Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med. DOI: 10.1056/NEJMoa2114255

Study protocol: Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. Yinon Bar-On et al.

Objectives

On July 30, 2021, a third (booster) dose of the Pfizer BNT162b2 vaccine was approved in Israel for all individuals 60 years or older who had been fully vaccinated (i.e., received two doses) for at least five months. The objective of this observational study is to estimate the reduction in relative risk for confirmed infection and severe COVID-19 provided by the booster dose in a real-world setting.

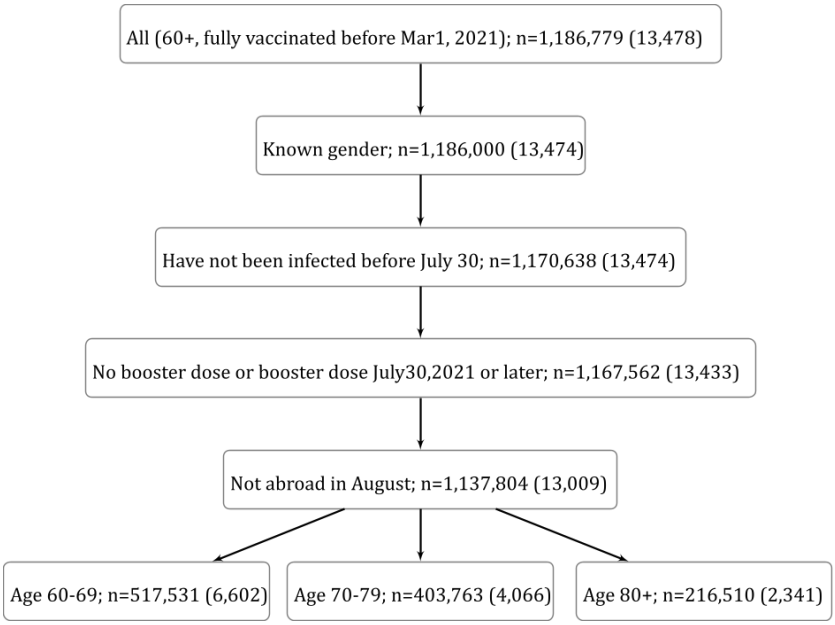
Methods

Context and Data

Israel has a centralized health system, where all COVID-19 related data are reported to the Ministry of Health. This observational study uses data collected by the Israeli Ministry of Health, containing information on all Pfizer vaccine doses administered to the Israeli population, as well as outcomes related to COVID-19, namely: qPCR tests (sampling dates and results), date of hospitalization (if relevant) and clinical status (mild/severe). In addition, the database contains basic demographic information such as age, gender, and demographic sector.

Study population

- Inclusion criteria (all eligible residents for the booster dose according to the Ministry of Health guidelines):
    - Age 60 years or older.
    - Being fully vaccinated (7 days after 2nd dose) for at least 5 months on start day.
    - Have not been infected before start day.
    - Alive on start day.
- Exclusion criteria
    - Missing gender.
    - Returned from abroad in August.
    - Have received a booster dose before the start day.
    - Became fully vaccinated before January 16, 2021.
- Sample size - 1.1 million Israeli residents; see the diagram.



Study Population:The participants in the study included persons who were 60 years of age or older and who had been fully vaccinated before March 1, 2021, had available data regarding sex, had no documented positive result on polymerase-chain-reaction assay for SARS-CoV-2 before July 30, 2021, and had not returned from travel abroad in August, 2021. The number of confirmed infections in each population is shown in parentheses.

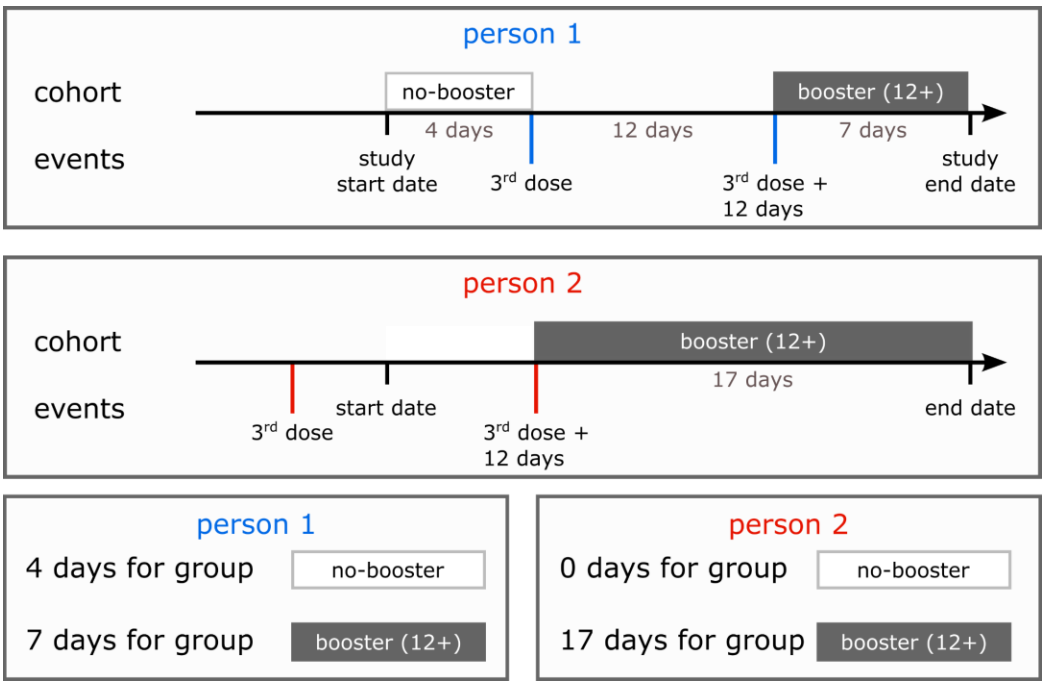
Study Design and data time period

This is a prospective dynamic cohort design on the whole Israeli population (1,186,779) above 60 years of age eligible for the booster dose. The dynamic cohort design is similar to that used by Goldberg et al. (2021) and Dagan et al. (2021).

- Participant data was extracted on September 2, 2021.
- The study follows all eligible participants, those who received the 3rd dose and those who did not.
- Participants start in the ‘no-booster’ cohort and leave it when receiving the booster dose.
- Participants enter the ‘booster’ cohort 12 days after receiving the booster dose, provided they are not found PCR positive in the interim.
- This 12-day time lag is based on allowing 7 days for the booster to fully stimulate the immune system plus another 5 days between infection to its detection by PCR tests.
- Study period is between July 30, 2021 (start of the booster vaccination campaign) until August 31, 2021 for analyzing confirmed infections and until August 26, 2021 for analyzing severe disease.

    - We omit infections occurring in the last two days of available data (Sep 1-2) for confirmed infections to minimize missing outcome data owing to delays in reporting of test results.
    - For severe cases, we omit cases confirmed between August 26 and September 2 to allow for a week of follow-up for determining whether severe illness had developed.
- Events and person-days at risk for each group are counted over the period August 10 until August 31, 2021 for the confirmed infections analysis and until August 26, 2021 for severe disease analysis.
- The onset of severe cases was taken to be the date of the confirmed infection.

The following figure demonstrates how person-days at risk were calculated:



A schematic illustration of the allocation for the dynamic cohorts. We show two example timelines for two different individuals, and detail the cohort they contribute to at each point in time as well as the total person-days at risk for each person in each cohort.

Variables (Definitions, measurement of, and time periods)

Outcomes

- Confirmed COVID-19 infection (by PCR).
- Severe COVID-19 (a resting respiratory rate of >30 breaths per minute, oxygen saturation on room air of <94%, or a ratio of PaO2 to FiO2 of <300).

Exposures

- Cohort - before booster / 12+ days after booster.
- Number of days after the booster shot.

Covariates (for main analysis)

- Gender
- Age group (60-70,70-80,80+)
- Demographic sector (general Jewish, Arab, ultra-orthodox Jewish)
- Period of full vaccination (Jan-16 to Jan-31, Feb-1 to Feb-15, Feb-16 to Feb-28)
- Calendar date

Statistical analysis plan

Primary analysis

- Poisson regression analysis with log link adjusted for the covariates with cohort as the exposure variable and person-days at risk added as an offset on the log scale.
- Poisson regression analysis with log link adjusted for the covariates with days from booster dose as a factor and person days at risk added as an offset on the log scale.

Secondary analyses

  - Poisson regression comparing the 'booster' cohort (12+ days after booster shot) to an interim period (4-6 days after the booster shot). The effect of the booster dose is not yet observed after 4-6 days, but people might perform less testing and be more cautious just after getting the booster vaccination, so we conjecture that the effect of the booster dose is biased downward in this analysis.

Sensitivity analyses

- Matched analysis - matching individuals on their date of booster shot to those not yet receiving the dose, following the method of Dagan et al. (2021).
  - Matching using age group, gender, demographic sector and time being fully vaccinated (7 days after second vaccine dose).
  - Pairs are censored at the time the control individual received the booster dose or at the end of the period.
  - Cumulative incidence curves comparing the risk of infection between the two curves will be drawn using the Kaplan-Meyer method.
  - Analysis will contain only events occurring after day 12 from the matching day.
- Weighting analysis - We matched person-days for those in the booster group to those in the nonbooster group and weighted them so that the effective person-days for both groups would be the same.

    - For each date independently, people in the booster group (12+ days after vaccination) are matched to all people who have not yet received the booster dose.
    - Matching only people who have not been infected.
    - Matching using Age, Gender, Sector, City, and time being fully vaccinated.
    - Within each matching group, the nonbooster group was weighted such that their total person-days at risk would equal the booster group.
    - The sum of weighted outcomes (confirmed infections and severe disease) in the two groups are calculated and the between-group ratio is used.

- Sub-group analysis for the general population (as there are significant behavioral differences between the main demographic groups in Israel), as well as for different periods of booster vaccination (August, 1-3; August 4-6; August 7-9).

PRIVACY

The raw data extracted are coded and do not contain any identifiable information. Analyses are performed on aggregated tables that will be made publicly available after publication.

References

Goldberg, Y. *et al*. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel. medRxiv 2021.04.20.21255670; doi: https://doi.org/10.1101/2021.04.20.21255670

Dagan, N. *et al.* BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N. Engl. J. Med.* **384**, 1412–1423 (2021).