for individuals aged > 14 years, with exceptions

granted upon request by the child's family and accepted by the GP. GPs in Spain operate within the National Health System, which is publicly funded, serving as the primary point of contact for all patients within the system. Each individual is assigned a GP [21]. While the study methodology has been previously published [22-25], certain aspects are reiterated here to enhance comprehension of the present study.

Objective of the Study:

The objective was to compare the effectiveness of the two COVID-19 vaccine boosters (third and fourth doses) in preventing symptomatic infections during the pandemic and the subsequent endemic.

Diagnosis of COVID-19:

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing [26] performed in health services or at home by the patient themselves.

Vaccines Used:

Pfizer-BioNTech, AstraZeneca, Moderna, and Janssen vaccines were used in the first doses. The first booster dose was administered with Moderna and Pfizer-BioNTech mRNA vaccines, and the second booster with Moderna and Pfizer-BioNTech's bivalent COVID-19 vaccines [26]. 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 completing the vaccination schedule and after 3 months in case of having received a dose of Janssen/Johnson & Johnson vaccine. This first booster dose was administered with mRNA vaccines (0.3 ml of Pfizer-BioNTech or 0.25 ml of Moderna vaccine – half the usual dose in primary vaccination). Any mRNA vaccine was used to administer the booster dose, regardless of the vaccine used in the primary vaccination. In people with an incomplete regimen (in vaccines that require two doses as primary vaccination), the regimen was completed first with mRNA vaccine (0.3 ml of Pfizer-BioNTech or 0.5 ml of Moderna vaccine) [27,28]. In the patients included in the study, bivalent Pfizer-BioNTech (Original/Omicron BA.1) and bivalent Pfizer-BioNTech (Original/Omicron BA.4-5) or bivalent Moderna vaccine (Original/Omicron BA. 1) and bivalent Moderna vaccine (Original/Omicron BA.4-5) were used in the second booster dose (4th dose). The vaccination campaign began in Spain on September 26, 2022 [29-33].

Results

From December 2021 to February 2022, 31 cases of primary COVID-19 infection with a vaccine booster shot ≥ 15 days and 15 cases with a vaccine booster

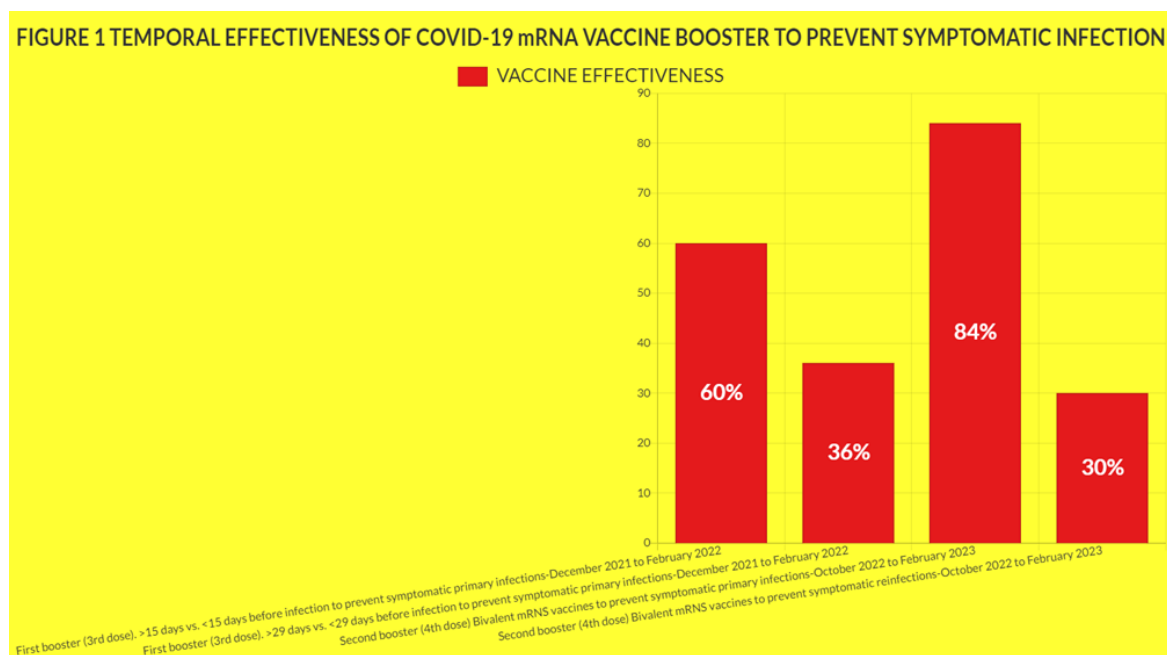


Fig-1: Temporal Effectiveness of Covid-19 MRNA Vaccine Booster to Prevent Symptomatic Infection

shot < 15 days before infection were included, with the relative vaccine booster effectiveness for a vaccine booster shot ≥ 15 days of 60%. During the same period, 18 cases of primary COVID-19 infection with a vaccine booster shot ≥ 29 days and 28 cases with a vaccine booster shot < 29 days before infection were included, with the relative vaccine booster effectiveness for a vaccine booster shot ≥ 29 days of 36%. From October 2022 to February 2023, 5 cases of primary COVID-19 infection in vaccinated individuals with the 4th dose of the COVID-19 vaccine and 31 cases in vaccinated individuals without the 4th dose were included, with the effectiveness of the 4th dose of the COVID-19 vaccine being 84%. Furthermore, from October 2022 to October 2023, 5 cases of reinfection with the 4th dose of bivalent COVID-19 vaccine and 7 cases of reinfection without the 4th dose of the COVID-19 vaccine were included, with the 4th dose of bivalent mRNA VE to prevent reinfections being 30% (see Table-1, Fig-1).

Discussion

Main Findings:

In the general practice setting in Toledo, Spain, from February 2021 to October 2023, boosters with mRNA vaccines showed acceptable effectiveness against primary infection of symptomatic covid-19, but that appears to decrease over time (and is replenished with the second booster) and a more modest protection to prevent reinfections (VE in 2021 60%-36%; In 2022 84%, and in 2022-2023 to prevent reinfections was 30%).

To adequately assess these results, it is necessary to contextualize them within several facts:

A) In Spain, as in other countries after the health alert ceased, since March 2022, covid-19 cases were no longer measured in the general population and monitoring was restricted to those over 60 years of age [34,35]. However, because GP are the gateway for all patients to the system, and each person is assigned a

Table-1: Temporal Effectiveness of Covid-19 mRNA Vaccine Booster to Prevent Symptomatic Infection

Periods of Time	Virus Variant	Vaccine Type	Epidemiological Evaluation	Incidence Rate with Booster	Incidence Rate without Booster	Vaccine Effectiveness
From December 2021 to February 2022	Delta and especially Omicron variants	First booster. mRNA vaccines (0.3 ml of Pfizer-BioNTech or 0.25 ml of Moderna – half the usual dose in primary vaccination)	3rd dose. Homologous or heterologous booster doses <15 days vs. ≥ 15 days before infection [after two doses (primary immunization) of the vaccine)] to prevent primary symptomatic infections	33% (Booster <15 days before infection)	67% (Booster ≥ 15 days before infection)	60%
From December 2021 to February 2022	Delta and especially Omicron variants	First booster. mRNA vaccines (0.3 ml of Pfizer-BioNTech or 0.25 ml of Moderna – half the usual dose in primary vaccination)	3rd dose. Homologous or heterologous booster doses <29 vs. ≥ 29 days after two doses (primary immunization) of the vaccine) to prevent primary symptomatic infections	61% (Booster <29 days before infection)	39% (Booster ≥ 29 days before infection)	36%
From October 2022 to February 2023	Omicron lineages	Second booster. Bivalent Pfizer-BioNTech, Original/Omicron BA.1 and bivalent Pfizer-BioNTech, Original/Omicron BA.4-5 or bivalent Moderna, Original/Omicron BA.1 and bivalent Moderna, original/omicron BA.4-5	4th dose Moderna and Pfizer-BioNTech's bivalent vaccines to prevent primary symptomatic infections	14%	86%	84%
From October 2022 to October 2023	Omicron lineages	Second booster Moderna and Pfizer-BioNTech's bivalent vaccines	4th dose Moderna and Pfizer-BioNTech's bivalent covid-19 to prevent symptomatic reinfections	41%	58%	30%

GP, based on a geographical population [21], the data of covid-19 cases at the GP consultation level (with tests done at home or in health services) would be an acceptable indicator [36,37]. In any case, probably a certain number of cases of symptoms of viral infections in the community may not be done diagnostic tests for different reasons, and those that were performed will be more likely in at-risk and/or vulnerable patients. Therefore, it can be thought that the number of infections at GP level will be possibly underestimated.

B) Omicron variant predominated in Spain since January 2022 [38,39]. According to the weekly report, published on December 12, 2022, on the update of variants by sequencing of random samples in week 47 of 2022 (21 to 27 November), the Omicron percentage stood at 100%. Lineages BQ.1 and derivatives of it, including BQ.1.1 accounted for 78.4%. The BA.4 and BA.5 lineages ranged from 87% to 96.3% and for the BA.2 lineage, from 0% to 39.9% [40].

And C) The data of lower VE to prevent reinfections (but a high VE to prevent primary infections) can be understood taking into account that according to a study in the same population as the current one, patients with reinfection are more frequently immunosuppressed [41].

Comparison with Other Studies:

When the World Health Organization (WHO) declared covid-19 a global pandemic in March 2020, almost everything about the novel coronavirus was an unanswered question. There is now strong evidence that vaccination makes the disease less severe [42].

Furthermore, since March 2021, the coronavirus has continued to mutate. As of early July 2021, the delta variant had become the most dominant strain of SARS-CoV-2 circulating in the US. What has been seen in these almost two years is that the changes in the variants were not so radical, so that the vaccines, based on the original sequence of the virus, continued to provide very good protection against different later variants. Omicron variant accumulates a significantly greater number of mutations, some already present in other variants and others new [43].

Moderna and Pfizer's mRNA vaccines were not specifically designed to prevent the delta variant. While they still generally they have provided excellent protection after the full two doses [1], but they only partially provide protection [43]. Furthermore, the effectiveness of the booster also tends to decrease over time. Thus, it has been reported that for the two-dose regimens of mRNA vaccines, Pfizer-BioNTech (30µg per dose) and mRNA Modern vaccine (100µg per dose), VE 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 Janssen vaccine (5×10¹⁰ viral particles), the efficacy against covid-19 was 74.8% at month and decreased to 59.4% at 5 months [44-47].

In May 2023, the WHO Technical Advisory Group on Covid-19 Vaccine Composition (TAG-CO-VAC) recommended updating vaccines to better induce neutralizing antibodies against the omicron XBB.1 lineage and its descendants that were in circulation at that time. TAG-CO-VAC suggested the use of monovalent or descendant lineage XBB.1 (e.g., XBB.1.5) and specifically recommended moving away from including the ancestral index virus, first detected in 2019, in vaccines [48].

Since September 2022, Moderna and Pfizer-BioNTech bivalent SARS-CoV-2 vaccines containing equal amounts of spiked mRNA from the ancestral BA.4-BA.5 and omicron subvariants replaced their monovalent counterparts as booster doses for people over 12 years old. It is strongly suggested that a bivalent booster may preserve the safety and serological efficacy of the original monovalent booster while broadening the spectrum of antibody response, helping to restore protection that might have diminished since the last previous dose [29,33,49-56].

A report on community-dwelling resident populations aged ≥50 years in six European countries reported that compared with full primary vaccination, the relative VE of a second booster restored protection soon after administration in the fall of 2022 in people ≥65 years of age, to figures of 76-79% against hospitalization for covid-19 and 76-85% against deaths

related to covid-19. The relative EV also decreased over time, falling to $\leq 50\%$ after 24 weeks. In the most recent estimate, between February and March 2023, the relative VE of the second booster ranged between 33 and 49% versus hospitalization, 50% and 63% versus mortality between 12 and 24 weeks after administration. Overall, results indicated that booster doses restored protection soon after administration but decreased in the period up to 24 weeks after administration [57].

In a study of SARS-CoV-2 infections with symptoms from September 15, 2022 to January 31, 2023, the bivalent Pfizer-BioNTech BA.4/5 vaccine improved protection against symptomatic COVID-19 during a period when Omicron sublineages related to BA.4/5 and XBB circulated. The absolute VE (vs. unvaccinated) was 22% to 60%, and the relative VE (vs. vaccinated with 2 to 4 doses of wild type) was 31% to 64% [10].

Limitations and Strengths of the Study

- The number of cases was small, so the results should be interpreted with caution.
- There may be underreporting of infections to GPs for patients with positive tests at home. However, considering the GP's role as the gateway to the health system, the vast majority of positive COVID-19 tests at home are likely to be reported to the GP's office.
- Asymptomatic cases that did not attend GP consultations are missing, as no surveillance or systematic screening was conducted.
- The study's strength lies in its longitudinal nature, a characteristic of general medical research.

Conclusions

In the general practice setting in Toledo, Spain, from December 2021 to October 2023, the first booster (third dose) provided acceptable and early protection against SARS-CoV-2 primary infection and symptomatic COVID-19, but it appears to decrease over time. On the other hand, the effectiveness of the 4th dose (second booster) of the mRNA bivalent vaccine against primary COVID-19 infection was high, restoring immune levels. Finally, the effectiveness of the 4th dose of the bivalent mRNA vaccine in

preventing symptomatic reinfections was modest. In short, the effectiveness of booster doses with mRNA vaccines against SARS-CoV-2 primary infection and symptomatic COVID-19 waned over time, but protection remained high with the new bivalent booster. However, the booster vaccine's effectiveness is more modest in preventing symptomatic reinfections that likely occur in people at risk. All in all, it is worth completing the booster vaccination.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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