Effectiveness of the Bivalent mRNA Vaccine in Preventing Severe Covid-19 Outcomes: an observational cohort study

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Abstract

Background

During Late 2022, the SARS-CoV-2 Omicron BA.5 sublineages accounted for most of the sequenced viral genomes worldwide. Bivalent mRNA vaccines contain an ancestral SARS-CoV-2 strain component plus an updated component of the Omicron BA.4/BA.5. Since September 2022, a single bivalent booster dose has been recommended for adults who have completed a primary vaccination series and are at high risk for severe Covid-19 disease. Evidence regarding the effectiveness of the bivalent vaccine in reducing hospitalizations and death due to Covid-19 is warranted.

Methods

This retrospective cohort study included all members of Clalit Health Services, aged ≥65, eligible for a bivalent booster. Hospitalizations and death due to Covid-19 among participants who received the bivalent vaccine were compared with those who did not. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between the bivalent vaccine and Covid-19 outcomes while adjusting for demographic factors and coexisting illnesses.

Findings

A total of 622,701 participants met the eligibility criteria. Of those, 85,314 (14%) received a bivalent-booster during the 70-day study period. Hospitalization due to Covid-19 occurred in 6 bivalent recipients and 297 participants who did not, adjusted hazard ratio (HR): 0.19 (95% CI, 0.08-0.43). Death due to Covid-19 occurred in 1 bivalent recipient and 73 participants who did not, adjusted HR 0.14: (95% CI, 0.02-1.04).

Interpretation

Participants who received the bivalent vaccine had lower hospitalization and mortality rates due to Covid-19 than non-recipients up to 70 days after vaccination.

Funding

None.

Research in context

Evidence before this study

Bivalent mRNA COVID-19 booster doses containing an Omicron sublineage component have been approved and used globally since September 2022. The vaccine effectiveness (VE) of the bivalent boosters in preventing severe COVID-19 outcomes has not been established by randomized trials.

Added value of this study

This study is one of the first to evaluate the real-world effectiveness of the bivalent vaccine for preventing covid-19 hospitalizations in non-hospitalized subjects. Our findings suggest that in adults aged ≥65, VE is 81% for Covid-19 related hospitalizations and 86% for Covid-19 death.

Implications of all the available evidence

Bivalent booster vaccination of adults aged ≥65 is an effective and essential tool for reducing their risk for Covid-19 hospitalizations and death.

Introduction

During Late 2022, the SARS-CoV-2 Omicron BA.5 sublineages accounted for most of the sequenced viral genomes worldwide (1). Bivalent mRNA vaccines contain an ancestral SARS-CoV-2 strain component plus an updated component of the Omicron BA.4/BA.5 sublineages. On Aug. 31, 2022, the US FDA approved the Moderna and Pfizer bivalent boosters for adults who had completed a primary vaccination series. The approval was based on the safety and immune response data of the bivalent boosters and the effectiveness data of the monovalent boosters (2). The bivalent boosters are prioritized in Israel for subjects at high risk for severe Covid-19 disease (3), primarily aged ≥65 (4), to prevent severe Covid-19 disease (5,6).

To date, there is no data from randomized controlled trials evaluating the clinical efficacy of the bivalent boosters. Early evidence from the US suggests significant protection from the bivalent boosters in preventing severe Covid-19 disease, with estimated effectiveness ranging from 38% to 73% (7,8). However, these studies were limited to hospitalized patients. The evidence regarding the effectiveness of the bivalent vaccine for reducing hospitalizations and death due to Covid-19 in non-hospitalized patients is still warranted. Therefore, our objective was to evaluate the bivalent vaccine effectiveness in preventing Covid-19 hospitalizations and deaths.

Methods

Study design and participants

This observational, retrospective population-based cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), a large healthcare organization that covers approximately two-thirds of the Israeli population aged 65 and above. The CHS data repositories were previously described in Covid-19 studies (7). The study commenced on Sep. 24, 2022, when the bivalent vaccination campaign was initiated in CHS. The bivalent vaccine supplier was Pfizer-BioNTech. Participants were followed until Dec. 12, 2022, and for at least 14 days after vaccination. The data extraction date was Dec. 14, 2022.

The cohort included all CHS members aged 65 and above eligible for the bivalent vaccine. Per the Israeli MOH guidelines, subjects vaccinated or infected in the previous 3 months or those who did not complete the primary 2-dose series were excluded.

The primary endpoint was hospitalization due to Covid-19. The secondary endpoint was death due to Covid-19.

Data extraction

The following demographic data were extracted for each participant: age, geographical district of primary healthcare clinic, population sector, and the score for socio-economic status. The following Covid-19 data were extracted: Covid-19 vaccination dates and vaccine type, PCR and state-regulated rapid antigen test dates and results, hospitalizations, and death due to Covid-19.

Data regarding the following clinical risk factors for severe Covid-19 disease in the adult population (3) were also collected: diabetes mellitus, chronic obstructive pulmonary disease, asthma, chronic kidney failure, lung cancer, hypertension, ischemic heart disease, chronic heart failure, obesity, and a history of stroke, transient ischemic attack and smoking.

Statistical analysis

Descriptive statistics were used to characterize the study participants. Since the independent variable (bivalent booster) varied over time, appropriate univariate and multivariate survival analyses were performed with time-dependent covariates. All covariates were tested for interactions with the variable of interest (bivalent vaccination). The proportional-hazards assumption was tested for each variable by comparing survival curves and performing Schoenfeld's global test. Variables that met the testing criteria and were significantly associated with the outcome were included in the multivariate regression analysis.

We used a multivariate Cox proportional-hazards regression model with time-dependent covariates adjusted for sociodemographic factors and coexisting illnesses to estimate the association of all covariates and bivalent-booster vaccination uptake, Covid-19 hospitalizations, and corvid-19 mortality.

Participants were censored in cases of death from any cause or at the end of follow-up. Bivalent recipients were censored from the unvaccinated group seven days after receiving a bivalent vaccine as per the study design previously utilized in our first and second booster studies (9,10).

To avoid immortal time bias (11), participants were transferred from the 'unvaccinated' risk set to the 'vaccinated' risk set seven days after being vaccinated, modifying their vaccination status from unvaccinated to vaccinated. Consequently, the follow-up of vaccinated patients started at the end of the immortal period and for a minimum of 14 days to allow sufficient time for hospitalization events.

R statistical software version 3.5.0 (R Foundation) was used for the univariate and multivariate survival analysis with time-dependent covariates. SPSS software, version 26 (IBM), was utilized for all other statistical analyses. A two-sided P value of less than 0.05 was considered to indicate statistical significance in all analyses.

Results

Study participants

The study population is described in table 1. The participants in the bivalent recipient group tended to be older, of the male sex, and in the general Jewish population demographic group.

Table 1: Characteristics of the vaccinated versus unvaccinated study participants

	Bivalent - No	**Bivalent-Yes**	**All**
	N (%)	N (%)	N (%)
Total Participants	537,387 (86)	85,314 (14)	622,701 (100)
Sociodemographic variables			
Age: Mean (STD)	75.0 (7.5)	77.2 (7.6)	75.3 (7.5)
Age group:			
SES: Median (IQR)	6 (3)	7 (2)	6 (2)
Sex- Female (%)	299,335 (56)	44,514 (52)	343,849 (55)
Sector: General Jewish: N (%)	458,926 (85)	83,457 (98)	542,383 (87)
Ultra-orthodox Jewish: N (%)	19,874 (4)	1,244 (1)	21,118 (3)
Arab: N (%)	58,587 (11)	613 (1)	59,200 (10)
Clinical risk factors			
BMI: Mean (STD)	28.0 (5.2)	27.5 (4.8)	27.9 (5.2)
Asthma: N (%)	35,154 (7)	5,974 (7)	41,128 (7)
CHF: N (%)	30,428 (6)	4,820 (6)	35,248 (6)
CRF: N (%)	43,184 (8)	8,076 (9)	51,260 (8)
COPD: N (%)	33,865 (6)	4,814 (6)	38,679 (6)
Diabetes: N (%)	191,570 (36)	28,938 (34)	220,508 (35)
Hypertension: N (%)	311,029 (58)	53,490 (63)	364,519 (59)
IHD: N (%)	113,767 (21)	20,278 (24)	134,045 (22)
Obesity: N (%)	196,877 (37)	28,117 (33)	224,994 (36)
History of CVA: N (%)	51,726 (10)	8,025 (9)	59,751 (10)
History of Smoking	219,096 (41)	33,952 (40)	253,048 (41)

Bivalent Vaccine Uptake

The association of vaccine uptake with sociodemographic and clinical variables is detailed in Table 2. Uptake was significantly higher in adults aged >75, males, and higher socio-economic status and significantly lower in the Arab and Ultra-orthodox Jewish sub-populations.

Table 2: Results of the multivariate regression for bivalent vaccine uptake

	HR (95% CI)
Sex: Female (Ref.)	
Sex: Male	1.16 (1.14-1.18)
Age at Follow-up start, 65-74 (Ref.) 75+ vs. under 75	1.48 (1.46-1.50)
Demographic group-General Jewish (Ref.)	
Demographic group-Arab	0.16 (0.14-0.17)
Demographic group -Ultra_Orthotdox_Jewish	0.58 (0.55-0.62)
Socio-economic score	1.32 (1.32-1.33)
Asthma	1.08 (1.05-1.11)
CHF	0.93 (0.90-0.96)
Chronic Renal Failure	1.05 (1.03-1.08)
COPD	0.96 (0.93-0.99)
Diabetes	1.00 (0.99-1.02)
Hypertension	1.15 (1.13-1.17)
IHD	1.05 (1.03-1.07)
Obesity	1.01 (0.99-1.02)
History of CVA	0.92 (0.90-0.94)
Current or former smoker	0.96 (0.95-0.98)

Assessment of vaccine effectiveness for the primary endpoint

Hospitalization due to Covid-19 occurred in 6 bivalent recipients and 297 participants who did not. The crude event rate per 0.27 versus 0.73 per 100,000 person-days at risk, and the adjusted hazard ratio (HR) is 0.19 (95% CI, 0.08 to 0.43). Figure 1 depicts the cumulative hazard of hospitalization for the bivalent versus no bivalent status.

The results of the multivariable regression for the primary endpoint of Covid-19 hospitalizations are detailed in Table 3. Age and male sex were associated with higher Covid-19 hospitalization rates, while the Arab sector was associated with lower risk. CHF, CRF, COPD, and previous CVA were all associated significantly with a higher risk for Covid-19 hospitalization.

Table 3 - Association of Bivalent- vaccine and Covid-19 hospitalizations

Variables	HR (95% CI)
BiValent Vaccination (Effective)	**0.19 (0.08-0.42)**
SEX	1.28 (1.01-1.62)
Age at Follow-up start	1.08 (1.06-1.09)
Demogorphic_group: Arab	0.27 (0.13-0.57)
CHF	1.82 (1.39-2.38)
Chronic Renal Failure	1.68 (1.26-2.24)
COPD	1.80 (1.30-2.50)
Diabetes	1.48 (1.17-1.88)
Hypertension	1.34 (0.99-1.81)
History of CVA	1.66 (1.25-2.18)

Assessment of vaccine effectiveness for the secondary endpoint

Death due to Covid-19 occurred in 1 bivalent recipient and 73 participants who did not, HR 0.14: (95% CI, 0.02 to 1.04).

The results of the multivariable regression for the secondary endpoint of Covid-19 mortality are detailed in Table 4. Age, CHF, COPD, and previous CVA were all significantly associated with a higher risk for Covid-19 hospitalization.

Table 4 - Association of Bivalent- vaccine and Covid-19 mortality

Variables	HR (95% CI)
BiValent Vaccination (Effective)	**0.14 (0.02-1.03)**
Age at Follow-up start	1.12 (1.09-1.16)
CHF	2.21 (1.38-3.54)
COPD	2.99 (1.72-5.20)
Hypertension	1.83 (0.94-3.55)
History of CVA	1.77 (1.05-2.99)

Discussion

Summary of Results

Our results demonstrate that vaccination with a bivalent booster among eligible adults aged ≥65 was associated with a statistically significant 81% reduction in Covid-19 hospitalizations. The bivalent booster was also associated with a borderline statistically significant 86% reduction in Covid-19 mortality, probably due to the relative scarcity of Covid-19 mortality events.

Our results show a low response rate (<14%) to the bivalent campaign in adults aged ≥65. This may result from different reasons, including vaccine misinformation, reports of side effects, or the belief that the vaccine is unnecessary as COVID-19 infection is sufficient to obtain immunity. Our findings highlight the importance of bivalent-booster vaccination in this high-risk population and the necessity to increase efforts to encourage eligible people to be vaccinated. This can be obtained with government efforts to scatter misinformation, increase confidence in vaccine safety and effectiveness, increase trust in the healthcare system, and the participation of healthcare providers in endorsing vaccination.

Comparison to Previous Evidence

Two recent US CDC reports have evaluated the bivalent booster's vaccine effectiveness (VE) in the hospital setting. The first one included 798 patients and compared bivalent recipients to patients who had received ≥2 monovalent-only mRNA vaccine doses. The relative VE of a bivalent booster dose was 73% (7). The second report concluded that bivalent vaccines administered after ≥2 monovalent doses provided additional protection compared with past monovalent vaccination, with relative protection increasing with time since receipt of the last monovalent dose from 31% to 50% (8).

Limitations

Our study has some noteworthy limitations. The primary limitation is that a relatively low number of Covid-19 related hospitalizations and even lower deaths were observed during the study period. However, our study provides critical primary evidence that may further drive the engagement of patients and their healthcare providers for vaccination.

Our study was based on hospital reports regarding the cause of hospitalization death. However, it is possible that participants in this study were hospitalized or died from other causes but were reported as Covid-19 related because they happened to have been SARS-Cov-2 positive when hospitalized. Nevertheless, a recent study analyzing excess deaths during the Covid-19 pandemic demonstrated that the Israeli rate of excess death is in accordance with its Covid-19 mortality reports (12).

The data on Covid-19 infections during the study period is limited for various reasons: some infections are asymptomatic, and some were self-diagnosed in-home antigen tests that are not recorded in the CHS database. Therefore, we could not assess the effectiveness of the bivalent booster in reducing infection rates.

As in any retrospective cohort study, confounding clinical and sociodemographic characteristics may have biased the observed effectiveness. We attempted to overcome these biases by adjusting for the variables known to affect severe Covid-19 outcomes. However, some sources of bias may not have been measured or corrected adequately, like social dissimilarities between participants who chose to receive the bivalent booster and those who decided not to. The main demographic groups in Israel – the general population, the Ultra-orthodox Jewish population, and the Arab population, also manifest different health-related behavioral patterns. As demonstrated in table 2, bivalent uptake was significantly lower in the

minority Arab and Ultra-orthodox Jewish groups. However, our analysis adjusted for these subpopulations to overcome such possible bias.

Our analysis included only the Pfizer-Biontech mRNA bivalent vaccine, as it was the primary supplier in Israel during the study period. Generalizability of these results to the second bivalent booster, produced by Moderna, should be done with caution, although most monovalent studies found Moderna vaccines have comparable or somewhat better effectiveness.

The evaluation of adverse events and safety data reports was beyond the scope of this study. Future studies will be needed to assess bivalent booster administration's short- and long-term safety in real-world settings.

Conclusions and Implications for policy

In conclusion, our results suggest that the bivalent booster is associated with a lower risk of severe Covid-19 outcomes infection in adults aged ≥65 years. These findings highlight the importance of bivalent-booster vaccination in this high-risk population and the necessity to increase efforts to encourage eligible people to be vaccinated.

Declarations

1. The study was conducted using CHS's internal resources without external funding.
2. The CHS Institutional Helsinki and Data Utilization Committees approved the study.
3. All authors report no conflict of interest.

Data Sharing Statement

According to this study's CHS Helsinki and data utilization committees' guidelines, no patient-level data is to be shared outside the permitted researchers.

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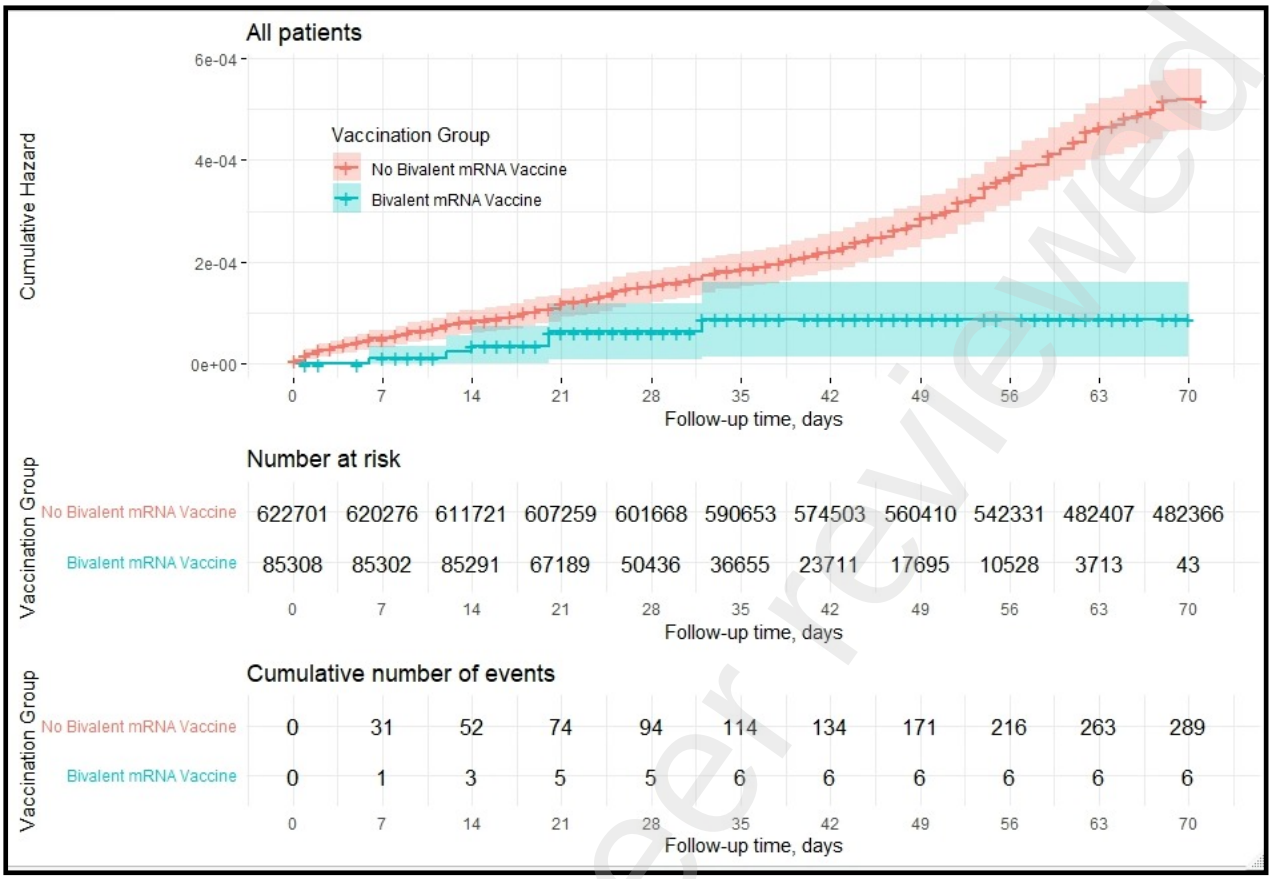

Figure 1: Cumulative hazard for Covid-19 hospitalization