Second Booster Vaccine and Covid-19 Mortality in Adults 60 to 100 Years Old

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Abstract

The rapid emergence of the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus-2 led to a global resurgence of coronavirus disease 2019 (Covid-19). Israeli authorities approved a 4th Covid-19 vaccine dose (second-booster) for individuals aged 60 and above who received a first booster dose four or more months earlier. Evidence regarding the effectiveness of a second-booster dose in reducing mortality due to Covid-19 is warranted.

This retrospective cohort study included all members of Clalit Health Services, aged 60 to 100, eligible for the second-booster. Mortality due to Covid-19 among participants who received the second-booster was compared with participants who received one booster dose. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between the second-booster and death due to Covid-19 while adjusting for demographic factors and coexisting illnesses. A total of 563,465 participants met the eligibility criteria. Of those, 328,597 (58%) received a second-booster dose during the 40-day study period. Death due to Covid-19 occurred in 92 second-booster recipients and in 232 participants who received one booster dose (adjusted hazard ratio 0.22; 95% confidence interval 0.17 to 0.28). This study demonstrates a substantial reduction in Covid-19 mortality by the second-booster in eligible subjects.

Background

Towards the end of 2021, the B.1.1.529 (omicron) variant of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has led to an unprecedented worldwide resurgence of coronavirus disease 2019 (Covid-19) (Figure S1). Due to the significant rise in breakthrough infections by the omicron variant in individuals who already received three vaccine doses, the Israeli Ministry of Health initiated a fourth vaccine (second-booster) dose campaign to protect the population at high risk for severe disease. On January 2nd, 2022, the second-booster dose was approved to subjects 60 years and older, high-risk populations, and healthcare workers who received a first booster dose at least four months earlier (1,2).

Due to the lack of epidemiological and large-scale clinical evidence, the decision on an additional booster dose was made highly controversial (3-6). Initial short-term results of the effectiveness of providing a second-booster dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) for the aging population in lowering rates of confirmed Covid-19 and severe illness have been published recently (2). However, evidence regarding the effectiveness of the additional booster dose in avoiding death due to Covid-19 is warranted. Therefore, our objective was to assess any decrease in mortality due to Covid-19 associated with providing the elderly population a second-booster dose.

Results

Study Population

During the study period, 563,465 participants met the eligibility criteria. The assessment for eligibility is detailed in Figure 1. The mean age of the study participants was 73.0 years, and 53% were female. The most common co-morbidities were hypertension, obesity, and diabetes (Table 1).

Second-Booster Uptake

Of the entire population cohort, 328,597 participants (58%) received the second-booster dose during the 40-day study period. The association between patient characteristics and the second-booster uptake rate is described in Table 2. Uptake was notably higher in the older age groups and among participants with a higher socioeconomic status. Uptake was lower within the Ultra-Orthodox Jewish and Arab populations.

Study Outcomes

During the study, death due to Covid-19 occurred in 92 of the second-booster recipients and 232 participants in the first-booster group. The adjusted hazard ratio for death due to Covid-19 in the second-booster group compared with the first-booster group was 0.22 (95% CI: 0.17-0.28). Cumulative hazard-ratio curves are shown in Figure 2.

The Cox proportional-hazards regression model results with time-dependent covariates are shown in Table 3. The model included the variables that met the criteria for the proportional-hazards assumption based on Schoenfeld's Global Test (Table S1). In the Cox regression model, higher age group, male sex, ultra-orthodox Jewish, chronic heart failure, chronic obstructive pulmonary disease, and diabetes were confounding variables that had a significant association with death due to Covid-19.

Subgroup Analysis by Age Groups

Among participants aged 60 to 69, death from Covid-19 occurred in 5 of 111,776 participants in the second-booster group and 32 of 123,786 participants in the first-booster group (adjusted hazard ratio, 0.16; 95% CI, 0.06 to 0.41; P<0.001) (Table S2).

Among participants aged 70 to 79, death from Covid-19 occurred in 22 of 134,656 participants in the second-booster group and 51 of 74,717 participants in the first-booster group (adjusted hazard ratio, 0.28; 95% CI, 0.17 to 0.46; P<0.001) (Table S3).

Among participants aged 80 to 100, death from Covid-19 occurred in 65 of 82,165 participants in the second-booster group and 149 of 36,365 participants in the first-booster group (adjusted hazard ratio, 0.20; 95% CI, 0.15 to 0.27; P<0.001) (Table S4).

Discussion

Our study demonstrates that among the older adult population that had received a first booster dose at least four months earlier, mortality due to Covid-19 during the omicron surge was significantly lower among those who had received an additional booster dose.

The first-booster dose of the BNT162b2 vaccine was approved in Israel at the start of the B.1.617.2 (delta) variant wave due to a rise in breakthrough infections among vaccinated individuals. The fast deployment of the booster dose in Israel, especially in the elderly, significantly reduced infections, hospitalizations, and mortality rates due to Covid-19 (7-9). However, this observed immunity waned substantially after a few months, along with the rapid emergence of the omicron variant that spread widely, even in communities with a high level of vaccination (10,11). The frequent symptomatic infections among fully vaccinated individuals had increased the pressure to consider the approval of an additional booster dose to protect the vulnerable population from possible severe or fatal Covid-19.

Although the omicron variant appeared to produce less-severe illness than earlier variants (12), the unprecedented surge in SARS CoV-2 infections has brought the Israeli authorities to approve administering the additional booster vaccine dose to the most vulnerable populations. The UK Government has also recently decided to offer an additional booster dose for people aged 75 years and older, those in care homes, and those aged 12 years and over with a weekend immune system (13). Nevertheless, providing the second-booster dose is still highly controversial, mainly because of the lack of evidence of effectiveness and major concerns regarding global vaccine inequity and the critical need to make vaccines globally available to stand against the emergence of novel variants of concern (3-6).

Our study results may provide primary evidence regarding the life-saving potential of an additional booster dose. However, while providing booster vaccine doses to high-risk groups seems beneficial, it is still critical to vaccinate those who have not yet been vaccinated to achieve sustainable control of Covid-19 and prevent further morbidity and mortality (4).

Our study has several strengths. First, the results are based on the integrated medical records system of Clalit Health Services, with detailed demographic, clinical, and laboratory testing data, including data on coexisting conditions that could have significantly affected mortality rates and were therefore adjusted for in the statistical analysis. The second important strength is the large cohort of participants available for analysis. A third strength is focusing on avoiding death due to Covid-19, the most critical outcome of Covid-19 vaccination, and is not biased by possibly different testing rates between the groups. However, the observed effect of a 78% reduction in mortality rates was somewhat lower than the observed effect of the first booster dose on mortality in the elderly population in Israel (90%) (7).

Our study also has several limitations. The primary limitation is its relatively short period (40 days). However, during this time, the infection rate in Israel from the omicron variant rose to be the highest in the world (Figure S3). Moreover, during this period, almost no social-distancing restrictions were imposed on the public in Israel. Therefore, exposure to SARS-CoV-2 was substantial, and accordingly, the number of Covid-19 severe events was sufficient to demonstrate significant associations between the second-booster dose and reduced Covid-19 mortality rates.

Our study was based on hospital reports regarding the cause of death. However, most medical centers test every patient for SARS-CoV-2 upon admittance at this point in the epidemic. It is possible that participants in this study died from other causes but were reported as death due to Covid-19 because they

happened to have been SARS-Cov-2 positive when they died. 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 (14).

It should be noted that, 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 Covid-19 mortality. However, some sources of bias may not have been measured or corrected adequately, like social dissimilarities between participants who chose to receive the second-booster and those who decided not to.

A further limitation is that the rate of infections and thus exposure to disease had changed during the study period. However, we assume that after adjustment for all covariates, these changes similarly affected the second-booster and first-booster populations.

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. We observed significantly lower uptake of the second booster in these minority population sectors. Our regression analysis adjusted for these subpopulations to overcome such possible bias.

An important drawback of this study is the absence of safety data, as it was out of the scope of this short-term study. Future studies will be needed to assess the safety of the second booster administration. Finally, our findings were limited to the BNT162b2 vaccine. Although there is evidence that the mRNA-1273 vaccine is slightly more effective than the BNT162b2 vaccine in participants who had received two vaccine doses (15), we cannot deduce whether this observation is relevant also regarding a second-booster dose.

Although this study is observational in nature, we believe that its significant findings and the observed potential for avoiding the most severe Covid-19 outcomes could assist decision-makers in assessing the benefit of providing the second-booster to targeted populations. Our study showed that in participants 60 years and older, at least four months after a BNT162b2 vaccine booster, mortality due to Covid-19 was significantly lower after a second booster shot. However, studies with longer-term follow-up to determine the durability of the second-booster effectiveness and safety are still warranted.

Methods

Study Population

This observational, retrospective cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), a large healthcare organization covering approximately 52% of the entire Israeli population and almost two-thirds of the country's older population. The study included all CHS members aged 60 years to 100 who were entitled to receive a second-booster vaccine at the study start date.

The exclusion criteria included participants with a documented previous SARS-CoV-2 infection, participants who received a first-booster dose less than four months before, or a 4th Covid-19 vaccine dose before the study start date. To minimize calendar time bias, participants who became entitled to the second-booster during the study follow-up period were also excluded from the study as well. Since CHS started administering the mRNA-1273 (ModernaTX) vaccine in August 2021, primarily to patients who already had recovered from Covid-19, mRNA-1273 recipients were also excluded. Participants who received an oral anti-Covid-19 therapy (nirmatrelvir-ritonavir or molnupiravir) during the study period were also excluded.

Study Design

The study period started on January 10, 2022, 7 days after the initiation of Israel's second booster vaccination campaign for the population aged 60 and above. The study period ended on February 20, 2022, the last date with confirmed Covid-19 mortality at the data extraction date (February 27, 2022). During the study period, the dominant SARS-CoV-2 variant in Israel was the B.1.1.529 (omicron) (Figure S2).

The study population was divided into two groups, those who had received a second-booster dose ('second-booster' group) and those who had not ('first-booster' group). Participants were included in the 'second-booster' group seven days after receiving their second-booster vaccine dose (effective date) to allow time for antibodies to build effectively (5,6). To that date, participants were evaluated as part of the 'first-booster' group. Participants infected with SARS-CoV-2 during the seven-day period after receiving the second-booster dose were excluded from the analysis. A description of participants' transition from the 'first-booster' to the 'second-booster' status is presented in Figure S2.

The study was approved by the CHS Community Helsinki Committee and the CHS Data Utilization Committee. The study was exempt from the requirement for informed consent from the patients, owing to the retrospective design. No financial or in-kind support was provided for the conduct of the study.

Study outcomes

The study's primary outcome was death due to Covid-19. A subgroup analysis was performed according to three age groups: 60 to 69, 70 to 79, and 80 to 100.

Data sources and organization

We evaluated integrated patient-level data maintained by CHS from two primary sources: the primary-care operational and Covid-19 databases. The operational database includes sociodemographic data and comprehensive clinical information, such as coexisting chronic illnesses, history of community care visits, medications, and results of laboratory tests. The Covid-19 database includes PCR and state-regulated rapid antigen tests, vaccinations, and Covid-19-related hospitalizations and mortality and is updated daily from the central Covid-19 repository of the Israeli Ministry of Health. These same

databases were used in the primary studies that evaluated the effectiveness of the BNT162b2 vaccine in real-world settings (6,7). A description of the data repositories used in this study is provided in the Supplementary Appendix.

For each participant in the study, the following sociodemographic data were extracted: age, sex, demographic group (general Jewish population, ultra-Orthodox Jewish population, or Arab population), the score for socioeconomic status (ranging from 1 [lowest] to 10 [highest], as described in the Supplement).

The following Clinical data were extracted: Covid-19 vaccination dates and vaccine type, PCR and state-regulated rapid antigen test dates and results, and death due to Covid-19. Data regarding the following clinical risk factors for severe Covid-19 in the general population (6) 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. The utilization of the two oral anti-Covid-19 medications approved in Israel since January 2022 for high-risk populations, molnupiravir, and nirmatrelvir/ritonavir, was also extracted.

Statistical Analysis

Descriptive statistics were used to characterize the study participants. Kaplan-Meier analysis with log-rank testing was performed for univariate analysis. Since the independent variable (second booster) varied over time, univariate and multivariate survival analyses were performed with time-dependent covariates according to the study design. Participants were censored in cases of death from any cause or at the end of follow-up. Participants were censored from the first-booster group seven days after receiving a second-booster vaccine as per the study design. We used a multivariate Cox proportional-hazards regression model to estimate the association of all covariates and second-booster vaccination uptake.

The association of second-booster and mortality was estimated using a multivariate Cox proportional-hazards regression model with time-dependent covariates, adjusted for sociodemographic factors and coexisting illnesses. All covariates were tested for interactions with the variable of interest (second-booster vaccination). The proportional-hazards assumption was tested for each variable by comparing survival curves and by performing Schoenfeld's global test. Variables that met the testing criteria and were significantly associated with the outcome served as the inputs for multivariate regression analysis.

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.

Data availability

Due to the Clalit Health Services data privacy regulations, and per the institutional Helsinki and data utilization committee approvals for the study, the patient-level data used for this study cannot be shared.

Code availability

R statistical software version 3.5.0 (R Foundation) was used for the univariate and multivariate survival analysis with time-dependent covariates. The following R packages were used: survival, foreign, ggplot2, ggfortify, ggpubr, survminer, gmodels, and g summary. All R packages are freely available. SPSS software, version 26 (IBM), was utilized for all other statistical analyses.

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Declarations

Acknowledgments

None.

Author contributions

All authors contributed to the study design. TB extracted the data under the supervision of SY and AP. RS cleaned and analyzed the data with the guidance of MF. RA drafted the initial manuscript, and AH made the primary revisions. AP, SY, and DN revised and approved the clinical aspects of the manuscript. All authors revised the manuscript for critical content and clarity and approved it. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics Declaration

Competing interests

The authors declare no competing interests

Tables

Table 1: Characteristics of the Participants at Baseline

Characteristic	All Participants (N=563,465)
Age	
Mean ± SD - yr	73.0 ± 8.4
Distribution- no. (%)	
60-69 yr	235,562 (42)
70-79 yr	209,373 (37)
80-100 yr	118,530 (21)
Female sex - no. (%)	300,349 (53)
Population sector- no. (%)	
General Jewish	508,681 (90)
Ultra-Orthodox Jewish	17,195 (3)
Arab	37,589 (7)
Median score for socioeconomic status, Median (IQR)	6 (2)
BMI ± SD	27.9 ± 5.1
Clinical risk factors - no. (%)	
Asthma	35,476 (6)
Chronic heart failure	30,534 (5)
Chronic kidney failure	43,483 (8)
Chronic obstructive pulmonary disease	32,615 (6)
Diabetes	187,234 (33)
Hypertension	310,987 (55)
Ischemic heart disease	115,589 (21)
Obesity	194,745 (35)
Lung Cancer	4,647 (1)
History of stroke	48,613 (9)
History of transient ischemic attack	23,544 (4)
Current or former smoking	238,369 (42)

Table 2: Association between participant characteristics and Second-Booster Uptake*

Characteristics	Adjusted Hazard Ratio (95% CI)
Age group	
60-69	Reference
70-79	1.49 (1.48-1.50)
≥ 80	1.57 (1.56-1.59)
Female Sex	1.13 (1.12-1.14)
Population sector	
General Jewish	Reference
Ultra-orthodox Jewish	0.81 (0.79-0.83)
Arab	0.59 (0.57-0.60)
Socio-Economic Status**	1.18 (1.18-1.18)*
Clinical risk factors	
Asthma	1.04 (1.03-1.06)
Chronic heart failure	0.94 (0.92-0.95)
Chronic kidney failure	1.04 (1.02-1.05)
Chronic obstructive pulmonary disease	0.97 (0.96-0.99)
Diabetes	1.02 (1.01-1.03)
Hypertension	1.11 (1.10-1.12)
Ischemic heart disease	1.05 (1.04-1.06)
Obesity	1.03 (1.03-1.04)
Lung Cancer	1.08 (1.04-1.12)
History of stroke	0.93 (0.92-0.94)
History of transient ischemic attack	1.02 (1.01-1.04)
Current or former smoking	0.99 (0.98-1.00)

* The association between all covariates and second-booster uptake was estimated using a multivariate Cox proportional-hazards regression model. The higher the hazard ratio, the greater the association between the listed characteristic and vaccine uptake.

** A hazard ratio of more than 1.00 indicates an association between a higher score for socioeconomic status and second-booster uptake. The HR was 1.179 (1.176-1.181).

Table 3: Association between the second-booster and Death Due to Covid-19, Adjusted for Confounding Variables

Variable	Hazard Ratio for Death Due to Covid-19 (95% CI)
Second booster received	0.22 (0.17-0.28)
Age group 60-69 70-79 ≥ 80	 Reference 2.24 (1.51-3.34) 9.95 (6.93-14.28)
Male sex	1.59 (1.26-1.99)
Population sector General Jewish Ultra-Orthodox Jewish	 Reference 1.61 (1.00-2.59)
BMI	0.96 (0.94-0.98)
Chronic Heart Failure	4.11 (3.22-5.25)
Chronic obstructive pulmonary disease	1.82 (1.35-2.43)
Diabetes	2.06 (1.64-2.58)
History of stroke	1.84 (1.44-2.37)

Figures

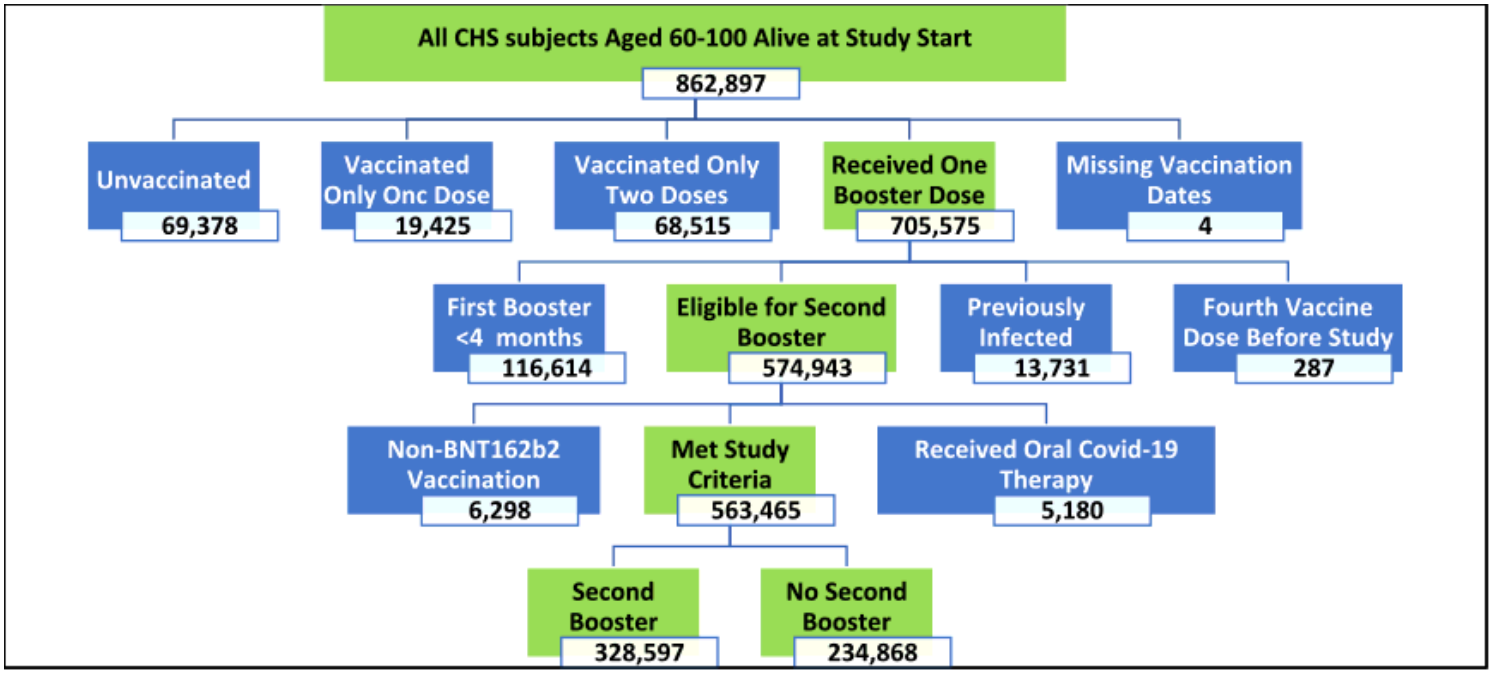

Figure 1

Assessment for Eligibility

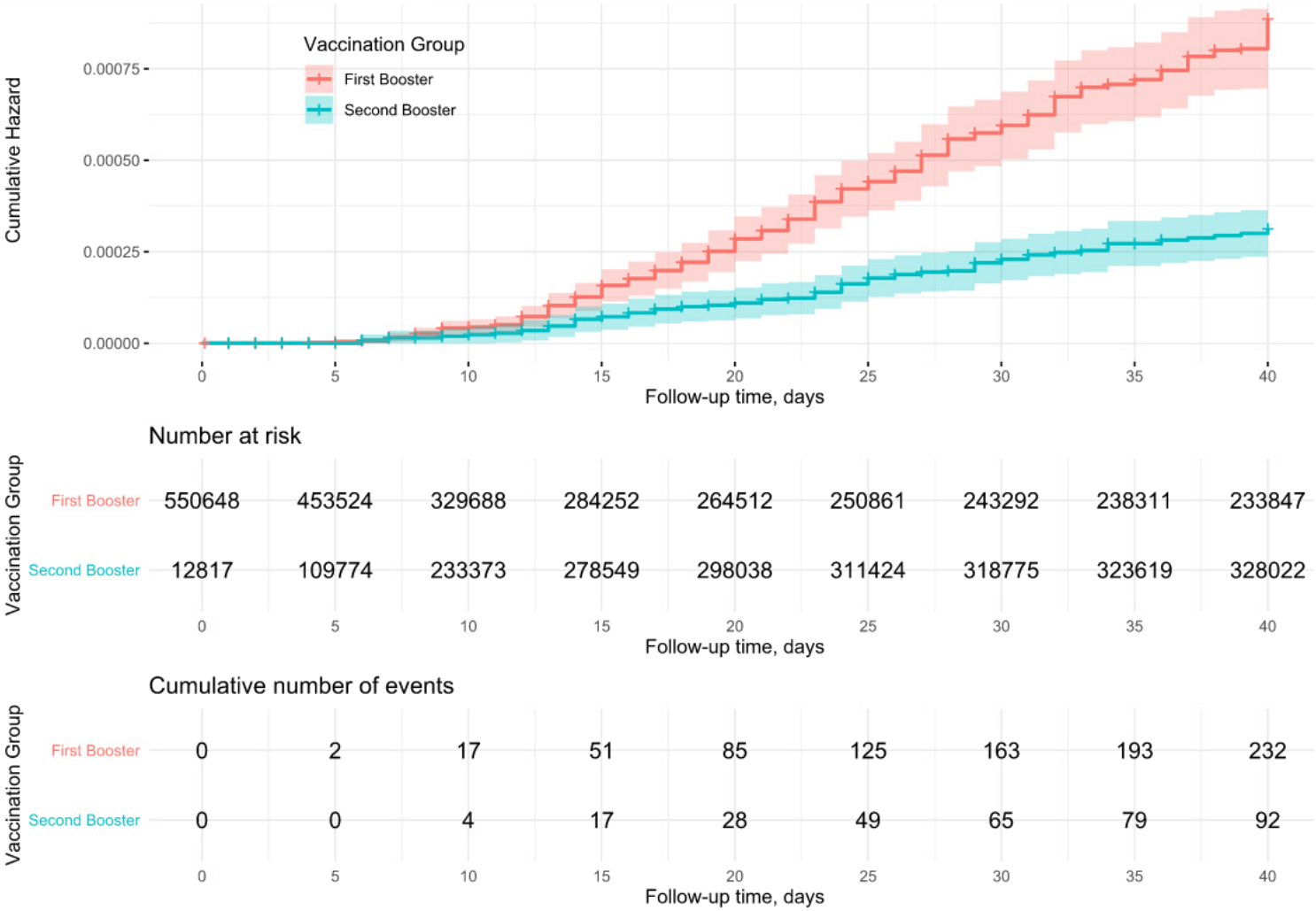

Figure 2

Cumulative Covid-19 Mortality Rates During the Study Period

Supplementary Files

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- SupplementaryMaterialSecondBoosterMortality.docx
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- flatArbelrs.pdf