ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

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Brighton Collaboration-ISPE Vax SIG Journal Club

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Background

- Israel requires health insurance
- EHR date to 2000
  - 1-2% annual drop out
- Clalit Health Services (CHS) insures 4.7 million people
  - Insures 53% of Israel's population
  - It's 1 of 4 health systems nationwide
- BNT162b2 mRNA vaccine used
- No referral needed for PCR testing
- Variants
  - B.1.1.7 variant was common
  - The B.1.351 variant was estimated to be rare

Limitations of Clinical Trials

- Expensive, time-consuming
- Highly-controlled conditions unlikely to be replicated in real life settings
- Imperfect product adherence, distribution in real life settings
- Post-licensure studies are still needed to evaluate long-term safety and effectiveness

Real-Word Data for Real-World Evidence

- “Real-world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.” (FDA)
  - Electronic health records
  - Claims and billing data
  - Registries
- RWD → RWE
- RWE plays an increasingly important role in development and regulation of vaccines

“https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

RWE Methods: Data Source

- Analyzed data from Clalit Health Services
  - 4.7million patients, 53% of Israeli population
- Is this a valid source of RWD? What are the pros and cons?

RWE Methods: Retrospective Recruitment

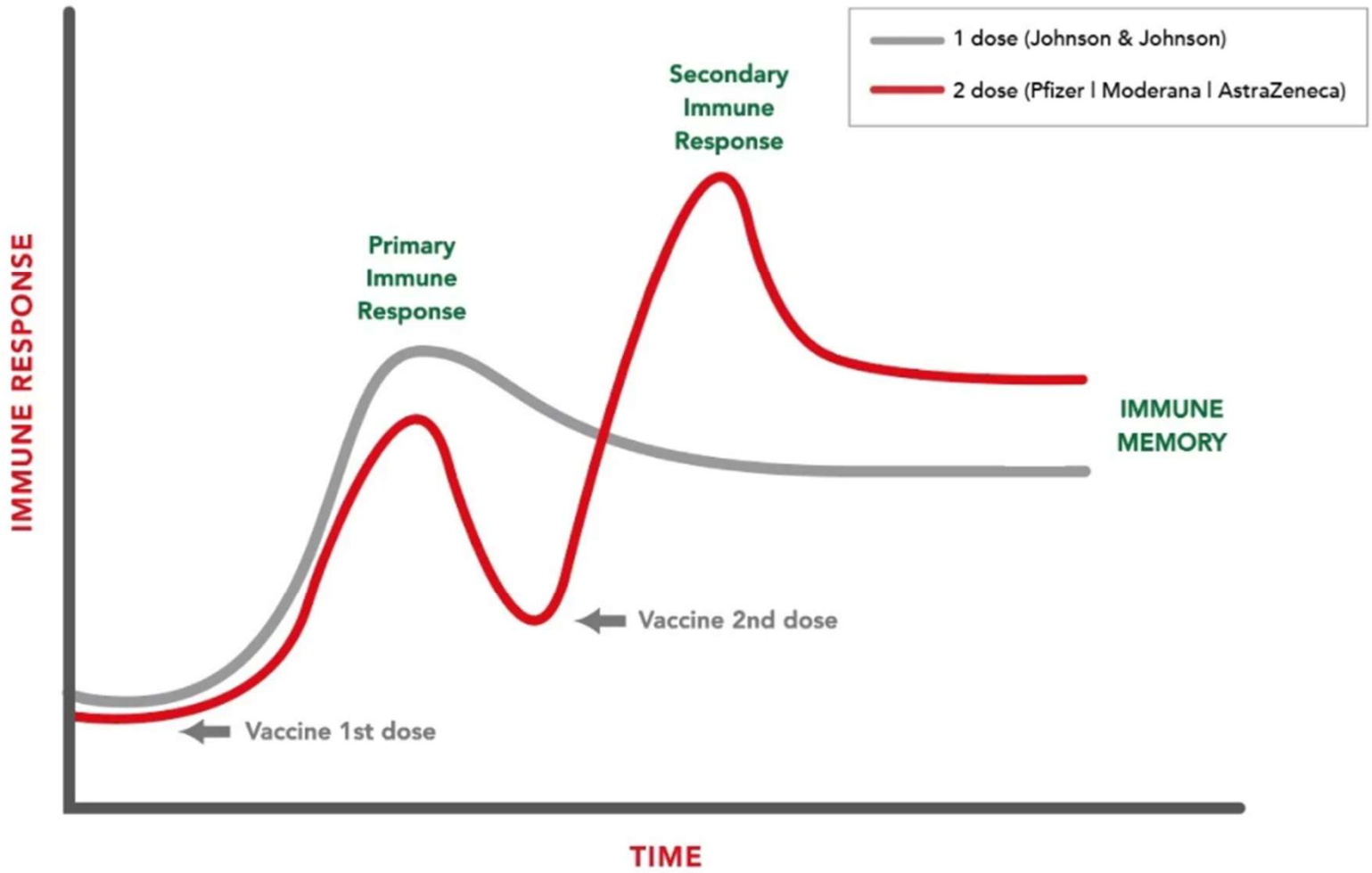
- Enrolled persons >=16 years old vaccinated Dec. 20 to Feb. 1 2021
  - Could not have had previous PCR+ test
  - Must be enrolled in health plan for previous 12 months
- Various exclusions made
  - No documented geostatistical living area
  - Interactions with the health care system in last 3 days
  - Health care workers
  - Nursing home residents
  - Persons medically confined to the home

RWE Methods: Exposure and Outcome Classification

- Administrative codes for diagnoses and procedures
- Review of medical records
- Sensitivity analysis for exposure/outcome misclassification
- Outcomes
  - Documented infection
  - Symptomatic COVID-19
  - COVID-19-related hospitalization
  - Severe illness
  - Death

RWE Methods: Confounder Control

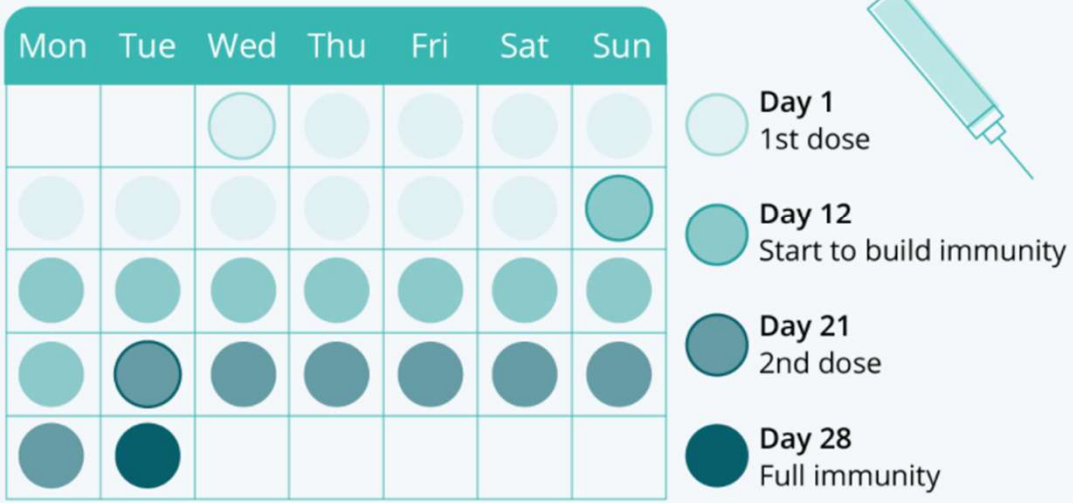
- 1:1 matching using a “rolling cohort” design
  - Age
  - Sex
  - Pregnancy
    - Associated with disease severity & vaccination recommendations that changed over time
  - Total number of preexisting high-risk conditions for COVID
    - As defined by the CDC on Dec. 20 2021
  - Sector (general Jewish, Arab, or ultra-Orthodox Jewish)
  - Residential neighborhood
    - COVID incidence and vaccine uptake vary by geostatistical factors
  - History of influenza vaccination in the previous 5 years
    - 0, 1, 2, 3, 4, >=5 years



https://www.usacs.com/covid-19-vaccine

The Pfizer/BioNTech Vaccination Process

Vaccination process for the Pfizer/BioNTech Covid-19 BNT162b2 vaccine



Source: Pfizer/BioNTech via BBC

RWE Methods: Mitigate Potential Selection Bias

- Periods of of risk changed to days 0-20 and 0-27
- Sensitivity analysis at day 6 estimated HR for all outcomes
- Sensitivity analysis for potential informative censoring
  - When controls became vaccinated, they were censored 7 days post-vaccination + median time from COVID-19 diagnosis to the outcome being studied

Slide 11

1 @nadjavielot@gmail.com can you help clarify why they did this?
Reassigned to Nadja Vielot
Jennifer Gerber, 4/6/2021

2 and add additional slides as needed to highlight RWE-specific methods
Jennifer Gerber, 4/6/2021

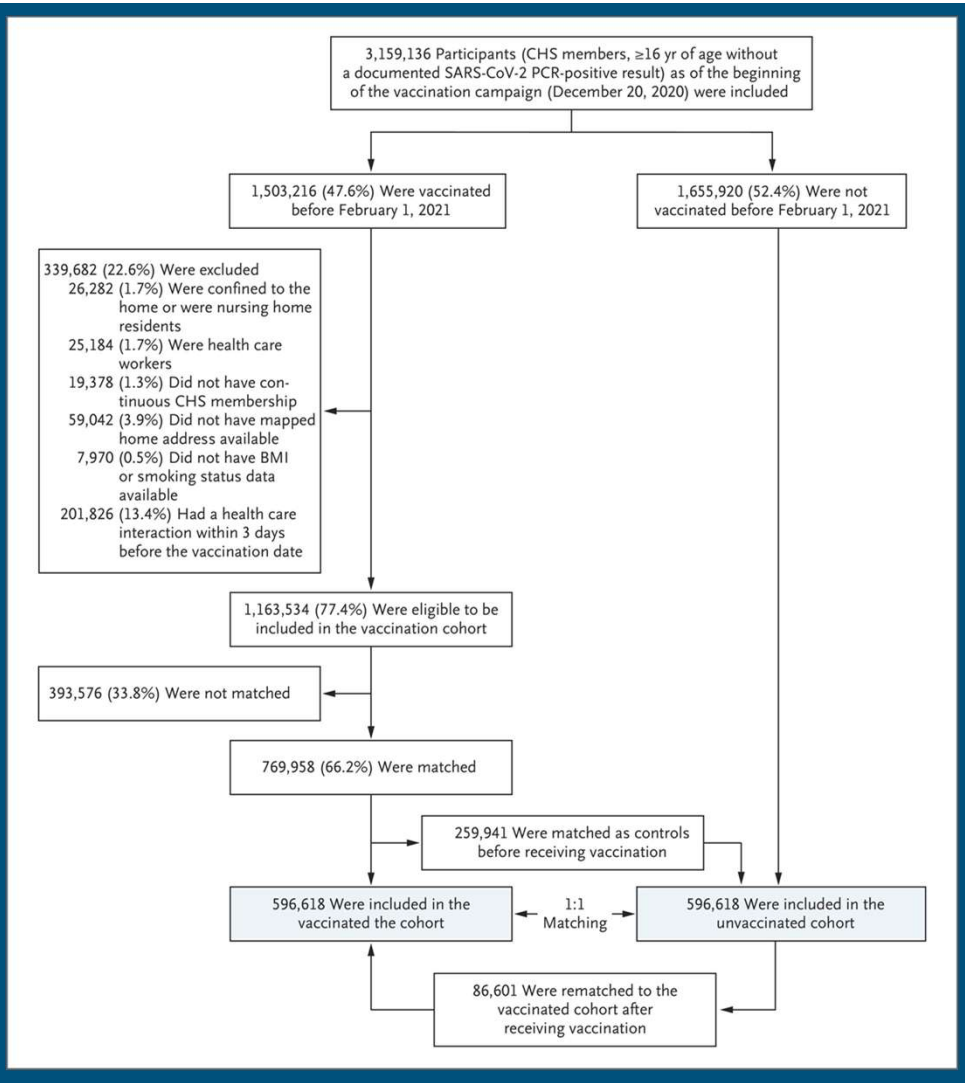
Statistical Methods Used

- Follow-up ended with one of the study outcomes
  - Controls could later move to the vaccinated arm
- Covariate balance evaluated
  - Plotted the mean differences between standardized values for the control vs. vaccinated group
  - Differences <=0.1 acceptable
- Estimated VE as 1-RR using Kaplan-Meier estimator to compare risk of events in matched pairs
  - After 1st dose: Days 14-20
  - After 1st dose: Days 21-27
  - After 2nd dose: Day 7-end of follow-up
- VE = 1-RR in vaccinated vs. unvaccinated for each outcome

Results: Enrollment

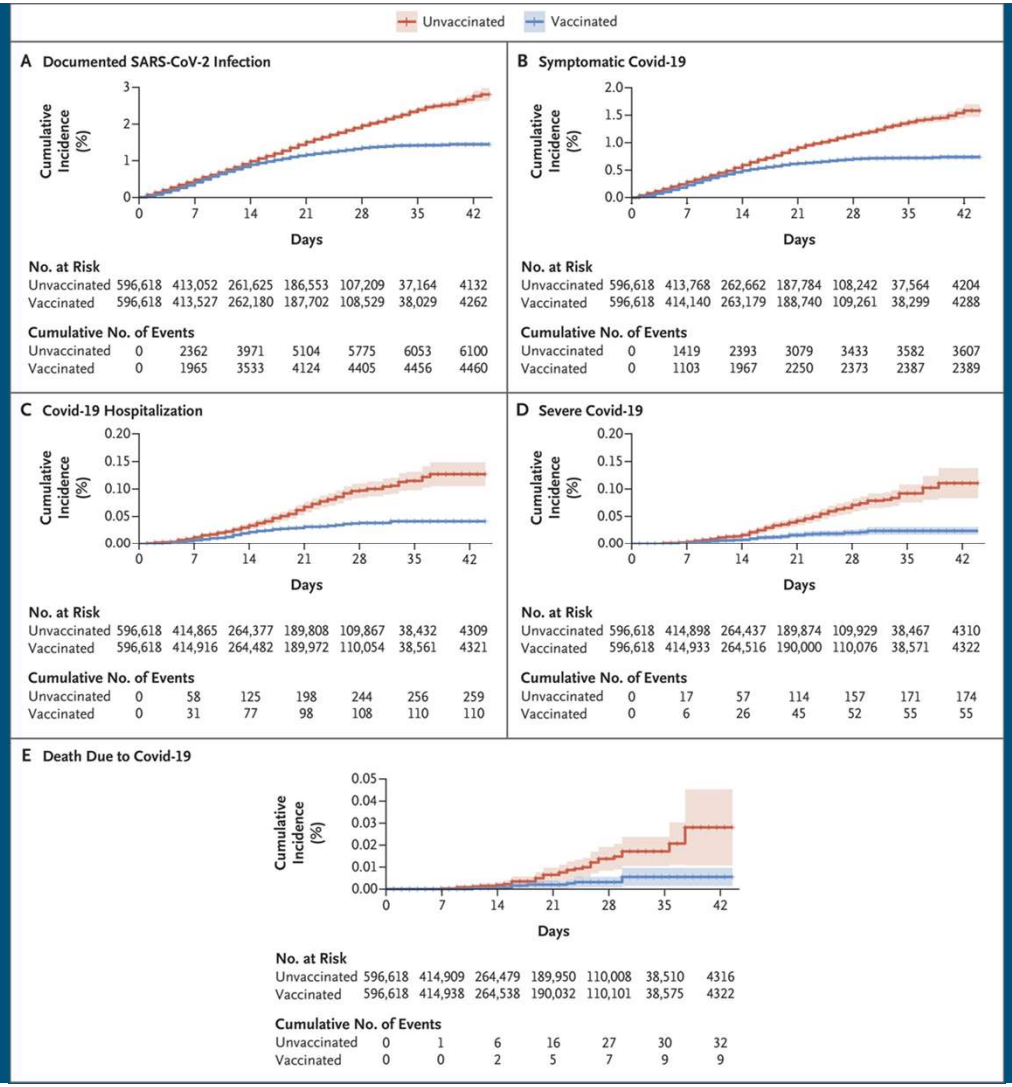
Table 1

N=59,618 unvaccinated in each group (vaccinated & unvaccinated)



Results: HR by Outcome

Figure 2



Results: VE During 3 Time Periods

Table 2

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

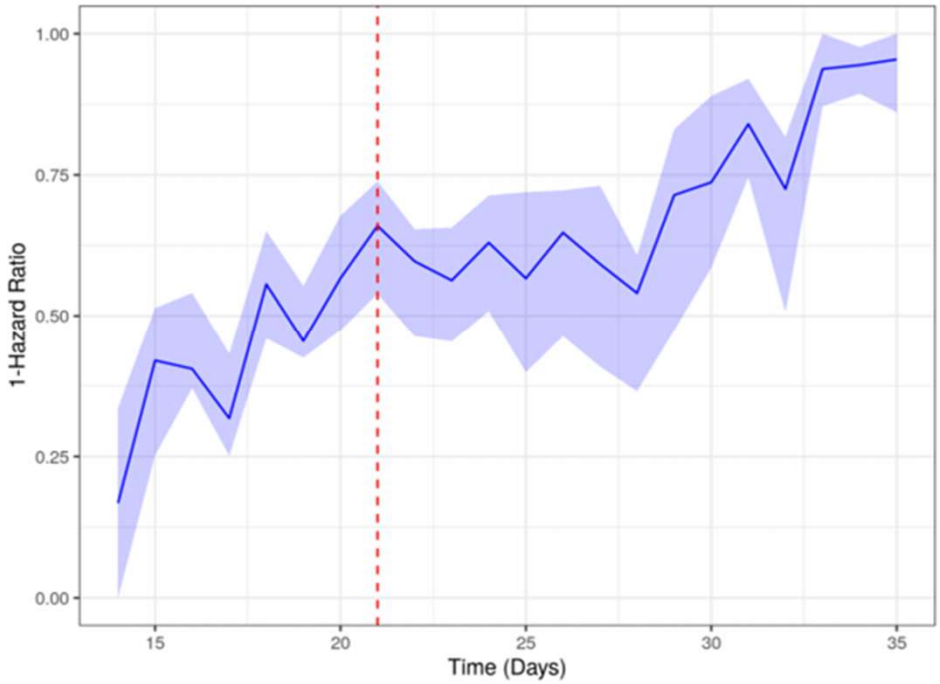
Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*	*% (95% CI)*	*no./1000 persons (95% CI)*
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

Results: HR for Documented Infection

Figure S4

Figure S4 – Daily Hazard Ratio for the Documented Infection Outcome



Legend: One-minus the hazard ratio between vaccinated and unvaccinated groups for the documented infection outcome, per day, for days 14-35 after the first dose. The shaded region is the daily 95% confidence interval, derived using the percentile bootstrap method with 500 repetitions. A vertical dashed red line denotes 21 days, the intended receipt day of the second dose.

Results: VE by Time Period

Table S3

Table S3 – Vaccine Effectiveness for Asymptomatic Infection Proxy

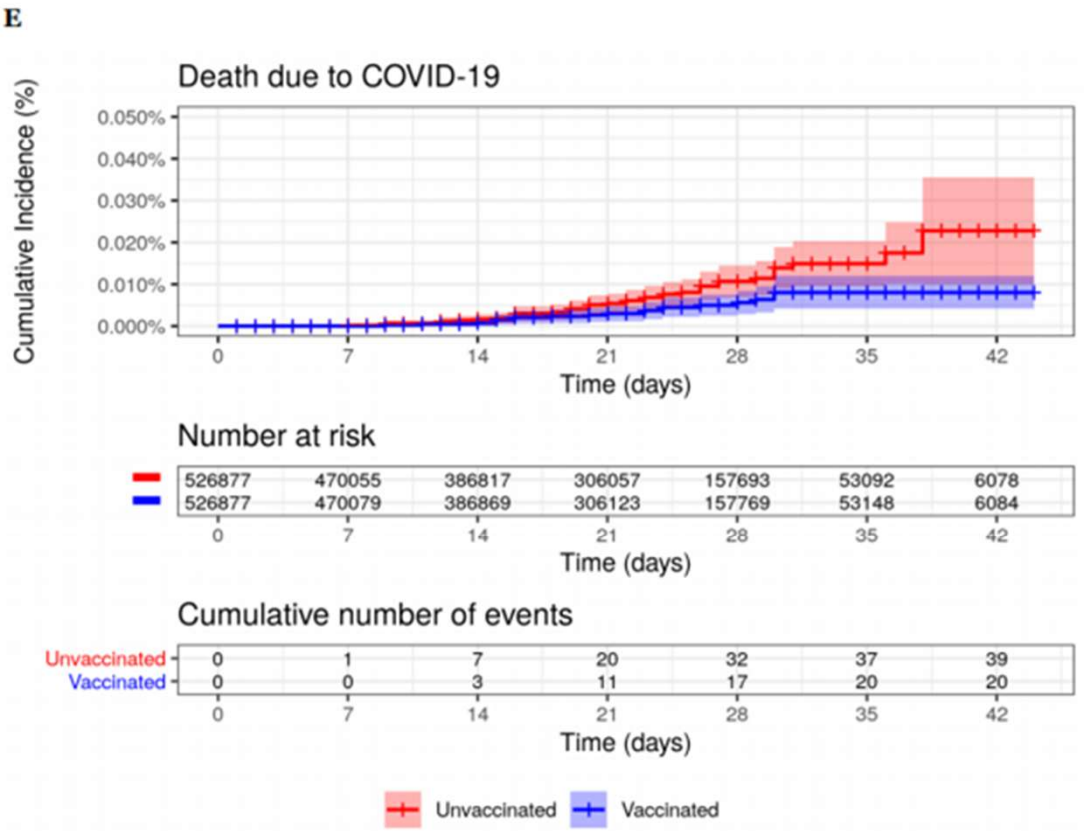
Period	Asymptomatic Infection Proxy	
	1-RR	RD
14 - 20	29% (17%-39%)	0.51 (0.27-0.75)
21 - 27	52% (41%-60%)	0.93 (0.68-1.16)
0 - 20	8% (1%-14%)	0.44 (0.07-0.80)
0 - 27	19% (13%-24%)	1.49 (0.99-1.95)
0 – end of follow-up	42% (34%-49%)	5.08 (3.78-6.72)
2nd - 2nd+6	59% (48%-69%)	1.06 (0.80-1.36)
2nd+7 - end of follow-up	90% (83%-94%)	3.82 (2.46-5.45)

Legend: Estimates and 95% confidence intervals for one minus the risk ratio and the risk difference per 1,000 patients for the asymptomatic infection outcome over different time periods for different populations. Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were only calculated for cells with more than 10 outcomes across both groups. The cumulative incidence curve is included in Figure S5.

Abbreviations: RR, Risk ratio; RD: Risk difference.

Results - High Levels of Uncertainty in VE in Preventing Death

Figure S7, Part E



Legend: Cumulative incidence curves (one minus the Kaplan-Meier risk) for the COVID-19 related death outcome when delaying the censoring of vaccinated controls. Shaded areas are 95% confidence intervals. The tables below the curve show the number at risk at each time point and the cumulative number of events. Vaccine effectiveness estimates are included in Table S5.

Discussion

- Similar results to RCT for VE against symptomatic COVID-19 7 days after the 2nd dose
- Estimates for severe COVID in the RCT were based on 10 cases - there were 229 cases in this study
- Study size allowed for more granular estimates of VE by age than in the RCT
- HCWs not excluded from the RCT but were excluded here

Discussion Question

"The estimated efficacy between the first dose and the second dose was **52% in the trial, as compared with 29% in our study**. This difference may reflect the **high level of transmission in Israel during the study period**,14 which affected both the vaccinated persons and the controls equally during the first 12 days after administration of the first dose. **To eliminate this distortion, we estimated first-dose effectiveness of the vaccine against Covid-19 for the period from days 14 through 20; the estimated effectiveness was 57%.**"

Do you agree with this adjustment?

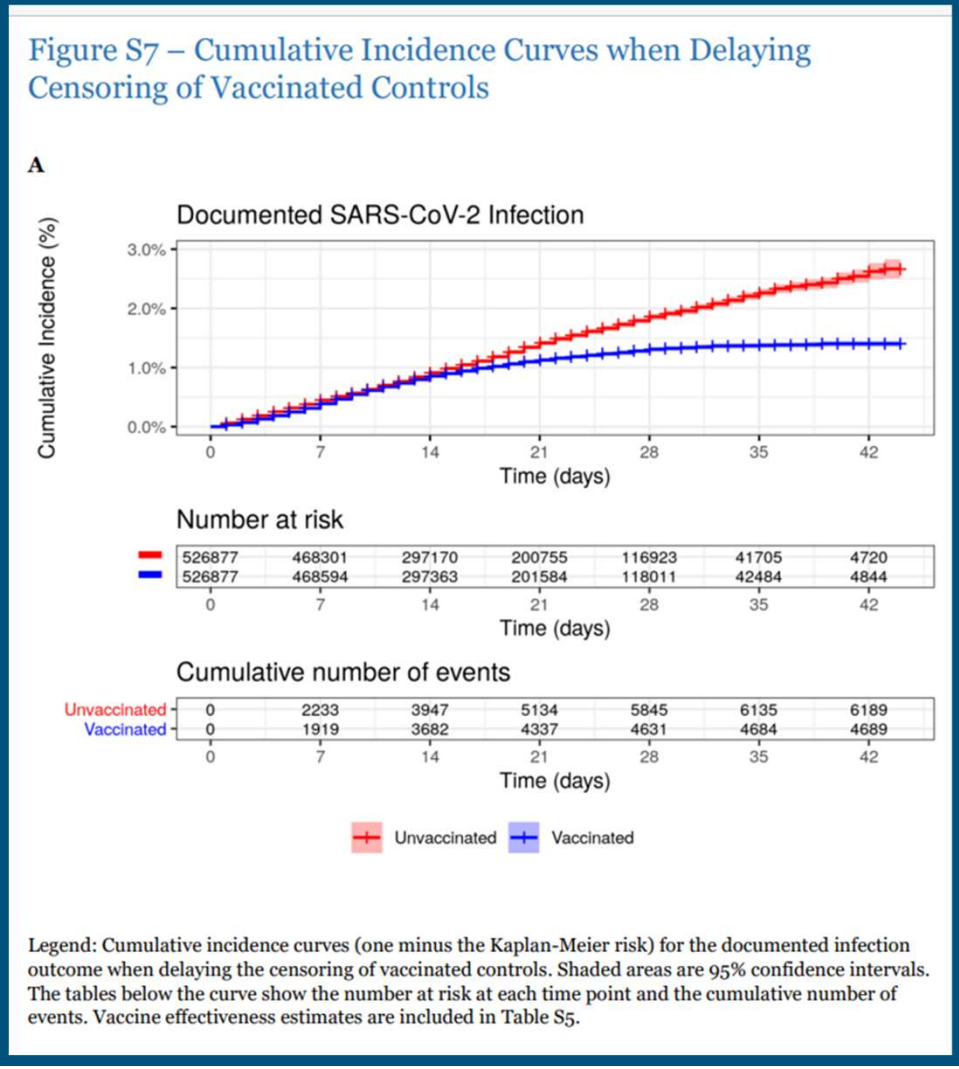
Additional Discussion Questions

1. What do you think of the modifications made to counteract the “healthy vaccinee/ health user” bias?
2. Do you think additional sensitivity analyses should have been done?
3. What modifications would need to be made to do a similar RWE study in your own country?
4. If we could analyze data from all 4 health systems in Israel, what safety outcomes would there likely be sufficient power to study?
5. Is it important for future studies to look at VE by vaccine type and age group? What sample size might be needed?

Extra Slides

Sensitivity Analyses: Informative Censoring

Figure S7



Sensitivity Analyses: Informative Censoring

Table S5

Table S5 – Risk Ratios and Risk Differences for the Sensitivity Analysis when Delaying Censoring of Vaccinated Controls

Period	Documented Infection		Symptomatic Infection		Hospitalization		Severe Disease		Death	
	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)	1-RR (95-CI)	RD (95-CI)
Days 14-20 after 1st dose	43% (38%-49%)	1.87 (1.56-2.18)	54% (48%-60%)	1.40 (1.18-1.66)	64% (44%-77%)	0.18 (0.11-0.26)	46% (23%-67%)	0.09 (0.04-0.16)	44% (-36%-83%)	0.01 (-0.01-0.04)
Days 21-27 after 1st dose	60% (54%-66%)	2.30 (1.96-2.61)	65% (58%-71%)	1.32 (1.09-1.57)	79% (59%-91%)	0.21 (0.13-0.29)	77% (54%-91%)	0.14 (0.08-0.20)	62% (-5%-91%)	0.03 (-0.00-0.07)
Day 7 after 2nd dose - end of follow-up	92% (87%-95%)	8.12 (6.42-10.01)	95% (89%-99%)	4.43 (3.23-6.03)	89% (60%-100%)	0.23 (0.10-0.38)	92% (70%-100%)	0.24 (0.09-0.42)	NA	NA

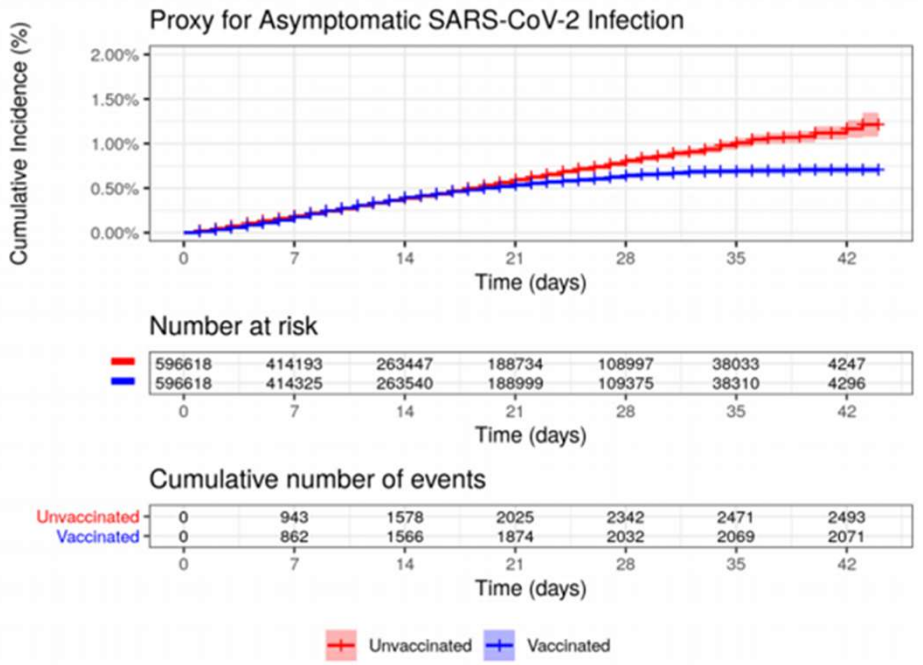
Legend: Estimates and 95% confidence intervals for one minus the risk ratio and the risk difference per 1,000 patients for different outcomes over different time periods for the entire study population in the analysis delaying censoring of vaccinated controls. This analysis does not allow vaccinated controls to re-enroll as exposed, so individuals do not contribute time to both study groups. Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were only calculated for cells with more than 10 outcomes across both groups. Cumulative incidence curves are included in Figure S7.

Abbreviations: RR: Risk ratio; RD: Risk difference; NA: Not available.

Results - RWE Impact on Ability to Measure Asymptomatic Infections

Figure S5

Figure S5 – Cumulative Incidence of Asymptomatic Infection Proxy



Legend: Cumulative incidence curve (one minus the Kaplan-Meier risk) for the proxy for the asymptomatic infection outcome starting from the day of the first dose. Shaded areas are 95% confidence intervals. The tables below the curve show the number at risk at each time point and the cumulative number of events. Vaccine effectiveness estimates are included in Table S3.

In the absence of systematic periodic testing for SARS-CoV-2 among asymptomatic people in Israel, documented asymptomatic infections do not account for all asymptomatic infections, and likely cannot accurately capture vaccine effectiveness for this outcome.