Supplementary Appendix

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

Supplement to: 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

Supplementary Materials

Contents

Data Sharing

Aggregated data and code for reproducing the results of our primary analysis could be found in the following link: https://github.com/yairgoldy/BNT162b2_booster_dose

Methods - matching and weighting approaches

In order to validate our findings, we conducted two independent secondary analyses which rely on matching fully vaccinated individuals who received a booster dose with similar individuals who received only two vaccine doses and on weighting.

The matching approach was similar to that conducted by Dagan et.al. [1], and aimed at comparing individuals' risk rather than rate based on person-days Briefly, each individual in the 'booster' cohort was matched to an individual who was in the 'no-booster' cohort on the booster-vaccination day. Matching was conducted based on the following characteristics: age group (60-69,70-79 and 80+), gender, second vaccine dose week and demographic group (general Jewish, Arab, ultra-Orthodox). Follow-up for both individuals ended at the time of infection. Both individuals in a pair were censored at the end of the study or at the time the 'no-booster' individual got a booster dose. We calculated the probability of being free of infection in the two cohorts as a function of time using the Kaplan-Meier estimator, and compared the survival probabilities of the two cohorts at the end of the study. For each cohort, we calculated the probability of an event occurring between day 12 following the boost and the end of the study, among individuals still at risk on day 12. We used the ratio between the probabilities of the two cohorts as an estimate for the risk ratio for our population over the study time. We generated 95% confidence intervals around this estimate using the percentile bootstrap method with 200 repetitions.

A second approach aims at calculating the rates of infection and severe COVID-19 using a finer tabulation than in the Poisson regression. This was done by weighting person-days, ensuring that days in the two cohorts are comparable (standardization of days). For both groups, 'booster' and 'no-booster', we tabulated person days according to the following set of variables: calendar date (each day a separate category), city (small cities representing less than 1000 individuals were grouped together), age group (five-year categories), gender, second vaccine dose week and demographic group (general Jewish, Arab, ultra-Orthodox Jewish). In each category combination, we weighted the 'no-booster' group so that their effective number of person-days matched that of the 'booster' group in the same category combination. (Thus, the corresponding weights for the 'booster' group were set to 1.) We then summed, over the category combinations, the weighted number of infections and severe COVID-19 cases. For the latter, we considered only infections documented at least one week before the date on which the data were extracted, in order to minimize the effect of censored information. Using the weights, rates per 100,000 person days were calculated for the 'booster' and 'no-booster' groups, and their ratio and difference were computed. Confidence intervals were calculated using non-parametric bootstrapping with 200 bootstrap samples.

Supplementary Analysis 1

For the matched analysis, we obtained an estimate of 11.6-fold (95% CI [4.5-18.5]) reduction in rate ratio for confirmed infection. Due to the very small number of severe cases, and the high censoring proportion, calculation for severe COVID-19 was not possible.

For the weighted approach, our analysis yielded an estimate of 9.3 (95% CI: [8.5, 10.4]) for the rate ratio of confirmed infection, and an estimate of 13.2 (95% CI: [9.8, 20.2]) for severe infection; the incidence rate differences per 100,000 person days are 75.2 and 8.8, respectively.

Supplementary Figures

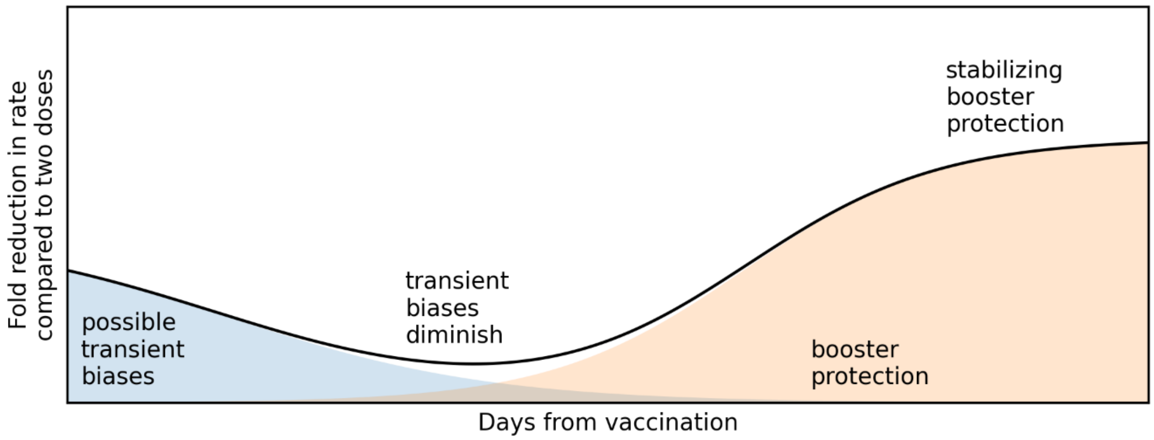

Figure S1. A conceptual schematic demonstrating the possible underlying dynamics of the results in Figure 2.

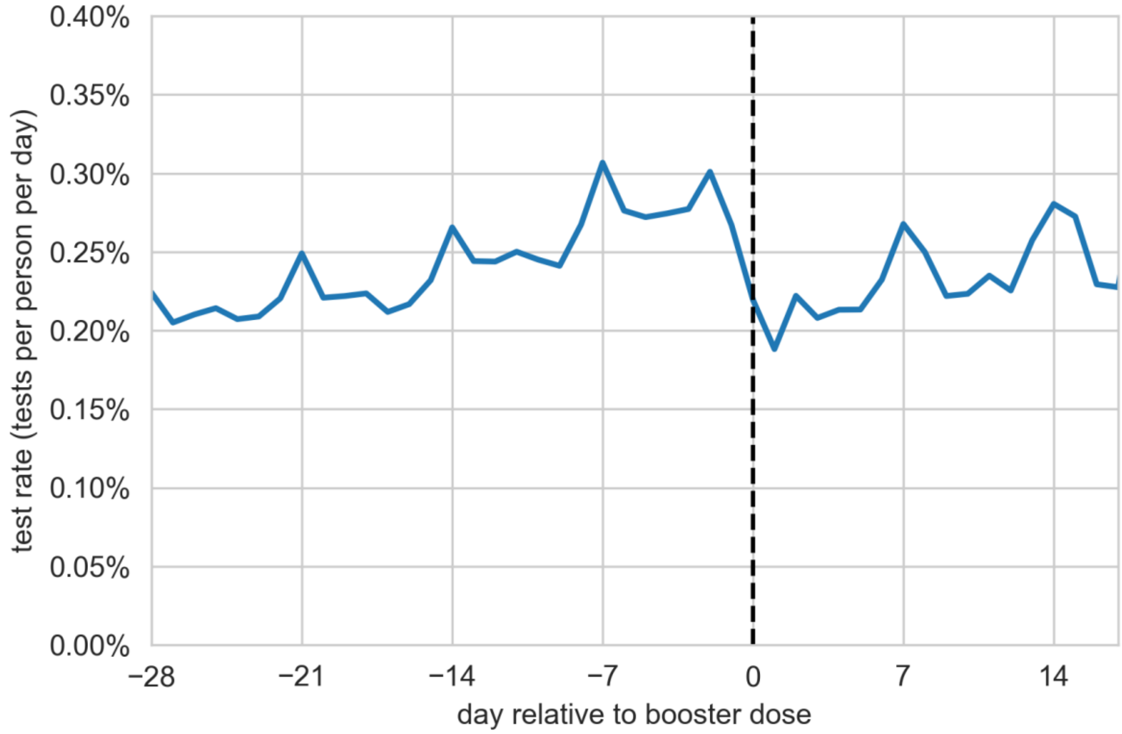

Figure S2. The daily rate of PCR tests per person as a function of the time relative to the administration of the booster dose. A decrease in the rate of testing is observable just after the administration of the booster, likely reflecting transient behavioural changes in care-seeking behaviour or risk-avoidance.

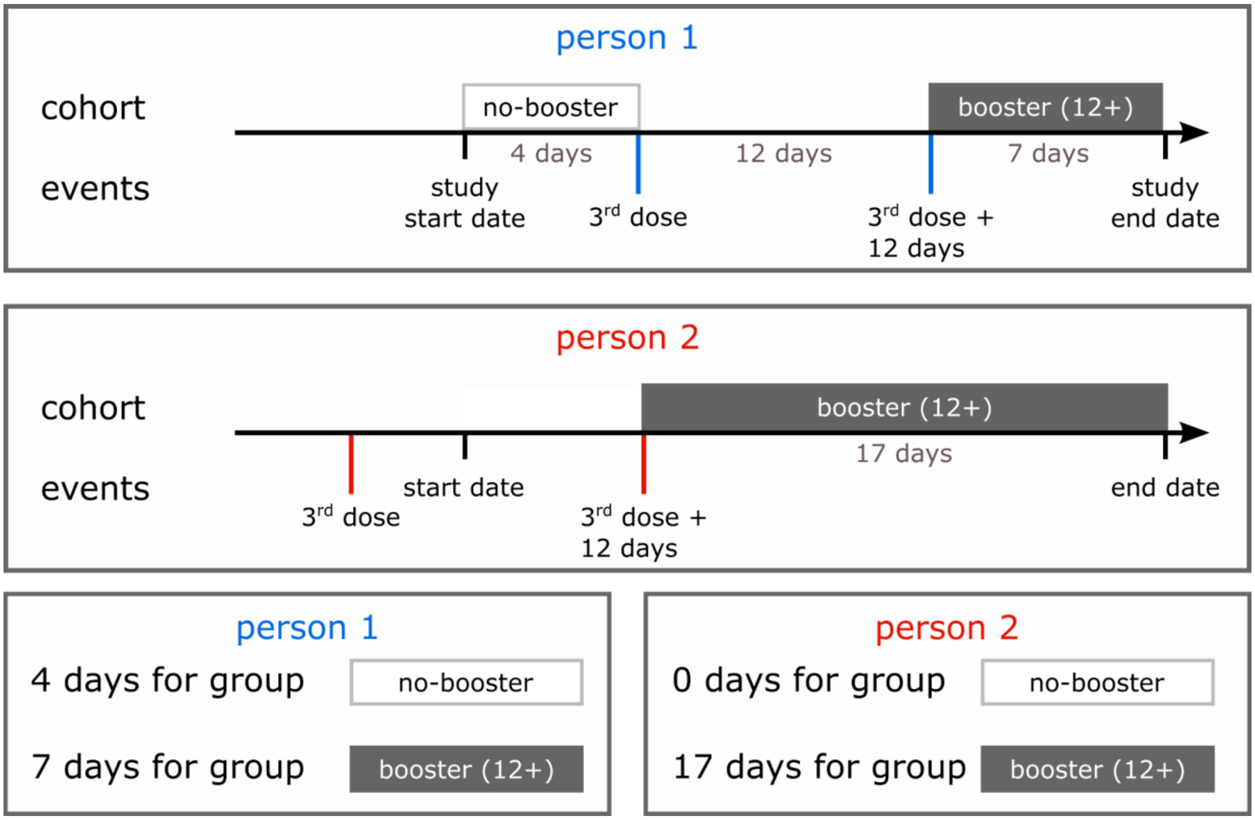

Figure S3. A schematic illustration of the allocation for the dynamic cohorts. We show two example timelines for two different individuals, and detail the cohort they contribute to at each point in time as well as the total days-at-risk for each person in each cohort.

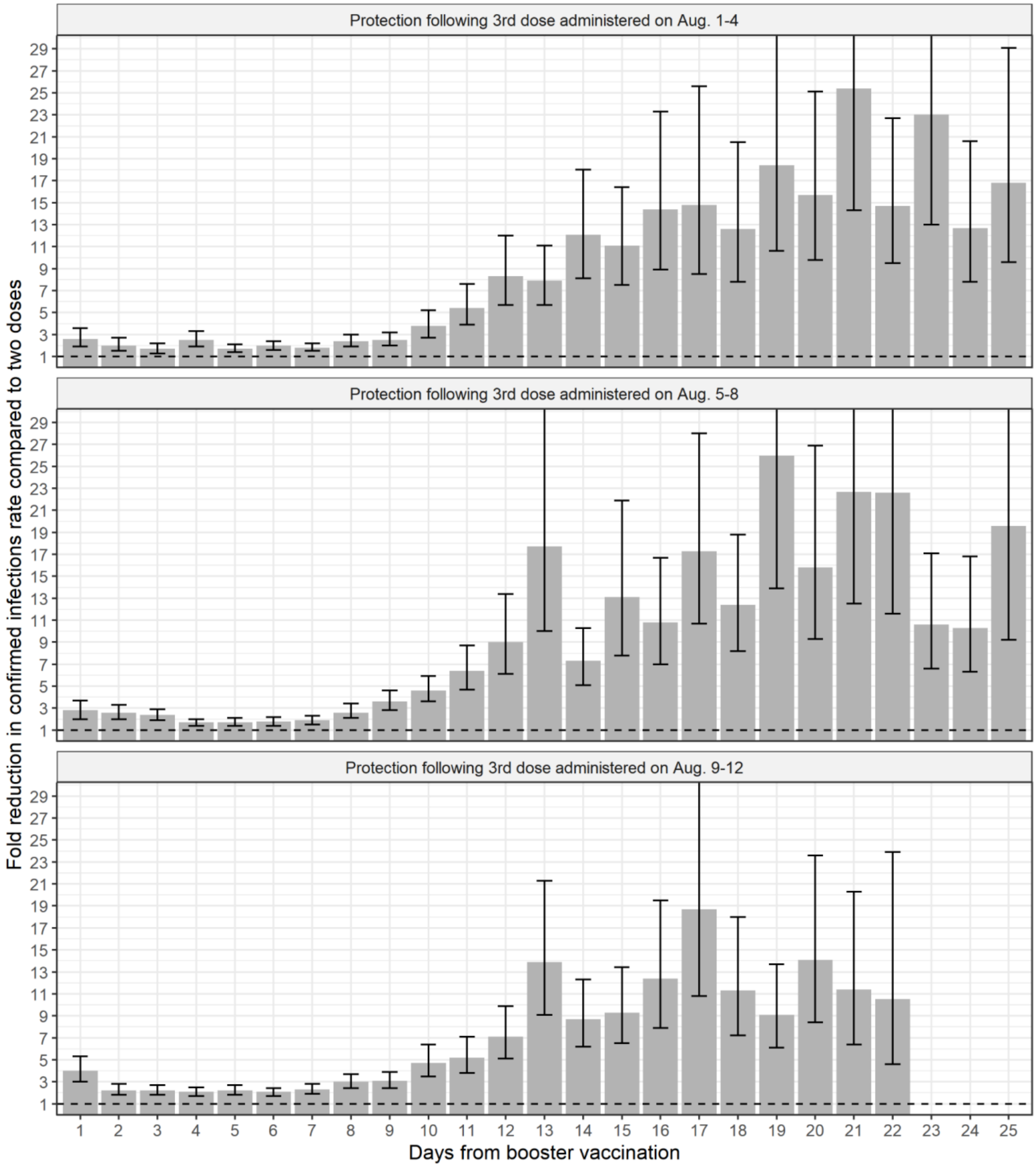

Figure S4. Sensitivity analysis across periods of booster vaccination for the booster protection against confirmed infection as a function of the number of days following the booster dose. Protection is given as a fold change in risk relative to people who received only two vaccine doses.

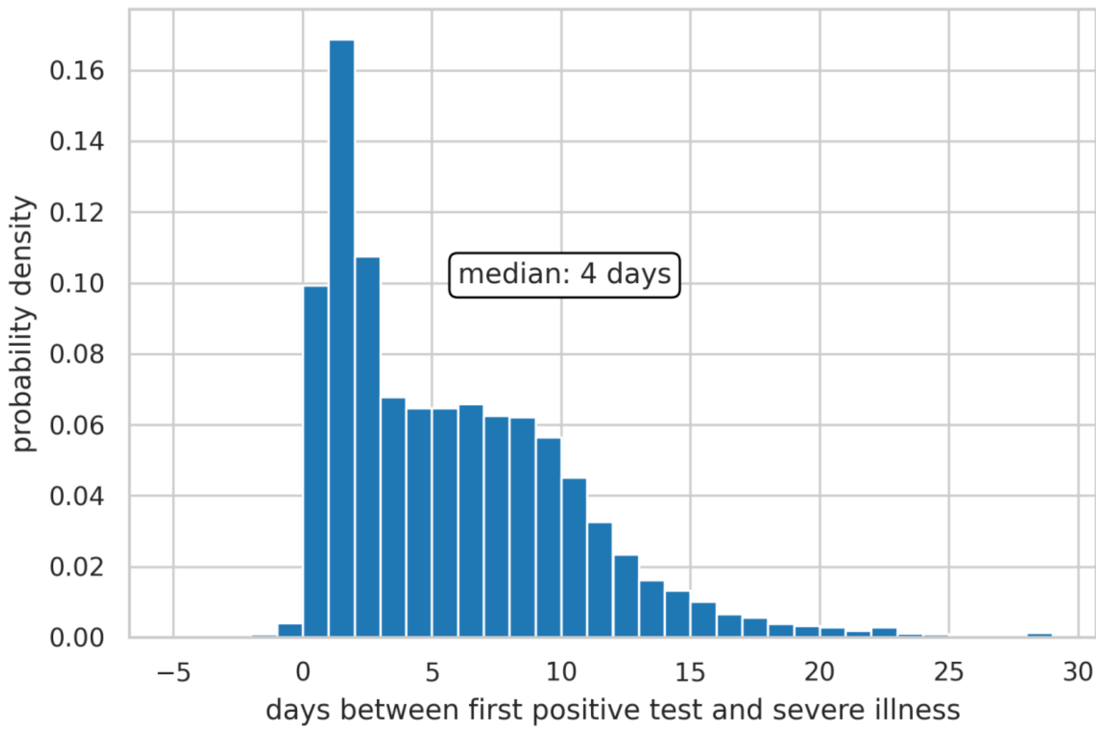

Figure S5. The distribution of time between first positive sample and severe illness for confirmed cases between November 1st, 2020 and March 1st, 2021.

Table S1: Poisson regression results for confirmed SARS-CoV-2 infection. Reference group for dates is 2021-08-10.

term	*estimate*	*std.error*
(Intercept)	-7.05	0.05
Age category = 70-79 v <70	-0.13	0.03
Age category = 80+ v <70	-0.08	0.04
Gender = male v female	0.17	0.03
Date 2021-08-11	0.07	0.07
Date 2021-08-12	-0.10	0.08
Date 2021-08-13	-0.52	0.09
Date 2021-08-14	-0.77	0.10
Date 2021-08-15	0.51	0.07
Date 2021-08-16	0.24	0.07
Date 2021-08-17	0.31	0.07
Date 2021-08-18	0.35	0.08
Date 2021-08-19	0.21	0.08
Date 2021-08-20	-0.35	0.10
Date 2021-08-21	-0.56	0.11
Date 2021-08-22	0.36	0.08
Date 2021-08-23	0.23	0.08
Date 2021-08-24	0.30	0.08
Date 2021-08-25	0.27	0.08
Date 2021-08-26	0.38	0.08
Date 2021-08-27	-0.19	0.10
Date 2021-08-28	-0.47	0.11

Date 2021-08-29	0.31	0.08
Date 2021-08-30	0.21	0.09
Date 2021-08-31	0.10	0.09
Vac period Feb 1-15 v Jan 16-30	-0.08	0.03
Vac period Feb 16-28 v Jan 16-30	-0.18	0.05
Sector = Arab v General Jewish	-0.61	0.05
Sector = Ultra-Orthodox v General Jewish	0.49	0.05
Cohort = 'booster' v no booster	-2.43	0.04

Table S2: Poisson regression results for severe COVID-19 disease. Reference group for dates is 2021-08-10.

term	*estimate*	*std.error*
(Intercept)	-10.85	0.23
Age category = 70-79 v <70	0.78	0.15
Age category = 80+ v <70	1.76	0.14
Gender = male v female	0.80	0.11
Date 2021-08-11	0.10	0.26
Date 2021-08-12	0.10	0.28
Date 2021-08-13	-0.12	0.30
Date 2021-08-14	-0.09	0.30
Date 2021-08-15	0.65	0.25
Date 2021-08-16	0.37	0.28
Date 2021-08-17	-0.19	0.34
Date 2021-08-18	0.63	0.27
Date 2021-08-19	0.59	0.28
Date 2021-08-20	-0.18	0.37
Date 2021-08-21	-0.18	0.37
Date 2021-08-22	0.46	0.30
Date 2021-08-23	0.62	0.29
Date 2021-08-24	-0.03	0.37
Date 2021-08-25	0.01	0.37
Date 2021-08-26	0.23	0.35
Vac period Feb 1-15	-0.19	0.12
Vac period Feb 16-28	-0.53	0.21

Sector = Arab v General Jewish	-0.26	0.20
Sector = Ultra-Orthodox v General Jewish	0.05	0.26
Cohort = ‘booster’ v no booster	-2.97	0.21

References

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