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Title: Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel

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Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

Worldwide shortage of vaccination against SARS-CoV-2 infection while the pandemic is still uncontrolled leads many states to the dilemma whether or not to vaccinate previously infected persons. Understanding the level of protection of previous infection compared to that of vaccination is important for policy making. We analyze an updated individual-level database of the entire population of Israel to assess the protection of both prior infection and vaccination in preventing subsequent SARS-CoV-2 infection, hospitalization with COVID-19, severe disease, and death due to COVID-19. Outcome data were collected from December 20, 2020 up to March 20, 2021. Vaccination was highly protective with overall estimated effectiveness for documented infection of 94.5% (CI: [94.3, 94.7]); hospitalization 95.8% (CI: [95.2, 96.2]); severe illness 96.3% (CI: [95.7, 96.9]); and death 96.0% (CI: [94.9, 96.9]). Similarly, the overall estimated level of protection from prior SARS-CoV-2 infection for documented infection is 94.8% (CI: [94.4, 95.1]); hospitalization 94.1% (CI: [91.9, 95.7]); and severe illness 96.4% (CI: [92.5, 98.3]). Our results should be considered by policymakers when deciding whether or not to prioritize vaccination of previously-infected adults.

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Introduction

Israel was among the first countries to roll out a rapid vaccination campaign in order to reduce both SARS-CoV-2 infection and the number of COVID-19 cases. The BNT162b2 vaccine, developed by BioNTech in cooperation with Pfizer (BioNTech, Mainz, Germany; Fosun Pharma, Shanghai, China; Pfizer, New York, NY)[1], and for which an Emergency Use Authorization (EUA) was issued by the US Food and Drug Administration (FDA)[2], was administered to all eligible residents in two doses, with a 21-day interval between them. Israel launched its COVID-19 vaccination program on December 20, 2020. The vaccine became available, free of charge, to different risk groups in stages: first to those older than 60 years old, nursing home residents, healthcare workers, and patients with severe comorbidities, and then gradually to younger age groups[3]. As of February 4, 2021, the vaccine was made available to all individuals aged 16 or older not previously infected by SARS-CoV-2[4]. As of March 20, 2021, 77% of the eligible population was vaccinated. Due to the high caseload and the local detection of viral mutants such as B.1.1.7, Israel went into a third nationwide lockdown during the vaccination campaign. A light lockdown began on December 27, 2020, and was tightened on January 8, 2021. Restrictions were eased in stages starting February 7, 2021[5]. The dynamics of the epidemic as well as the vaccination campaign appear in Figure 1.

At the time this manuscript was written, SARS-CoV-2 testing in Israel was carried out according to the following policy: individuals might request testing due to either symptoms or contact with an individual who was tested positive. These polymerase chain reaction (PCR) tests were given free of charge. Individuals who had come into contact with an individual who was tested positive were required to self-quarantine for 14 days. This quarantine period could be shortened to 10 days if the individual was tested twice during the first 10 days, and both test results were negative. Individuals who have received both vaccine doses, and had the second dose seven days or more before contact with a positive individual, and did not have symptoms, were not required to self-quarantine, and thus had

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less motivation to get tested. In addition to voluntary testing, Israel conducted routine testing of all nursing-home workers.

Recent results based on aggregated data[4,6] and individual level data[7–11] have shown that the vaccine substantially reduces the number of severe COVID-19 cases. Two studies also indicate that the viral load of vaccinated individuals is significantly reduced.[12,13] These encouraging initial results are based on a short follow-up of vaccinated individuals. Results on previous COVID-19 infection [14–17] suggest protection against reinfection compared to uninfected unvaccinated individuals.

In this study, we estimate the protection of both the vaccination and previous infection in reducing documented SARS-CoV-2 infection and severe COVID-19 disease. We focus on five cohorts: unvaccinated individuals; vaccinated individuals followed from first dose to two weeks later, vaccinated individuals 15 days after the first dose to two weeks after the second dose; vaccinated individuals followed from two weeks after the second dose onward, and the Recovered Cohort of unvaccinated individuals previously infected with SARS-CoV-2. All efficacies, of vaccine or previous infection, are compared to the unvaccinated cohort.

Methods

Data

The database included two main tables. The first table was of all 1373 municipalities in Israel, with data on the number of residents, the daily count of PCR tests, and the daily positive results. This table was constructed based on data from the Israel Ministry of Health and the Israel Central Bureau of Statistics.

The second table was an individual-level table on persons aged 16 and above collected by the Israeli Ministry of Health based on data received routinely from all Health Maintenance Organizations (HMOs) and hospitals and linked using the person's identity number. This table contained basic demographic data and information on dates of first and second

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vaccinations, if received, and dates and results of all PCR tests performed from March 1, 2020, up to March 20, 2021. For individuals with a positive PCR test, the table contained information on symptoms, as well as the maximum severity status throughout the course of the disease (hospitalization, severe disease, death). The definition of hospitalization, severe disease, and death due to COVID-19 is based on international recommendations.[18] Specifically, hospitalization is defined as being admitted due to COVID-19. Disease is considered severe when a patient has >30 breaths per minute, oxygen saturation on room air <94%, or ratio of arterial 148 partial pressure of oxygen to fraction of inspired oxygen <300mm mercury. Data on symptoms were also available but we found them less reliable (only 3% of persons having a positive test reported symptoms), and thus did not include symptomatic COVID-19 as an outcome.

Thus, the table contained an entry for every adult (age ≥ 16) in Israel who had at least one PCR test or had received at least the first dose of the vaccine (with a total of 5,682,928 entries). Adults with no PCR test and no vaccination (668,975) were added to the table using data from the Israel Central Bureau of Statistics. Thus, this second table included 6,351,903 entries with basic demographic data of the total adult population in Israel, as well as their PCR tests and vaccination dates. Individuals under age 16 were not eligible for vaccination and were excluded from this study. A summary of the data appears in Table 1. A detailed description of the generation of this table and data exclusions appears in Web Appendix 1.

To account for environmental risk, we calculated a municipality daily risk index by the number of cases newly confirmed in the past seven days per 10,000 residents. We used a 7-day moving average since the number of PCR tests typically drops at weekends. The index was categorized into four risk levels (up to one , one to four, four to ten, and more than ten daily cases per 10,000) to yield the municipality daily risk category, and was used as a covariate in the risk model.

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Behavioral differences among people may result in different levels of exposure to infection and compliance with PCR testing guidelines. In addition to the time-dependent municipality risk mentioned above, we counted the number of PCR-test clusters that an individual underwent from March 1, 2020, to December 20, 2020 (i.e., prior to the vaccination program). A PCR-test cluster comprised all consecutive tests performed on the same individual within 10 days of each other, thus ensuring that a test repeated because of a previous inconclusive result was not counted separately. We categorized this variable into three levels: no PCR tests, one cluster, and two or more clusters, and this covariate was also included in the risk model. For previously-infected individuals, we set the level to one cluster and checked sensitivity to this value. Note that the time interval for defining this variable (up to December 20, 2020) did not overlap with the follow-up period.

Recovery from SARS-CoV-2 infection is not well-defined, and individuals may continue to show traces of the virus weeks and sometimes even months after the infection.[15] We defined as a recurrent infection only cases occurring three months or more after the first diagnosis. We also considered only individuals for whom the first infection was diagnosed between June 1 and September 30, 2020, omitting the beginning of the pandemic when we suspect that many infections could have been missed due to a shortage of PCR testing facilities. Hence, individuals infected before June 1, 2020 or between October 1, 2020 and December 20, 2020 were excluded from the analysis.

Statistical Modeling

To estimate the real world effectiveness of the Pfizer BNT162b2 vaccine in reducing documented SARS-CoV-2 infection and other COVID-19 events, we considered five dynamic sub-populations or cohorts:

- Cohort 0: Unvaccinated and not previously infected with SARS-CoV-2;
- Cohort 1A: Vaccinated and followed from the day of the first dose to 14 days later;

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- Cohort 1B: Vaccinated and followed from 15 days after the first dose to 13 days after the second dose;
- Cohort 2: Vaccinated and followed from two weeks after the second dose onwards;
- Recovered: Unvaccinated and previously diagnosed with SARS-CoV-2 between June 1 and September 30, 2020.

On any given calendar day, each individual included in the analysis belongs to a single cohort, but cohort membership is dynamic. Moreover, individuals may not only move between cohorts over time (for example, from cohort 0 to cohort 1A after first vaccination, or from cohort 1B to cohort 2 at 14 days after the second vaccination), but also exit from the follow-up on infection with SARS-CoV-2 or death, or at time of vaccination for recovered individuals. The outcomes, hospitalization, severe disease, and death, were attributed to the date on which COVID-19 was documented.

We modeled the daily risk of each individual from December 20, 2020 to March 20, 2021, as a function of calendar time, the cohort to which the individual currently belonged, and the individual's current risk factors, which included fixed covariates: age group (16-39, 40-49, 50-59, 60-69, 70-79, and 80+), sex, past PCR tests (0,1, and 2+), and the time-dependent variable: municipality risk level (low, medium, medium-high, and high). We refer to each combination of possible covariate values (age group, sex, past PCR tests, and municipality risk level) as the risk profile.

Our analysis model falls within the framework of multi-state survival models, where each cohort represents a separate state;[19] see Web Figure 1. Similar to the study of mRNA-1273, the vaccine developed by Moderna (Moderna Therapeutics, Cambridge, MA)[20], we defined the effectiveness of the vaccine and the protection of previous infection in terms of hazard ratios, where the main interest is in comparing the hazard of a fully vaccinated individual (Cohort 2) and a recovered individual (Cohort Recovered) to that of a non-vaccinated individual (Cohort 0).

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Our model assumes that for a given cohort and risk profile, the hazard was constant and did not depend on the time from entering the cohort. In other words, we assumed that the protection level did not change with time after the "completion" of the vaccination protocol or after previous infection. While protection by vaccination or previous infection is expected to decrease in the long run, our assumption is reasonable given the time frame of only three months after first vaccination, and six months after recovery, where waning immunity is not expected to play a significant role. This assumption may be too much of an approximation for cohorts 1A and 1B, in which protection may increase over time, and results for these cohorts should be regarded as averages over their respective periods. Following Skowronski and De Serres,[21] we considered, as a crude approximation, a constant hazard for each of these two sub-cohorts for every risk profile. Hazard ratios between cohorts and for each adjusting covariate were estimated via a generalized linear model with a Poisson distribution and logarithmic link function, and an offset for each risk profile.[22]

The formal definition of protection adopted was as follows. Consider any particular risk profile. Let h_i denote the hazard of an individual in one of cohorts 1A, 1B, 2, or Recovered, and let h_0 be the hazard of an individual having the identical risk profile in the unvaccinated group. Protection in cohort i for that risk profile is defined as $1 - h_i/h_0$. Note that the calendar time affects the hazards of the different cohorts only via the time-dependence of the municipality risk level. From the model assumptions, the ratio h_i/h_0 is the same for each risk profile, so the estimate of protection may be combined over all the risk profiles. For more details about the model see Web Appendix 2. We estimated protection separately for each of the following outcomes: documented infection, hospitalization, severe disease, and death. All analyses are stratified by age group, using an interaction term of age and cohort in the regression, as COVID-19 outcomes are strongly associated with age.

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Sensitivity Analyses

Infections are confirmed only by PCR tests, and since not all individuals having SARS-CoV-2 perform testing (as many have mild or no symptoms), some individuals who actually belong to the recovered cohort are misclassified and included in the other cohorts. Probably the most notable group is of individuals who are classified as unvaccinated but should have been included in the recovered cohort. Such misclassification may have a substantial effect on the estimates of vaccine effectiveness. We therefore conducted a sensitivity analysis in which we examined the effect of different misclassification rates on the results. The technical details are deferred to Web Appendix 3, with notation given in Web Tables 1 and 2, and results in Web Tables 3 and 4.

A person is considered fully vaccinated from days 14 after receiving the second dose. However, this 14 days lag may not be sufficient for the full immunological effect resulting in an underestimate of the true vaccine effectiveness. We therefore repeated our main analysis by re-defining Cohort 2 as individuals 21 days or more after receiving the second dose.

Results

The data are based on follow-up of the five cohorts from December 20, 2020 up to March 20, 2021, with over 573 million person-days of follow-up. The lengths of follow-up for the fully vaccinated and the recovered cohorts appear in Web Figures 2 and 3, respectively. During this time 4,606,250 PCR tests were performed (8,035 per million person-days), and 306,712 individuals tested positive (5.4 infections per 10,000 person-days). Of those testing positive, 14,019 (4.6%) required hospitalization, 8,463 (2.8%) were defined as severe cases, and 2,727 (0.9%) died. Table 2 presents these numbers by cohort and age group. The numbers of PCR tests performed per million person-days appear in Table 3. There is a decrease in the rate of PCR testing in both Cohort 2 and the Recovered Cohort compared to the other cohorts. This is likely due to the fact that fully vaccinated or recovered individuals

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(Cohorts 2 & Recovered) do not need to self-quarantine after contact with SARS-CoV-2 infected persons unless they develop symptoms.

We first investigated the dynamics of the vaccination program, disease outcomes, PCR testing, and municipality risk as a function of calendar time. Web Figures 4 and 5 present the proportion of vaccinated over time among different age and municipality risk groups, respectively. As can be seen from Web Figure 4, the Israeli vaccination policy was initially to immunize the older population, and as time progressed, younger age groups. Web Figure 5 shows the association between environmental risk and vaccination. Web Figure 6 shows the rates over time of the different age groups among those tested, infected, hospitalized, having severe disease, and dying.

Table 4 shows, by age group, the estimated vaccine effectiveness for the main outcomes for Cohort 2 (fully vaccinated) adjusted for sex, municipality risk, and past PCR. Note that for age groups below 60 years, there were, fortunately, none or very few events of severe illness and death, and thus estimates were omitted for these groups. The table shows that vaccine effectiveness was quite similar in all age groups with some decrease in effectiveness for the 80+ age category. Fitting a model without age-group/cohort interaction yielded overall vaccine effectiveness for documented infection of 94.5% (CI: [94.3, 94.7]); hospitalization 95.8% (CI: [95.2, 96.2]); severe illness 96.3% (CI: [95.7, 96.9]); and death 96.0% (CI: [94.9, 96.9]). We repeated the analysis with full vaccination defined as 21 days or more after the second dose. The results were similar (not shown).

Table 5 presents the results for the Recovered Cohort when the past PCR-based individualized risk was set to one PCR cluster. Again, the protection was quite similar in all age groups with some decrease in protection for the 80+ age category, and quite similar to the results in Table 4. The overall estimated protection of prior SARS-CoV-2 infection for documented recurrent infection was 94.8% (CI: [94.4, 95.1]); hospitalization 94.1% (CI: [91.9, 95.7]); and severe illness 96.4% (CI: [92.5, 98.3]). As there was only 1 death in the Recovered Cohort, protection against death was not estimated.

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The sensitivity analysis regarding misclassification of previously infected individuals is described in Web Appendix 3, exploring misclassification probabilities of 0.5 and 0.75. Misclassification has a small effect on the crude rates, leading to a slight underestimation of vaccine effectiveness. The largest effect is observed in the 16-39 age group where vaccine effectiveness is estimated to be 93.6% if 3 out of 4 infected individuals are misclassified, and 92.8% if 1 out of 2 is misclassified; the crude effectiveness assuming no misclassification is 92.5%. Similar, but smaller, effects are observed in the other age groups.

As described above, we assigned the recovered individuals to the middle PCR risk group, so that the estimated protection of a prior infection is compared to unvaccinated individuals having a single PCR cluster in the past. The protection levels afforded by a prior infection compared to unvaccinated persons who had no or 2+ past PCR tests are given in a sensitivity analysis shown in Web Table 5. In addition, Web Table 5 presents results of a model without PCR, which can be interpreted as the overall protection of a prior infection. As expected, the protection of a prior infection compared to unvaccinated persons who did not have past PCR tests is estimated to be smaller and compared to those who had 2+ tests is larger. The results when omitting the PCR variable are very similar to the figures in Table 5.

The results for Cohorts 1A and 1B appear in Web Tables 6 and 7, respectively. The results up to two weeks after the first dose (Cohort 1A) suggest low but statistically significant effectiveness. For Cohort 1B that comprises individuals at more than two weeks after the first dose, the overall effectiveness is higher, being 65.9% (CI: [65.4, 66.4]) for documented infection; 74.9% (CI: [73.5, 76.3]) for hospitalization; 72.1% (CI: [69.9, 74.1]) for severe illness; and 69.1% (CI: [65.5, 72.3]) for death. The coefficients of all four models used for analyzing the data appear in Web Tables 8-11.

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Discussion

This population-based observational study demonstrates the high protection of the BNT162b2 vaccine and prior SARS-CoV-2 infection against both subsequent SARS-CoV-2 infection and other COVID-19–related outcomes. There are a few characteristics that make this study unique. First, this is the first large-scale study that has explored the protection due to prior SARS-CoV-2 infection compared to the Pfizer BNT162b2 vaccine. Second, it is a nationwide study and thus represents the real-world protection of vaccination and prior infection on the adult population. Third, it uses individual-level data that enable, at least to some degree, to mitigate biases caused by the selection to get vaccinated, the selection to undergo PCR testing, and the time-changing level of risk, via adjustment for between-cohort differences in individuals' characteristics and municipality risk level. Forth, the study includes follow-up of the population for a period of three months, allowing follow-up of the fully vaccinated cohort over an extended duration.

There are some limitations to this observational study. One major source of confounding is related to possible population differences between individuals who recovered, were vaccinated, or neither. This confounding is partially addressed by controlling for risk factors. Specifically, for each individual we adjusted for sex, age group, number of past PCR tests and the time-dependent environmental exposure. Another major source of potential bias is related to detection of SARS-CoV-2 infection. As apparent from the PCR test counts in Table 3, individuals who are fully vaccinated or were previously infected get tested less often than the unvaccinated cohort. Our results for the outcomes of hospitalization, severe disease, and death do not suffer from this bias and thus are more reliable. The vaccine protection against infection might be biased upward as explained above, nevertheless the remarkable curtailing of the outbreak in Israel, which followed the high vaccine uptake by the Israeli population, further suggests that the vaccine is efficient in blocking transmission, see Figure 1.

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Misclassification of individuals into cohorts, and especially inclusion of undetected-infected individuals into the Unvaccinated cohort may potentially lead to a substantial systematic bias. However, the sensitivity analysis presented in Web Appendix 3 suggests that this is not the case in our analysis, and the effect of detection bias is rather small (Web Table 4). This is a consequence of the Recovered cohort being much smaller than the Unvaccinated cohort, leading to a low sensitivity of misclassification on the effectiveness measure.

The effectiveness estimates of the BNT162b2 vaccine in this study are similar to those reported by previous large-scale studies. For the severe disease outcome, the randomized trial of BNT162b2[1] reported 89% efficacy for severe disease. A study by the Israeli Ministry of Health using aggregated data[6] reported 96% effectiveness for people as defined in our Cohort 2. A study on data from Israel's largest HMO[7] split people as defined in our Cohort 1B and reported an effectiveness of 62% and 80% for the third and fourth weeks after the first vaccine, respectively, and of 92% for their Cohort 2. In comparison, our analysis showed effectiveness of 72% for Cohort 1B and 96% for Cohort 2. For other outcomes, the estimated vaccine effectiveness for Cohort 2 in our study were 94% and 96%, for documented infection and hospitalization, respectively. These estimates are similar to previous studies[6,7] that estimated effectiveness of 92% and 96% for documented infection, and of 87% and 96% for hospitalization. Our findings are based on a longer follow-up and a larger number of events than in the previous individual-level data reports. For example, the analysis of severe cases in the randomized clinical trial is based on only 10 cases, and that of Israel's largest HMO on 229.[7] In comparison, the analysis in our study is based on 8,463 cases, with 172among them being from Cohort 2. On the other hand, the other two studies [1,7] have the respective advantages of randomization and a detailed matching process which help in bias reduction.

The estimated protection against reinfection in this study is similar to that of the BNT162b2 vaccine. For documented SARS-CoV-2 reinfection, these results are similar to the results obtained in a large study from Qatar of 95% protection,[14] and suggest higher protection

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than reported by other previous studies. A large study from Denmark[15] suggested 80% protection against reinfection. A study on healthcare workers in the United Kingdom[17] reported that previous infection was associated with an 83% lower risk of infection. These two studies are based on 11,727 and 6,614 previously infected individuals, with 72 and 44 reinfections, respectively. In comparison, the Recovered cohort in our study comprised 187,549 individuals, with 894 reinfections. One possible reason for the differences in the estimated protection against reinfection could be related to detection bias of SARS-CoV-2 infection. However, our estimated high levels of protection against hospitalization and severe disease after reinfection are unlikely to be affected by detection bias, and are reassuring.

An important assumption made here is that rates of infection or hazards are independent of time from vaccination or previous infection. However, the rate of infection is expected to depend on time from vaccination or on time from previous infection. Studying the hazard as a function of time is crucial for understanding waning of the immunity conferred by infection and of the immunity conferred by vaccination, and its impact on the need for additional booster vaccinations. A longer follow-up is important for assessing time-dependent questions. We are planning a study that will deal with this crucial and required next step. The hazard may also depend on calendar time, not only via environmental exposure, but also because of new variants appearing against which the vaccine may have different effectiveness. During the period over which the data were collected, the COVID-19 variant B.1.1.7 (Alpha) was by far the most prevalent variant, and accounted for most of the documented cases, hence the approximation of a constant hazard is justified. Yet, it is of great importance to repeat this study in other populations in order to estimate the effectiveness for other variants and vaccines.

The BNT162b2 vaccine is associated with a lower infection rate and a lower potential of severe outcomes related to COVID-19 in the timeframe of our study. However, once fully recovered from initial infection, our findings suggest that prior SARS CoV-2 infection protects against subsequent SARS-CoV-2 infection and its related negative outcomes.

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Moreover, the level of effectiveness seems similar in both the recovered and fully vaccinated cohorts. With a paucity of vaccine doses, this should be one of several aspects that should be considered when deciding whether or not to prioritize vaccination of previously-infected adults.

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References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
2. Tanne JH. Covid-19: Pfizer-BioNTech vaccine is rolled out in US. *BMJ*. 2020;371:m4836. doi:10.1136/bmj.m4836
3. Shilo S, Rossman H, Segal E. Signals of hope: gauging the impact of a rapid national vaccination campaign. *Nat Rev Immunol*. 2021;21(4):198-199. doi:10.1038/s41577-021-00531-0
4. Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E. COVID-19 dynamics after a national immunization program in Israel. *Nat Med*. 2021;27(6):1055-1061. doi:10.1038/s41591-021-01337-2
5. Muhsen K, Cohen D. COVID-19 vaccination in Israel. *Clin Microbiol Infect*. 2021;0(0). doi:10.1016/j.cmi.2021.07.041
6. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *The Lancet*. 2021;397(10287):1819-1829. doi:10.1016/S0140-6736(21)00947-8
7. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. Published online February 2021. doi:10.1056/NEJMoa2101765
8. Yelin I, Katz R, Herzel E, et al. Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities [preprint]. *MedRxiv Prepr Serv Health Sci*. 2021. (doi:10.1101/2021.03.16.21253686). Accessed October 4, 2021.
9. Chodick G, Tene L, Patalon T, et al. Assessment of Effectiveness of 1 Dose of BNT162b2 Vaccine for SARS-CoV-2 Infection 13 to 24 Days After Immunization. *JAMA Netw Open*. 2021;4(6):e2115985. doi:10.1001/jamanetworkopen.2021.15985
10. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *The Lancet*. 2021;397(10277):875-877. doi:10.1016/S0140-6736(21)00448-7
11. Benenson S, Oster Y, Cohen MJ, Nir-Paz R. BNT162b2 mRNA Covid-19 Vaccine Effectiveness among Health Care Workers. *N Engl J Med*. 2021;0(0):null. doi:10.1056/NEJMc2101951
12. Levine-Tiefenbrun M, Yelin I, Katz R, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. *Nat Med*. Published online 2021:1-3.
13. Petter E, Mor O, Zuckerman N, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. Published online February 2021. doi:10.1101/2021.02.08.21251329
14. Abu-Raddad LJ, Chemaitelly H, Coyle P, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy.

ORIGINAL UNEDITED MANUSCRIPT

EClinicalMedicine. 2021;35:100861. doi:10.1016/j.eclinm.2021.100861
15. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *The Lancet*. 2021;397(10280):1204-1212. doi:10.1016/S0140-6736(21)00575-4
16. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *N Engl J Med*. 2021;384(6):533-540. doi:10.1056/NEJMoa2034545
17. Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet Lond Engl*. 2021;397(10283):1459-1469. doi:10.1016/S0140-6736(21)00675-9
18. National Institute of Health, US. Clinical Spectrum of SARS CoV-2 Infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ Accessed April 7, 2021.
19. Hougaard P. *Analysis of Multivariate Survival Data*. New York, NY: Springer; 2012.
20. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
21. Skowronski DM, De Serres G. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. Published online February 2021. doi:10.1056/NEJMc2036242
22. Myers RH, Montgomery DC, Vining GG, Robinson TJ. *Generalized Linear Models: With Applications in Engineering and the Sciences*. New York, NY: John Wiley & Sons; 2012.

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Table 1. Population level data for COVID-19 outcomes in Israel during the period December 20, 2020 to March 20, 2021.

Age	Male[a]	Female[a]	Total[a]	PCR	Positive	Hospitalization	Severe	Death
Total	(3,106)	(3,245)	(6,351)	(4,606,247)	(306,712)	(14,019)	(8,463)	(2,727)
16-39	1,513	1,484	2,997	2,414,803	183,617	2,722	684	44
40-49	531	542	1,073	810,988	49,373	1,614	814	64
50-59	404	423	827	575,853	34,411	1,978	1,252	153
60-69	345	386	731	399,149	21,073	2,242	1,528	406
70-79	207	249	456	207,538	10,410	2,358	1,757	674
≥80	106	161	267	197,916	7,828	3,105	2,428	1,386

PCR, polymerase chain reaction.

[a] Columns Male, Female, and Total are in thousands.

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Table 2: Person-day counts[a] and event counts in Israel for the different cohorts during the period December 20, 2020 to March 20, 2021.

Cohort and Age	Person Days	PCR	Positive	Hospitalization	Severe	Death
0[b]						
16-39	170.5	1,609,352	156,104	2,413	602	38
40-49	49.4	449,371	37,075	1,331	683	56
50-59	31.3	268,892	23,383	1,541	1,011	122
60-69	20.5	143,320	12,130	1,528	1,051	261
70-79	9.7	70,430	5,483	1,455	1,116	431
≥80	7.1	64,035	3,908	1,789	1,425	841
1A[c]						
16-39	27.3	287,539	19,707	231	63	5
40-49	11.4	107,441	7,619	201	99	6
50-59	9.6	85,134	6,355	290	165	17
60-69	8.8	61,433	4,638	400	269	74
70-79	6.5	30,853	2,247	418	304	113
≥80	3.6	32,731	1,759	643	490	262
1B[d]						
16-39	34.9	319,579	6,580	55	12	1
40-49	15.9	131,388	3,986	58	23	2
50-59	13.7	109,051	4,068	111	61	11
60-69	13.1	84,477	3,715	268	176	59
70-79	9.8	43,921	2,211	396	283	110
≥80	5.4	43,504	1,767	568	442	246
2[e]						
16-39	23.5	169,974	607	11	1	0

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40-49	17.0	114,882	568	20	9	0
50-59	18.4	106,603	518	29	12	3
60-69	22.9	105,959	553	41	29	12
70-79	18.3	60,645	457	83	53	20
≥80	9.7	56,085	380	101	68	36
Recovered[f]						
16-39	9.0	28,362	619	12	6	0
40-49	2.4	7,906	125	4	0	0
50-59	1.8	6,173	87	7	3	0
60-69	1.1	3,960	37	5	3	0
70-79	0.5	1,689	12	6	1	0
≥80	0.2	1,561	14	4	3	1

PCR, polymerase chain reaction.

[a] Person-day counts are in millions.

[b] Cohort 0: Unvaccinated and not previously infected;

[c] Cohort 1A: 1-14 days after first vaccine dose;

[d] Cohort 1B: 15 days after the first dose to 13 days after the second dose;

[e] Cohort 2: 14+ days after the second dose;

[f] Recovered: previously infected individuals.

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Table 3: PCR tests in Israel per million person days performed between March 1, 2020, and December 20, 2020.

Cohort	Age					
	16-39	40-49	50-59	60-69	70-79	≥80
0[a]	9,439	9,097	8,591	6,991	7,261	9,019
1A[b]	10,533	9,425	8,868	6,981	4,747	9,092
1B[c]	9,157	8,263	7,960	6,449	4,482	8,056
2[d]	7,233	6,758	5,794	4,627	3,314	5,782
Recovered[e]	3,151	3,294	3,429	3,600	3,378	7,805

PCR, polymerase chain reaction.

[a] Cohort 0: Unvaccinated and not previously infected;

[b] Cohort 1A: 1-14 days after first vaccine dose;

[c] Cohort 1B: 15 days after the first dose to 13 days after the second dose;

[d] Cohort 2: 14+ days after the second dose;

[e] Recovered: previously infected individuals.

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Table 4. Vaccination effectiveness (in percentage) for the different age groups adjusted for sex, municipality risk, and past PCR. Israel data during the period December 20, 2020 to March 20, 2021.

Age	Positive PCR		Hospitalization		Severe disease		Death	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
16-39	95.7	95.3, 96.0	95.4	91.7, 97.5	–[a]	–[a]	–[a]	–[a]
40-49	93.7	93.2, 94.2	94.3	91.1, 96.3	–[a]	–[a]	–[a]	–[a]
50-59	94.7	94.2, 95.1	95.8	93.9, 97.1	–[a]	–[a]	–[a]	–[a]
60-69	94.9	94.4, 95.3	97.2	96.1, 97.9	97.1	95.8, 98.0	95.3	91.6, 97.4
70-79	94.2	93.6, 94.7	96.2	95.2, 96.9	96.8	95.8, 97.6	96.9	95.1, 98.0
≥80	90.3	89.2, 91.3	94.5	93.3, 95.5	95.4	94.1, 96.4	95.8	94.1, 97.0
Overall[b]	94.5	94.3, 94.7	95.8	95.2, 96.2	96.3	95.7, 96.9	96.0	94.9, 96.9

CI, confidence interval; PCR, polymerase chain reaction.

[a] Estimates are not provided for severe disease and death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

[b] The overall estimates are based on models without cohort-age interaction.

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Table 5. Protection (in percentage) of prior SARS-CoV-2 infection for the different age groups adjusted for sex, municipality risk, and past PCR. Israel data during the period December 20, 2020 to March 20, 2021.

	Positive PCR		Hospitalization		Severe disease	
Age	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
16-39	94.5	94.1, 94.9	92.8	87.3, 95.9	–[a]	–[a]
40-49	95.1	94.2, 95.9	95.4	87.7, 98.3	–[a]	–[a]
50-59	95.2	94.1, 96.1	93.9	87.1, 97.1	–[a]	–[a]
60-69	96.1	94.6, 97.2	95.7	89.6, 98.2	96.1	87.8, 98.7
70-79	97.0	94.7, 98.3	94.1	86.8, 97.3	98.7	90.5, 99.8
≥80	91.4	85.5, 94.9	94.2	84.5, 97.8	94.2	81.9, 98.1
Overall [b]	94.8	94.4, 95.1	94.1	91.9, 95.7	96.4	92.5, 98.3

CI, confidence interval; PCR, polymerase chain reaction.

[a] Estimates are not provided for severe disease for the lowest age groups and for death for all age groups due to very low case numbers in the previously-infected cohorts.

[b] The overall estimates are based on models without cohort-age interaction.

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Figure 1. Documented new infections and cumulative vaccinated persons by date. The period of first infection of the recovered cohorts is marked by two vertical dashed lines. The study period is marked by two vertical dotted lines.

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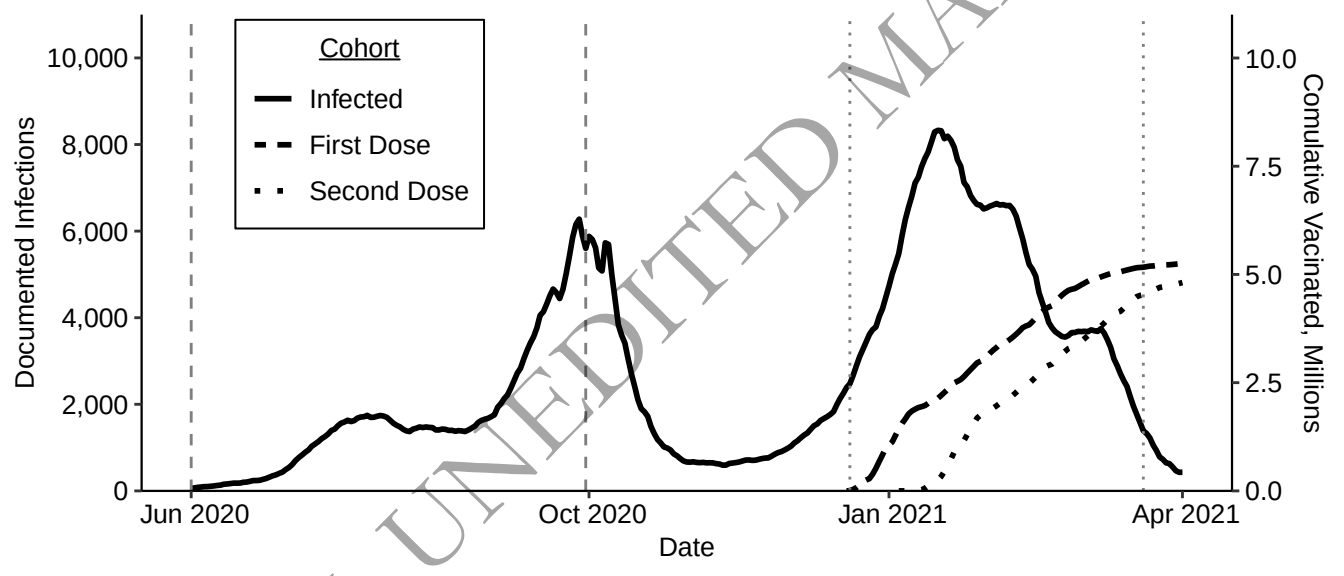
Cohort
Infected
First Dose
Second Dose
Documented Infections
Comulative Vacinated, Millions
10,000
8,000
6,000
4,000
2,000
0
10.0
7.5
5.0
2.5
0.0
Jun 2020
Oct 2020
Jan 2021
Apr 2021
Date
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