Protocol

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

Protocol for: Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. DOI: 10.1056/NEJMoa2101765

This supplement contains the following items:

ORIGINAL PROTOCOL

BACKGROUND AND STUDY RATIONALE

Clinical/Public health significance of research question

In late 2019, the novel severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19, was first identified. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic. As of December 17, 2020, 72,196,732 million cases and over 1,630,521 deaths had been reported to the World Health Organization (WHO). In Israel, as of December 16, 2020, there had been 357,627 confirmed cases of COVID-19 with 3,002 deaths[1].

International collaborative efforts have accelerated the development of COVID-19 vaccines. Different manufacturing platforms are being used with some very innovative technologies. As of December 8, 2020, 52 candidate vaccines were in clinical evaluation[2].

On December 21, 2020, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the Pfizer-BioNTech COVID -19 vaccine in individuals 16 years of age and older and for the Moderna vaccine was for individuals 18 years and older [3]. The Government of Israel has approved the Pfizer COVID-19 vaccine and the Moderna COVID-19 vaccine for similar use in Israel.

In Israel, health-care workers, adults over age 60, and adults with chronic medical conditions have been prioritized for COVID-19 vaccination. Eventually, however, vaccination will likely be offered to all adults. The WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply has prioritized similar groups for vaccination. In addition, the Israeli government has already prioritized health workers for vaccination [4,5].

Evaluating real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programs. Many factors impact real-world vaccine effectiveness (VE), including vaccine transportation and storage and how patients are vaccinated. In addition, the people who get the vaccine in clinical trials are often young and healthy, and therefore different from those who will receive vaccines in the real world[6].

Real-world VE studies can also answer questions about effectiveness by age-group and risk factors, duration of vaccine protection, protection against severe disease, relative effectiveness of different vaccines, relative effectiveness of one dose vs. two doses, and effectiveness of the vaccine against new strains of SARS-CoV-2 if they are to emerge.

How this research fills gaps/ adds new evidence to the literature

This study will allow us to answer critical questions about the real-world effectiveness of COVID-19 vaccine.

Study objectives

Assess COVID-19 vaccine effectiveness

METHODS

Context and Data

Clalit Health Services (CHS), the largest integrated health care service provider and payer system in Israel, has over 4.7 million active members. CHS has a comprehensive health care data warehouse which combines hospital and community medical records, laboratory and imaging information, pharmaceutical records, health care costs, and Ministry of the Interior vital statistics of all the members. Membership turnover within Clalit is less than 1% annually, facilitating the study of population trends over time.

Study Design and data time period

This is a retrospective study employing a cohort design.

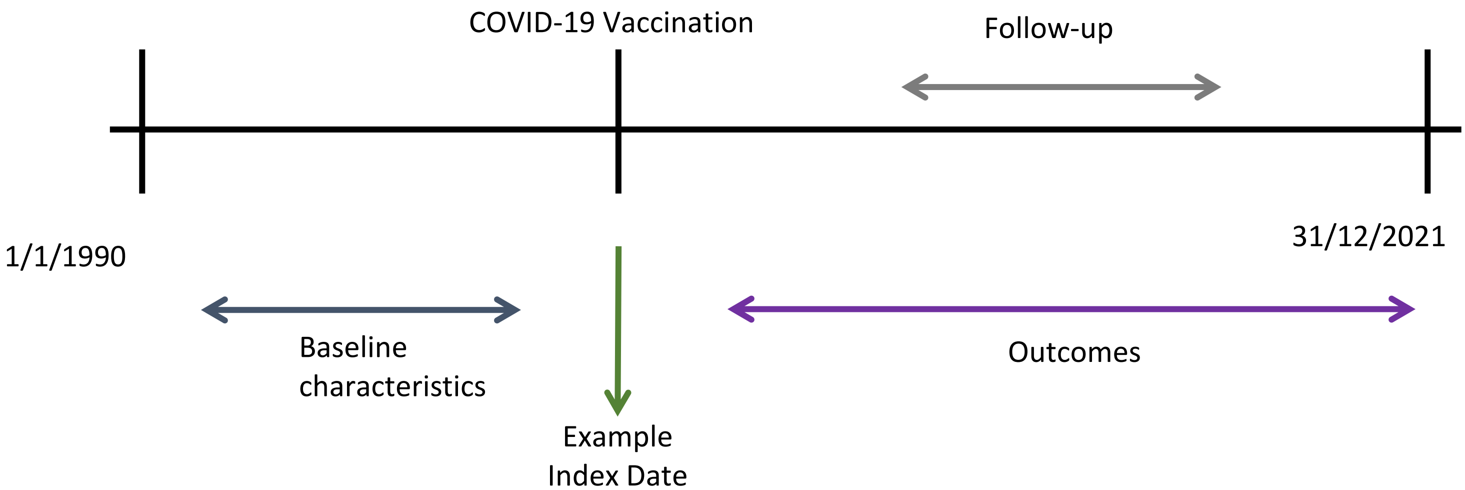
Retrospective cohort design (example in Figure 1)

- This design begins with vaccinated and unvaccinated and looks forward to see who develops the outcomes.
- Unexposed patients will be individually matched to exposed patients.
- Exposed are indexed on the exposure, unexposed are indexed as per their matched exposed participant.
- Exclusion of patients with COVID-19 prior to the index date or matched index date.
- Overall study period is 1/1/1990 – 31/12/2021
    - Patients will be recruited into the study starting from the first day of vaccination in Israel (20/12/2020).
    - Data will be extracted continuously, potentially until 31/12/2021.
    - Background information, e.g. regarding risk factors, will be extracted from the period before the index date.
- Exposed will be matched to unexposed on
    - Age

- Sex
- Population Sector
- Place of residence
- Being health care workers
- Residence in a long-term care facility
- Being confined to their home
- Influenza vaccines in the past 5 years
- Number of general practitioner visits in the past 5 years
- Socioeconomic Status
- A “prognostic score” (the risk for severe outcome from COVID-19, see SAP below).

- Unexposed who receive the vaccine will be censored, together with their matched exposed.

Figure 1: Example Study Design Chart – Cohort Design



Study population

- Inclusion criteria
    - Clalit membership
    - Age 16 or above at the index date
- Exclusion criteria
    - No Clalit membership
    - Age 15 or less at the index date
- Estimated sample size is 3.5 million patients.
- Special population (e.g. pregnant women) will be included as per the above-mentioned inclusion and exclusion criteria.

Variables (Definitions, measurement of, and time periods)

Data will be taken from the inpatient and outpatient Clalit data warehouses. For all variables:

Outcomes

- Diagnosed COVID-19 infection (per PCR)
    - Symptomatic
    - Asymptomatic
- COVID-19 hospitalization
- Defined severe due to COVID-19 infection
- COVID-19 mortality
- Any combination of the above

Exposures(s)

- COVID-19 vaccination, by type of vaccine, in the following periods:
    - 0-20 days after the first dose
    - 0-27 days after the first dose
    - 12-20 days after the first dose
    - 21-27 days after the first dose
    - 0-6 days after the second dose
    - 7+ days after the second dose

Covariates (socio-demographic, clinical, etc.)

- Covariates used for exclusion:
    a. As per list above
- Covariates to be Matched on:
    a. List of variables above to be matched on

Statistical analysis plan

- In each design, patients in the two groups will be matched for variables predicting vaccination, the risk of infection and the risk of severe disease.

- Matching for the risk of severe disease will be accomplished using a Prognostic Score -- the predicted probability of severe disease without the vaccine using all CDC "certain" and "possible" risk criteria.
- Matching will be exact or with a narrow caliper.
- Cumulative incidence curves comparing the risk of infection between the two curves will be drawn using the Kaplan-Meyer method.
- Survival analysis will be performed using the Kaplan-Meier estimator.
    a. Patients selected as matched controls (unexposed) who will then receive the vaccine will be censored at the date of vaccination, and their matched exposed patients will be censored at the same date.
    b. At time windows that do not start at day 0 (receipt of the first vaccine), analysis will contain only pairs of exposed and unexposed who both survived until start of the period.
- In all analyses, subgroup analysis will be performed for:
    a. Age groups
    b. Both Sexes
    c. Important pre-existing diseases
    d. Count of risk comorbidities
    e. Different time windows after receipt of the vaccine

PRIVACY

Data extraction and analyses will be conducted at the Clalit Research Institute (CRI) by employees of the CRI. The raw data extracted are coded, viewed and stored only within the CRI. Once data are analyzed and leave the CRI they are de-identified aggregated and do not contain any identifiable information.

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Real-world VE studies can also answer questions about effectiveness by age-group and risk factors, duration of vaccine protection, protection against severe disease, relative effectiveness of different vaccines, relative effectiveness of one dose vs. two doses, and effectiveness of the vaccine against new strains of SARS-CoV-2 if they are to emerge.

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    - ❖ Patients will be recruited into the study starting from the first day of vaccination in Israel (20/12/2020).
    - ❖ Data will be extracted continuously, potentially until 31/12/2021.
    - ❖ Background information, e.g. regarding risk factors, will be extracted from the period before the index date.
- ❖ Exposed will be matched to unexposed on
    - ❖ Age

- Sex
- Population Sector
- Place of residence
- Number of influenza vaccines in the past 5 years
- Number of CDC risk comorbidities
- Pregnancy

- Unexposed who receive the vaccine will be censored, together with their matched exposed, and then re-enrolled as vaccinated exposed with a new control.

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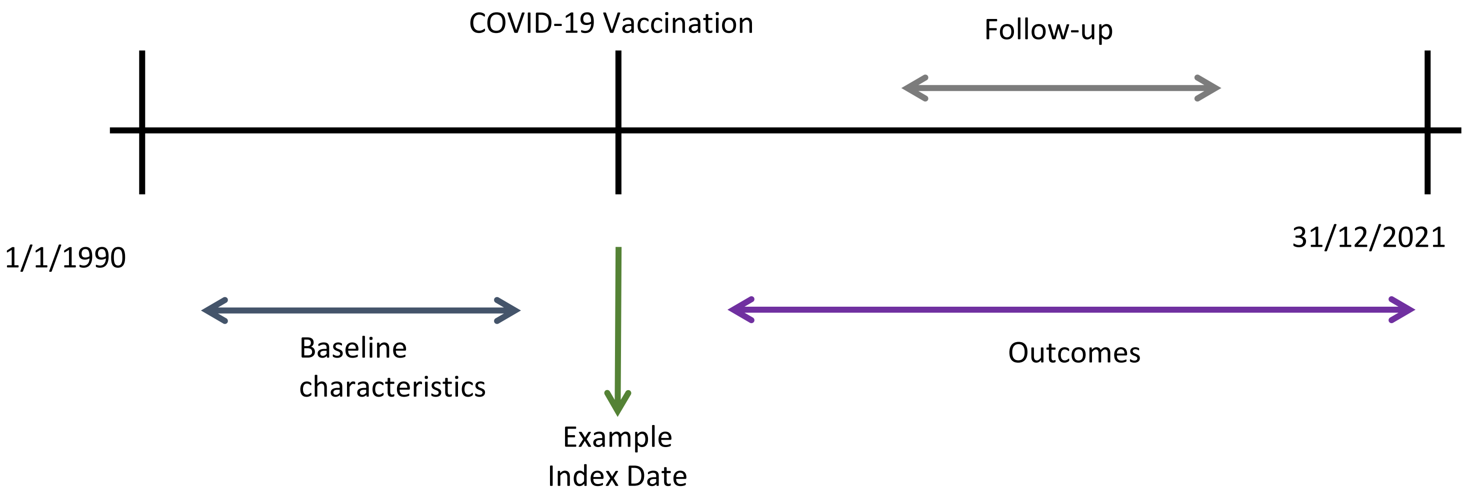

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  - Clalit membership
  - Age 16 or above at the index date
- Exclusion criteria
  - No Clalit membership
  - Age 15 or less at the index date
  - Missing data in BMI or smoking status
  - Unmapped place of residence
  - Being health care workers
  - Residence in a long-term care facility
  - Being confined to their home
  - Interaction with the healthcare system in the days before matching
- Estimated sample size is 3.5 million patients.
- Special population (e.g. pregnant women) will be included as per the above-mentioned inclusion and exclusion criteria.

Variables (Definitions, measurement of, and time periods)

Data will be taken from the inpatient and outpatient Clalit data warehouses. For all variables:

Outcomes

- ❖ Diagnosed COVID-19 infection (per PCR)
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- ❖ COVID-19 hospitalization
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SUMMARY OF CHANGES

- The list of matching variables was altered to its final form:
  - Age
  - Sex
  - Population Sector
  - Place of residence
  - Number of influenza vaccines in the past 5 years
  - Number of CDC risk comorbidities
  - Pregnancy
- The exclusion criteria were altered to their final form:
  - No Clalit membership
  - Age 15 or less at the index date
  - Missing data in BMI or smoking status
  - Unmapped place of residence
  - Being health care workers
  - Residence in a long-term care facility
  - Being confined to their home
  - Interaction with the healthcare system in the days before matching
- Controls who were then vaccinated, and accordingly censored, were allowed to re-enroll as exposed with a new control matched to them.

REFERENCES

[1] Israel: WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard n.d. https://covid19.who.int/region/euro/country/il (accessed August 30, 2020).
[2] Draft landscape of COVID-19 candidate vaccines n.d. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed December 17, 2020).
[3] FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine | FDA n.d. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19 (accessed December 15, 2020).
[4] World Health Organization. WHO SAGE Roadmap for Prioritizing Uses of COVID-19 Vaccines in the Context of Limited Supply n.d. www.who.int/docs/default-source/immunization/sage/covid/sage-prioritization-roadmap-covid19-vaccines.pdf?Status=Temp&sfvrsn=bf227443_2&ua=1 (accessed October 29, 2020).
[5] Israeli Health Ministry sets vaccination priorities - Globes n.d. https://en.globes.co.il/en/article-israeli-health-ministry-sets-vaccination-priorities-1001352844 (accessed December 17, 2020).
[6] Patel MM, Jackson ML, Ferdinands J. Postlicensure evaluation of covid-19 vaccines. JAMA - J Am Med Assoc 2020;324:1939–40. doi:10.1001/jama.2020.19328.
[7] Coronavirus COVID-19 Scientific Research and Resources | Pfizer n.d. https://www.pfizer.com/science/coronavirus (accessed December 17, 2020).
[8] WHO COVID-19 Case definition n.d. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1 (accessed December 17, 2020).