Supplementary Appendix

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

Supplement to: Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med. DOI: 10.1056/NEJMoa2114228

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_waning_immunity

Supplementary Methods 1 - Database

The Ministry of Health (MOH) in Israel collects all COVID-19 related variables in a central database. These include data on all PCR tests and results, vaccination dates and type (almost all received the Pfizer-BioNTech vaccine), daily clinical status of all COVID-19 hospitalized patients, and COVID-19 related deaths. Specifically, the data used for conducting the study included vaccination dates (first and second doses), PCR tests (dates and results), hospital admission dates (if relevant), clinical severity status (hospitalization, severe illness, death), and demographic variables such as age, sex, and demographic group (General Jewish, Arab, ultra-Orthodox Jewish). Severe disease is defined as a resting respiratory rate >30 breaths per minute, oxygen saturation on room air <94%, or ratio of PaO2 to FiO2 <300. Those who died from COVID-19 during the follow-up period were included as severe disease cases.The fact Israel has a central health care system increases the coverage and reliability of the data. A few individuals with missing observations on gender or demographic sector were removed from our analysis file. They comprised ≈0.1% of the total population and were most likely missing completely at random.

The MOH database collects data from multiple sources. These include all MOH-approved laboratories performing PCR testing in Israel, including private laboratories, hospitals and Health maintenance organizations (HMOs) which together insure the entire Israeli population. Quality assurance of data flow was performed extensively over the course of the pandemic, is monitored daily by the MOH and is continuously used for public health decision-making.

PCR testing for SARS-CoV-2 is free-of-charge and widely available in Israel. Testing is required for symptomatic persons (such as fever or acute respiratory illness), people who were in close contact with an infected individual, or travelers returning from abroad. In order to perform a test, persons are required to provide their unique identification number. A nasal or nasopharyngeal swab is collected and sent to a certified laboratory where it is tested (using national testing standards) by reverse transcription quantitative PCR. All sampling laboratories digitally report the data to the MOH database. Turn-around intervals between nasopharyngeal sampling and test result are 48 hours at most and typically within 24 hours..

Surveillance of COVID-19-associated hospitalizations is continuously performed by the MOH. Data from all hospitals are updated daily, and often twice a day. In accordance with national guidelines, health-care providers report all hospitalizations and deaths among individuals with laboratory-confirmed SARS-CoV-2 infection.

Table S1: Number of individuals and events for the different vaccination periods from July 11, 2021, to July 31, 2021.

Time period	Age category	N (individuals)	Positive SARS-CoV-2 tests	Severe COVID-19
Jan, 16-31	16-39	125977	464	1
Jan, 16-31	40-59	243741	967	9
Jan, 16-31	60+	706990	2348	241
Feb, 1-15	16-39	195961	751	1
Feb, 1-15	40-59	418282	1458	10
Feb, 1-15	60+	358592	973	97
Feb, 16-28	16-39	352722	1060	0
Feb, 16-28	40-59	328038	1051	4
Feb, 16-28	60+	67028	148	12
Mar, 1-15	16-39	549090	1474	0
Mar, 1-15	40-59	208064	565	3
Mar, 1-15	60+	61886	107	14
Mar, 16-31	16-39	496779	988	0
Mar, 16-31	40-59	190326	366	0
Mar, 16-31	60+	62317	105	5
Apr	16-39	217731	305	0
Apr	40-59	78281	118	1
Apr	60+	29189	36	4
May	16-39	67252	96	0
May	40-59	22230	31	0
May	60+	10922	15	1

Table S2: Demographic and clinical characteristics of persons aged 16-39 for the different vaccination periods. Positive SARS-CoV-2 PCR tests (confirmed infections) and Severe COVID-19 refer to the study period from July 11, 2021 to July 31, 2021.

Age group 16-39							
Variable (%)	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
Total vaccinated (n)	125,977	195,961	352,722	549,090	496,779	217,731	67,252
Positive SARS-CoV-2 PCR tests	464	751	1060	1474	988	305	96
Severe COVID-19	1	1	0	0	0	0	0
gender = male	65,494 (52%)	99,949 (51%)	183,461 (52%)	282,701 (52%)	240,892 (49%)	104,670 (48%)	31,761 (47%)
Previous SARS-CoV-2 PCR tests = 0	59,754 (47%)	109,421 (56%)	218,052 (62%)	360,572 (66%)	340,850 (69%)	155,581 (72%)	49,096 (73%)
Previous SARS-CoV-2 PCR tests = 1	29,329 (23%)	49,172 (25%)	86,795 (25%)	127,137 (23%)	106,037 (21%)	42,186 (19%)	12,187 (18%)
Previous SARS-CoV-2 PCR tests = 2+	36,894 (29%)	37,368 (19%)	47,875 (14%)	61,381 (11%)	49,892 (10%)	19,964 (9%)	5969 (9%)
Demographic: General Jewish Population	101,704 (81%)	158,622 (81%)	291,317 (83%)	446,622 (81%)	332,470 (67%)	130,511 (60%)	46,456 (69%)
Demographic: Arabs	15,929 (13%)	27,493 (14%)	38,059 (11%)	66,859 (12%)	130,832 (26%)	71,442 (33%)	15,165 (23%)
Demographic: ultra-Orthodox Jews	8344 (7%)	9846 (5%)	23,346 (7%)	35,609 (7%)	33,477 (7%)	15,778 (7%)	5631 (8%)

Table S3: Demographic and clinical characteristics of persons aged 40-59 for the different vaccination periods. Positive SARS-CoV-2 PCR tests (confirmed infections) and Severe COVID-19 refer to the study period from July 11, 2021 to July 31, 2021.

Age group 40-59							
Variable (%)	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
Total vaccinated (n)	243,741	418,282	328,038	208,064	190,326	78,281	22,230
Positive SARS-CoV-2 PCR tests	967	1458	1051	565	366	118	31
Severe COVID-19	9	10	4	3	0	1	0
gender = male	113,624 (47%)	200,339 (48%)	167,656 (51%)	102,223 (49%)	92,509 (49%)	37,876 (48%)	10,564 (48%)
Previous SARS-CoV-2 PCR tests = 0	134,347 (55%)	274,781 (66%)	231,481 (71%)	154,760 (74%)	145,572 (77%)	61,549 (79%)	17,790 (80%)
Previous SARS-CoV-2 PCR tests = 1	55,091 (23%)	93,148 (22%)	67,363 (21%)	37,247 (18%)	30,724 (16%)	11,198 (14%)	2865 (13%)
Previous SARS-CoV-2 PCR tests = 2+	54,303 (22%)	50,353 (12%)	29,194 (9%)	16,057 (8%)	14,030 (7%)	5534 (7%)	1575 (7%)
Demographic: General Jewish Population	215,792 (89%)	360,634 (86%)	274,639 (84%)	162,197 (78%)	128,495 (68%)	50,271 (64%)	16,873 (76%)
Demographic: Arabs	18,080 (7%)	44,278 (11%)	39,765 (12%)	37,530 (18%)	53,800 (28%)	24,625 (32%)	4184 (19%)
Demographic: ultra-Orthodox Jews	9869 (4%)	13,370 (3%)	13,634 (4%)	8337 (4%)	8031 (4%)	3385 (4%)	1173 (5%)

Table S4: Demographic and clinical characteristics of persons aged 60 or older for the different vaccination periods. Positive SARS-CoV-2 PCR tests (confirmed infections) and Severe COVID-19 refer to the study period from July 11, 2021 to July 31, 2021.

Age group 60+							
Variable (%)	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
Total vaccinated (n)	706,990	358,592	67,028	61,886	62,317	29,189	10,922
Positive SARS-CoV-2 PCR tests	2348	973	148	107	105	36	15
Severe COVID-19	241	97	12	14	5	4	1
gender = male	339,078 (48%)	158,963 (44%)	29,018 (43%)	25,447 (41%)	24,997 (40%)	11,073 (38%)	4027 (37%)
Previous SARS-CoV-2 PCR tests = 0	506,665 (72%)	270,999 (76%)	52,502 (78%)	49,523 (80%)	50,521 (81%)	23,418 (80%)	8810 (81%)
Previous SARS-CoV-2 PCR tests = 1	119,818 (17%)	54,817 (15%)	9594 (14%)	8192 (13%)	7326 (12%)	3489 (12%)	1268 (12%)
Previous SARS-CoV-2 PCR tests = 2+	80,507 (11%)	32,776 (9%)	4932 (7%)	4171 (7%)	4470 (7%)	2282 (8%)	844 (8%)
Demographic: General Jewish Population	653,286 (92%)	307,527 (86%)	51,157 (76%)	47,967 (78%)	45,589 (73%)	21,068 (72%)	8963 (82%)
Demographic: Arabs	27,994 (4%)	35,933 (10%)	12,465 (19%)	11,010 (18%)	13,743 (22%)	6731 (23%)	1391 (13%)
Demographic: ultra-Orthodox Jews	25,710 (4%)	15,132 (4%)	3406 (5%)	2909 (5%)	2985 (5%)	1390 (5%)	568 (5%)

Figure S1: Rate of documented SARS-CoV-2 infection (per 1,000 persons) from July 11, 2021, to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and a finer age grouping. White bars represent periods at which only designated groups (e.g. healthcare workers and severely immunocompromised adults) were allowed to receive vaccination. Confidence intervals are not adjusted for multiplicity.

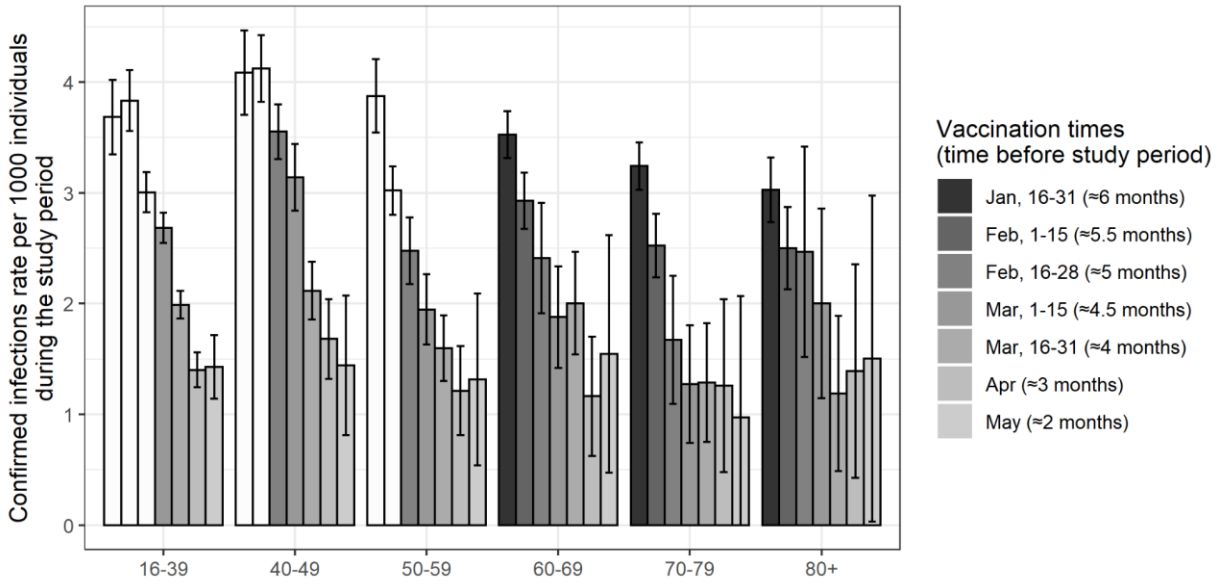


Table S5: Poisson regression results for documented SARS-CoV-2 infection by PCR.

Variable*	Estimate	Std.Error
(Intercept)	-7.660	0.034
Age: 40-59	0.186	0.040
Age: 60+	0.154	0.033
Past PCR tests = 1	0.377	0.021
Past PCR tests = 2+	0.474	0.024
Gender = male	-0.021	0.017
Week2	0.523	0.026
Week3	1.068	0.024
Arab	-1.306	0.044
Ultra-Orthodox Jewish	-0.739	0.053
Age 16-39: Jan 16-31	0.238	0.053
Age 40-59: Jan 16-31	0.100	0.045
Age 60+: Feb 1-15	-0.134	0.038
Age 16-39: Feb 1-15	0.319	0.045
Age 40-59: Feb 1-15	0.043	0.040
Age 60+: Feb 16-28	-0.250	0.085
Age 16-39: Feb 16-28	0.086	0.040

Age 40-59: Mar 1-15	-0.101	0.052
Age 60+: Mar 1-15	-0.497	0.099
Age 16-39: Mar 16-31	-0.165	0.041
Age 40-59: Mar 16-31	-0.346	0.061
Age 60+: Mar 16-31	-0.483	0.100
Age 16-39: Apr	-0.437	0.063
Age 40-59: Apr	-0.549	0.097
Age 60+: Apr	-0.791	0.168
Age 16-39: May	-0.499	0.105
Age 40-59: May	-0.729	0.182
Age 60+: May	-0.766	0.259

*Reference categories:

Age: 16-39; Past PCR tests: 0; Gender: female; Period of observation: Week1; Subpopulation: General Jewish; Age x Vaccination Period: for Age 16-39: Mar 1-15; for Age 40-59: Feb 16-29; for Age 60+: Jan 16-31

Table S6: Poisson regression results for severe COVID-19.

Variable*	Estimate	Std.Error
(Intercept)	-13.434	0.306
Age: 60+	2.877	0.275
Past PCR tests = 1	0.316	0.140
Past PCR tests = 2+	1.308	0.117
Gender = male	0.621	0.103
Week2	0.676	0.163
Week3	1.379	0.148
Arab	-0.442	0.232
Ultra-Orthodox Jewish	-0.033	0.256
Age 40-59: Jan	0.473	0.428
Age 60+: Feb	-0.183	0.116
Age 40-59: Mar	-0.790	0.636
Age 60+: Mar	-0.597	0.240

*Reference categories:

Age: 40-59; Past PCR tests: 0; Gender: female; Period of observation: Week1; Subpopulation: General Jewish; Age x Vaccination Period: for Age 40-59: Feb; for Age 60+: Jan

Supplementary Analysis 1 - Comparison to the unvaccinated group

We studied the infection rate of fully vaccinated individuals compared to that of unvaccinated individuals without evidence of prior infection with SARS-CoV-2 by PCR at the start of the study. As unvaccinated uninfected individuals were not part of the database (unless they performed a SARS-CoV-2 PCR test in the past), data on all residents of Israel stratified by age, gender, and demographic group were obtained from the Israel Central Bureau of Statistics, and were merged with the Ministry of Health database into a unified dataset of all residents of Israel (n=9,395,923): unvaccinated, vaccinated, and previously infected individuals.

The rates of documented SARS-CoV-2 infection and severe COVID-19 were compared to the rates of the unvaccinated group. Specifically, we repeated the analysis described in the Methods section on the unified data, including the unvaccinated group as an additional "vaccination period" in the model (reference group). We then compared infections and severe COVID-19 cases of vaccinated individuals in different periods adjusting for age, week, past PCR tests, demographic group, and gender. As in previous analyses, we included an interaction term between age and period of vaccination in the model in order to calculate age-specific effectiveness. Let RR denote the adjusted risk ratio of an outcome between people who were vaccinated in a certain period to unvaccinated individuals, we calculated effectiveness by (1-RR)×100%.

Table S7. Vaccine efficacy against documented SARS-CoV-2 infection and severe COVID-19 [95% CI] compared to the unvaccinated cohort for the different age groups, adjusted for week of infection, past PCR testing, demographic group, and gender. For severe COVID-19, estimates are not provided for the youngest age group and for the latest vaccination periods due to very low case numbers. Confidence intervals are not adjusted for multiplicity.

Positive SARS-CoV-2 PCR test

Age	Jan 1-16	Feb 1-15	Feb16-28	Mar 1-15	Mar 16-31	Apr	May
16-39	55% [50, 60]	52% [48, 57]	62% [59, 65]	66% [63, 68]	70% [68, 73]	77% [74, 80]	80% [75, 84]
40-59	57% [53, 61]	61% [57, 64]	63% [59, 66]	66% [63, 70]	73% [70, 77]	79% [74, 82]	83% [75, 88]
60+	57% [52, 62]	63% [58, 67]	67% [59, 73]	74% [68, 79]	73% [67, 79]	81% [73, 86]	82% [70, 89]

Severe COVID-19

Age	Jan	Feb	Mar
40-59	93% [86, 97]	96% [93, 98]	98% [94, 99]
60+	85% [81, 88]	88% [84, 91]	92% [87, 95]

Figure S2: Rate of severe COVID-19 (per 1000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group and including the unvaccinated cohort. White bars represent periods at which only designated groups (e.g. healthcare workers and severely immunocompromised adults) were allowed to receive vaccination. Confidence intervals are not adjusted for multiplicity.

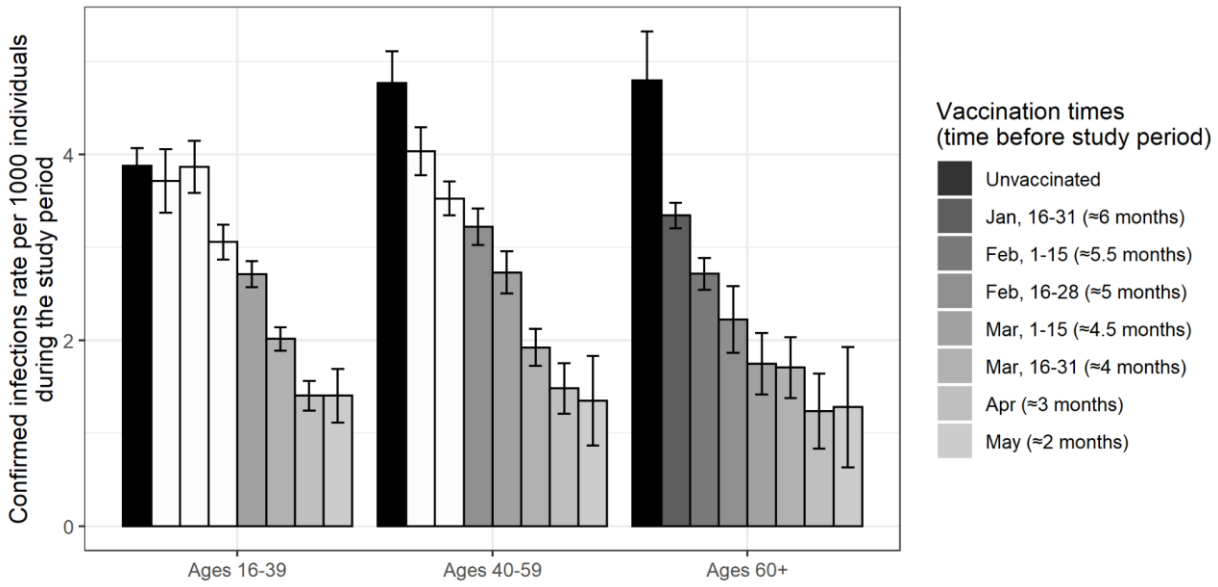


Figure S3: Rate of severe COVID-19 (per 1,000 persons) from July 11, 2021, to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group and including the unvaccinated cohort. White bars represent periods at which only designated groups (e.g. healthcare workers and severely immunocompromised adults) were allowed to receive vaccination. Confidence intervals are not adjusted for multiplicity.

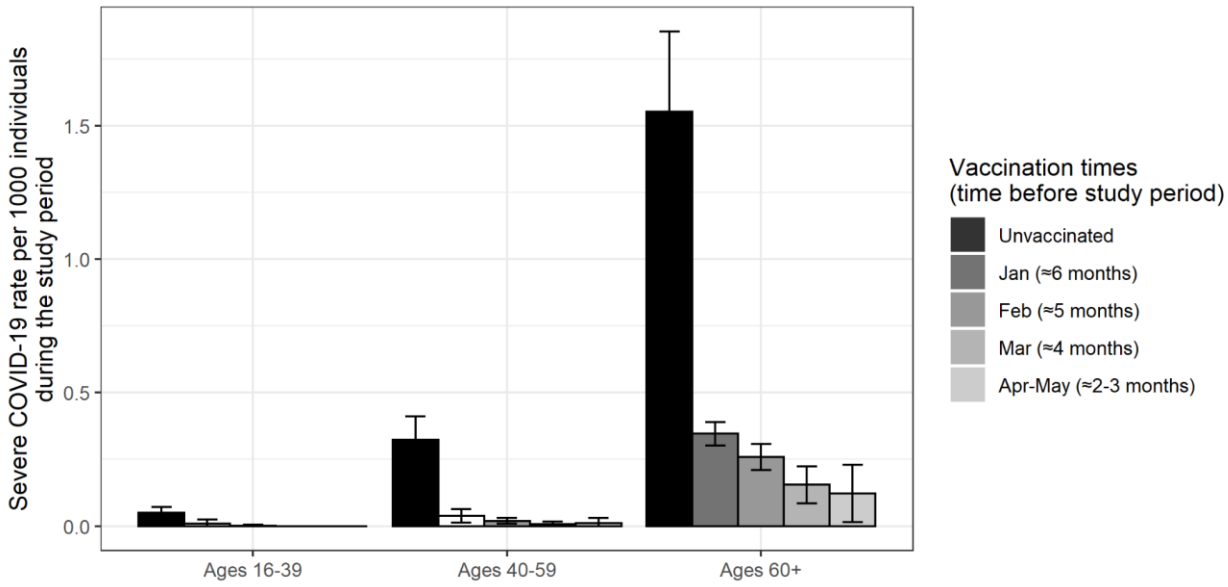
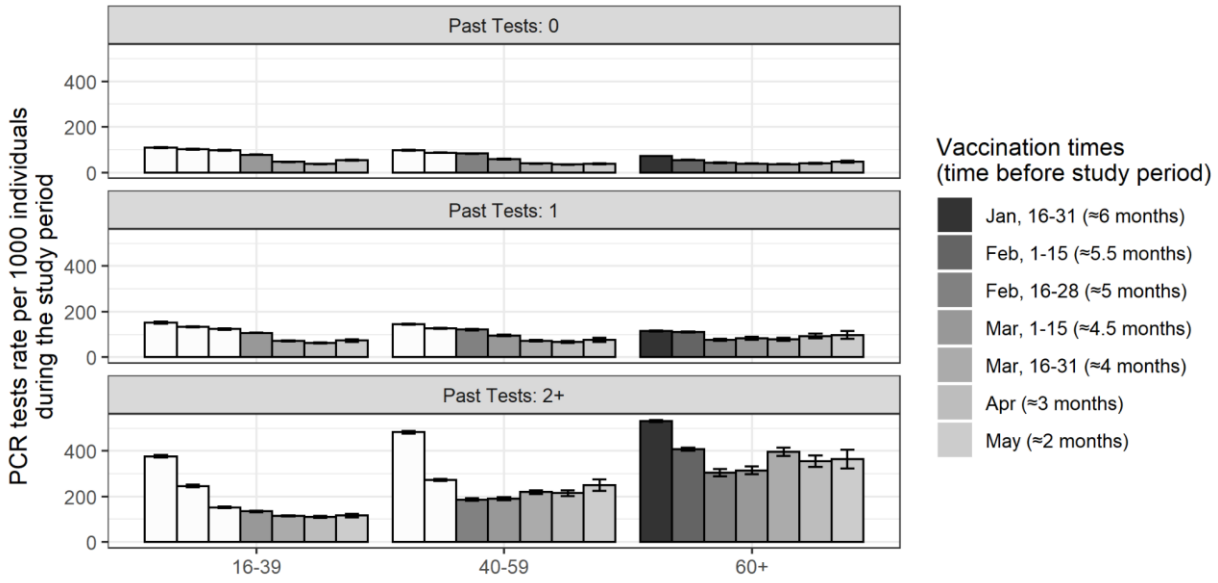


Figure S4. The number of SARS-CoV_2 PCR tests performed from July 11, 2021, to July 31, 2021, grouped by vaccination period and age group, and stratified by past PCR tests. White bars represent periods during which only designated groups (e.g. healthcare workers and severely immunocompromised adults) were allowed to receive the vaccine. Confidence intervals are not adjusted for multiplicity.



Supplementary Analysis 2

Observational studies are often subject to confounding bias and detection bias. The main risk factors for SARS-CoV-2 infection are patient characteristics and exposure risk. We adjusted for the former by including covariates known to be associated with infection, enabling the effect of age to vary among vaccination periods. Adjusting for exposure risk is more complicated. We, therefore, started our study period on July 11, 2021, a time when the disease was widespread throughout the country. The risk of exposure differs in Israel between demographic groups, which were adjusted for in the model. In addition, we fitted the models to the general Jewish population (which had the highest rates of infection and disease), excluding ultra-Orthodox Jews and Arabs, and obtained similar results (see Table S5). Finally, we added the week of infection as an additional covariate to the model to correct for the exponential growth of infection rate and exposure during this study period. However, we could not adjust our incidence rate estimates for certain confounders, especially comorbidities, because they are not recorded in the national database. Theoretically, less healthy people might tend to receive vaccination earlier, leading to an observed increase in rates with time since vaccination. While this might explain part of the observed waning, it is unlikely that this is the main factor. No priorities for vaccination were applied in Israel for the older group, and all people aged 60 years or older were eligible to receive vaccination as of December 30, 2020; in the other age groups, designated groups (e.g. healthcare workers and severely immunocompromised adults) were prioritized to receive vaccination from December 30, 2020, but others in these age groups became eligible only later. However, a similar reduction in rate ratios over time is observed among the three age groups. If comorbidities were the main factor affecting the rate ratios, we would expect an initial drop in the rate ratio during the first period that stabilizes afterward.

Eliminating detection bias is more difficult. As not all SARS-CoV-2 infections are diagnosed, fewer infections may be confirmed in sub-groups that perform fewer tests. However, if infections are more prevalent in a subgroup, more tests performed are expected. When observing many tests and a higher prevalence, it is difficult to untangle if more tests led to more positive tests, or whether a higher prevalence caused people to perform more tests. The national database does not contain reliable data on individuals' symptoms or on their reasons for performing PCR testing. We attempted to control for individuals who tend to have more PCR tests (e.g., healthcare workers or people in nursing homes) by including past PCR tests (0, 1, or 2+) as a covariate in the model. Figure S4 compares the number of PCR tests performed during the study period stratified by the number of PCR tests taken in the past. The association between the variables is evident, showing that including the number of past PCR tests can eliminate part of the bias. Except for those fully vaccinated during January, the numbers of PCR tests taken at the different vaccination periods are quite similar within each age group and past PCR testing level. This suggests that detection bias is not the main reason for the observed waning in Figure 3, and it is probably not a dominant factor. Moreover, all hospitalized patients with severe disease are tested for SARS-CoV-2 by PCR, and detection bias is minimal in this population. Thus, waning immunity against severe disease shown in Figure 4 gives further reassurance that detection bias cannot explain the exhibited increase in the rate of infection associated with time since vaccination.

Table S8: Sensitivity analysis for inclusion of socioeconomic status (SES) as an additional covariate, categorized to 0-3. Rate ratios of confirmed SARS-CoV-2 infections and severe COVID-19 [95% CI] compared to the first period in which each age group was eligible for vaccination (January 16-31 for ages 60+, February 16-28 for ages 40-59, and March 1-15 for ages 16-39). The analysis is adjusted for week of infection, past PCR testing (0, 1 or 2+), demographic groups, gender, and SES (0-3, 4-6, 7-10, and unknown). For severe COVID-19, estimates are not provided for the youngest age group and for the latest vaccination periods due to very low case numbers. Confidence intervals are not adjusted for multiplicity.

Positive SARS-CoV-2 PCR test

Age	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
16-39	0.8 [0.7, 0.9]	0.7 [0.7, 0.8]	0.9 [0.9, 1]	1	1.1 [1.1, 1.2]	1.5 [1.3, 1.7]	1.5 [1.2, 1.9]
40-59	0.9 [0.8, 1]	1 [0.9, 1]	1	1.1 [1, 1.2]	1.3 [1.2, 1.5]	1.5 [1.3, 1.8]	1.8 [1.2, 2.5]
60+	1	1.1 [1, 1.2]	1.2 [1, 1.4]	1.6 [1.3, 1.9]	1.5 [1.2, 1.8]	2 [1.4, 2.8]	1.9 [1.1, 3.2]

Severe COVID-19

Age	Jan	Feb	Mar
40-59	0.6 [0.3, 1.4]	1	2.2 [0.6, 7.5]
60+	1	1.2 [1, 1.5]	1.9 [1.2, 3]

Table S9: Sensitivity analysis - Poisson regression results when applied only to the General Jewish demographic group. Rate ratios of confirmed SARS-CoV-2 infections and severe COVID-19 [95% CI] compared to the first period in which each age group was eligible for vaccination (January 16-31 for ages 60+, February 16-28 for ages 40-59, and March 1-15 for ages 16-39). The analysis is adjusted for week of infection, past PCR testing (0, 1, or 2+), and gender. For severe COVID-19, estimates are not provided for the youngest age group and for the latest vaccination periods due to very low case numbers. Confidence intervals are not adjusted for multiplicity.

Positive SARS-CoV-2 PCR test

Age	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
16-39	0.8 [0.7, 0.9]	0.7 [0.7, 0.8]	0.9 [0.8, 1]	1	1.1 [1.1, 1.2]	1.5 [1.3, 1.7]	1.7 [1.3, 2.1]
40-59	0.9 [0.8, 1]	1 [0.9, 1.1]	1	1.1 [1, 1.2]	1.4 [1.2, 1.6]	1.8 [1.4, 2.1]	2 [1.4, 2.9]
60+	1	1.1 [1.1, 1.2]	1.3 [1.1, 1.6]	1.7 [1.4, 2.1]	1.6 [1.3, 1.9]	2.1 [1.5, 3]	2.3 [1.3, 3.9]

Severe COVID-19

Age	Jan	Feb	Mar
40-59	0.6 [0.3, 1.4]	1	2.3 [0.7, 8]
60+	1	1.2 [1, 1.5]	1.9 [1.2, 3.1]