Title

Infections, Hospitalizations, and Deaths Averted via Direct Effects of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Vaccination Campaign, Israel

Authors

Eric J. Haas* MD,[1,2] John M. McLaughlin* PhD,[3] Farid Khan MPH,[3] Frederick J. Angulo PhD,[3] Emilia Anis MD,[1,4] Marc Lipsitch DPhil,[5] Shepherd R. Singer MD,[1,4] Gabriel Mircus PhD,[6] Nati Brooks MA,[7] Meir Smaja BA,[7] Kaijie Pan MS,[3] Jo Southern PhD,[3] David L. Swerdlow MD,[3] Luis Jodar PhD,[3] Yeheskel Levy MD,[8] and Sharon Alroy-Preis MD[1]

*these two authors contributed equally

Affiliations

[1]Public Health Services, Israel Ministry of Health, Jerusalem, Israel

[2]Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

[3]Pfizer Inc., Collegeville, PA, USA

[4]Hadassah Braun School of Public Health, Hebrew University, Jerusalem, Israel

[5]Harvard T.H. Chan School of Public Health

[6]Pfizer Pharmaceuticals Israel Ltd, Herzliya, Israel

[7]Information Technology Department, Israel Ministry of Health, Jerusalem, Israel

[8]Israel Ministry of Health, Jerusalem, Israel

Corresponding author and reprint requests

Dr Sharon Alroy-Preis,

Public Health Services, Israel Ministry of Health, Jerusalem 9101002, Israel

sharon.alroy@moh.gov.il

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Summary

Background

Israel recently initiated a rapid nationwide COVID-19 vaccination campaign to immunize persons ≥16 years of age and used exclusively Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine according to schedule (two doses, 21 days apart). We provide the first estimates of the number of COVID-19 cases, hospitalizations, and deaths averted by a nationwide vaccination campaign.

Methods

We used national surveillance data from the first 112 days (Dec 20, 2020 – Apr 10, 2021) of Israel's vaccination campaign to estimate averted burden of four outcomes: SARS-CoV-2 infections and COVID-19-related hospitalizations, severe or critical hospitalizations, and deaths. The direct effects of the immunization program were estimated for all susceptible individuals (i.e., no previous evidence of laboratory-confirmed SARS-CoV-2 infection) who were at least partially vaccinated (defined as receipt of at least one dose with ≥14 days after the first dose). Cases averted were estimated based on cumulative daily, age-specific rate differences comparing rates among unvaccinated to those who were at least partially vaccinated for each of the four outcomes and the (age-specific) size of the susceptible population and proportion that was at least partially vaccinated.

Findings

Through Apr 10, 2021, we estimated that Israel's vaccination campaign averted 158,665 (95% uncertainty range: 115,899–201,431) SARS-CoV-2 infections, 24,597 (6,622–42,571) hospitalizations, 17,432 (3,065–31,799) severe and critical hospitalizations, and 5,533 (-1,146–12,213) deaths. Of these, 66% of hospitalizations and 91% of deaths averted were among those ≥65 years of age. Seventy-three percent of SARS-CoV-2 infections and 79% of COVID-19-related hospitalizations and deaths averted stemmed from the protective effects in fully vaccinated persons.

Interpretations

Without vaccination, Israel would have likely experienced triple the number of hospitalizations and deaths compared to what actually occurred during their largest wave of SARS-CoV-2 to date, which would have likely overwhelmed the healthcare system. Indirect effects and long-term benefits of the program, which could be substantial, were not included in these estimates and warrant future research.

Funding

None.

Research in context

Evidence before this work

Since the start of Israel's nationwide vaccination campaign, we have been closely monitoring the scientific literature (including preprint servers) and press coverage to identify reports describing the effectiveness or the impact of Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in a real-world setting. Observational studies from Israel and elsewhere describing the real-world effectiveness of BNT162b2 have been published. Additionally, preliminary evidence has emerged from Israel showing dramatic declines in SARS-CoV-2 activity corresponding with the rapid introduction of the vaccine. No studies, however, have estimated the number of COVID-19 cases, hospitalizations, and deaths averted by a nationwide vaccination campaign.

Added value of this work

Estimating the disease burden averted in a population following vaccine introduction helps to further elucidate and quantify the public-health benefits of vaccination and is critical information for policymakers and the public. Israel is the first setting where nationwide evaluation of a COVID-19 vaccination campaign is possible due to its high population-level vaccine coverage and robust public-health and information-technology infrastructure. We provide the first nationwide estimates of the number of COVID-19 cases, hospitalizations, and deaths averted via the direct effects of the vaccination campaign in Israel.

Implications of all the available evidence

Israel's COVID-19 vaccination campaign prevented thousands of hospitalizations and deaths. The campaign, which first prioritized the frail and elderly but ultimately achieved rapid and high coverage in the entire vaccine-eligible population, was rolled out during a surge in SARS-CoV-2 infections and likely averted at least (as potential indirect effects were not included) 158,665 SARS-CoV-2 infections, 24,597

hospitalizations (of which 17,432 would have been severe or critical), and 5,533 deaths in the population of 6.5 million vaccine-eligible persons ≥16 years in the first 112 days of the vaccination campaign. Most, hospitalizations (66%) and deaths (91%) averted were among those ≥65 years of age, contributing to the relatively high proportion of severe outcomes averted. These findings, in context with other data showing high effectiveness of two doses of BNT162b2 against all SARS-CoV-2 outcomes and in all ages, suggest that rapid introduction of the vaccine, according to schedule and prioritizing the frail and elderly, is an effective strategy to prevent hospitalizations and deaths during surges of SARS-CoV-2 and to help control the pandemic.

Introduction

At the time of writing, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in more than 160 million cases and 3.3 million deaths globally.[1] Israel, a country with a population of 9.2 million citizens, was one of the first to initiate a rapid nationwide Coronavirus Disease 2019 (COVID-19) vaccination campaign. The campaign, led by the Israel Ministry of Health (MoH), started on Dec 20, 2020 with the goal of administering the Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine according to schedule (two doses 21 days apart) to all persons ≥16 years of age. By April 10, 2021, >10 million doses of the vaccine had been administered, with >70% of Israelis ≥16 years of age having received two doses, including >90% two-dose coverage among the elderly.[2,3]

The vaccine program started at the same time as a large wave of COVID-19 cases that resulted in a nationwide lockdown a week after the vaccination program began. This setting of high vaccine uptake introduced during a time of high SARS-CoV-2 circulation has allowed for robust analyses of real-world vaccine effectiveness (VE) of BNT162b2 using national surveillance data and preliminary evaluations of whether high vaccine uptake could control the pandemic.[3-5] Two recently-published analyses demonstrated high effectiveness of BNT162b2 in Israel against all SARS-CoV-2 outcomes, including COVID-19-related hospitalizations and deaths, in all age groups, including the elderly.[3,4] Recent reports have also demonstrated marked declines in the incidence of SARS-CoV-2 infections and COVID-19-related hospitalizations and deaths that corresponded with increasing vaccine coverage. These declines have been sustained even after lifting the nationwide lockdown on Mar 7, 2021.[3,5] These findings corroborated data from the randomized controlled trial (RCT)[6] and other preliminary reports of high real-world effectiveness of BNT162b2 in other countries including Denmark,[7] the United Kingdom,[8,9] and the United States.[10]

No studies, however, have estimated the number of COVID-19 cases, hospitalizations, and deaths averted by a nationwide vaccination campaign. Estimating the disease burden averted in a population following vaccine introduction helps to further elucidate and quantify the public-health benefits of vaccination and is critical information for policymakers and the public. Israel, which has recorded

835,811 laboratory-confirmed cases and 6,292 COVID-19-related deaths from the beginning of the pandemic through Apr 10, 2021,[2] is the first setting where nationwide evaluation is possible, given its high population-level vaccine coverage and robust public-health and information-technology infrastructure. We provide nationwide estimates of the burden of SARS-CoV-2 averted via the direct effects of Israel's vaccination campaign.

Methods

Study design and population

We estimated the number of SARS-CoV-2 infections and COVID-19-related hospitalizations, severe or critical hospitalizations, and deaths averted via the direct effects of Israel's nationwide vaccination program from Jan 3, 2021 through Apr 10, 2021 among individuals ≥16 years of age. The beginning of the analysis period corresponded to 14 days after the start of the vaccination program in Israel, thus it was the first date that individuals could have received the vaccine and had ≥14 days of follow-up after the first dose.

The State of Israel, a geographically small Middle Eastern country located on the southeastern shore of the Mediterranean Sea, has a population of approximately 9.2 million citizens, of which 6.5 million are ≥16 years of age. The nationwide vaccination campaign initially targeted healthcare workers, long-term care facility residents, immunocompromised persons, and the elderly. Vaccination was subsequently offered to younger age groups, and by Feb 4, 2021, anyone ≥16 years of age was eligible for vaccination. Vaccination began around the same time as the largest surge in SARS-CoV-2 infections experienced by Israel to date, and a nationwide lockdown was instituted on Dec 27, 2020—only a week after the vaccination program began. Additional lockdown restrictions were implemented on Jan 8, 2021. Daily infections increased in Dec 2020, peaking at >10,000 on Jan 20, 2021. Phased re-opening occurred on Feb 7, 2021 and Feb 27, 2021. The lockdown was lifted on Mar 7, 2021. Despite the lifting of lockdown restrictions, rates of SARS-CoV-2 infections to-date have remained low (<150 new infections per day).[2,3,5]

Nationwide surveillance

Polymerase chain reaction (PCR) testing for SARS-CoV-2 is widely-available and provided with no out-of-pocket costs in Israel. PCR testing is required for persons returning from travel abroad, close contacts of an infected person, or persons with symptoms suggestive of COVID-19 such as fever or acute respiratory illness. However, anyone who wishes to be tested can do so without physician referral. All laboratory-confirmed SARS-CoV-2 infections, hospitalizations, and deaths are reported to the MoH. Surveillance of SARS-CoV-2 infections and vaccine uptake are part of the national pandemic response and are collected under Public Health Ordinance 1940. Only aggregate data, with no personal identifiers, were utilized in this analysis. As data collection and analysis were done as part of MOH legal authority for public health surveillance and to support policy decision-making and evaluation, no institutional review board review was required for this work.

Outcomes

We estimated the averted burden of four outcomes: SARS-CoV-2 infections and COVID-19-related hospitalizations, severe or critical hospitalizations, and deaths. As described previously,[3] SARS-CoV-2 infections were defined based on laboratory-confirmed PCR positivity, and hospitalizations and deaths were attributed to COVID-19 according to national guidelines which are based on international recommendations.[2,3] Hospitalizations were classified as severe (if a patient had a resting respiratory rate >30 breaths per minute, oxygen saturation on room air <94%, or ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300mm mercury) or critical (in the event of mechanical ventilation, shock, or cardiac, hepatic or renal failure).[2,3,11]

Statistical analysis

Based on data from the RCT[6] and consistent with recent real-world effectiveness studies,[3,4] it was assumed that no vaccine protection was conferred <14 days after receiving the first dose. The number of cases averted was calculated for all persons who were at least partially vaccinated (defined as receipt of at

least one dose with ≥14 days after the first dose) and two additional exposure group subsets of this population: i) fully vaccinated persons (defined as receipt of two doses with ≥7 days after the second dose consistent with the definitions used in Phase 3 efficacy trial[6] of BNT162b2 and a recent nationwide analysis of real-world effectiveness of BNT162b2 in Israel based on the same data as this analysis, albeit a shorter time period[3]) and ii) partially vaccinated persons (defined as receipt of only one dose with ≥14 days after the first dose or two doses with <7 days after the second dose).

We estimated the averted burden of SARS-CoV-2 outcomes in several steps. First, we excluded from the analysis persons <16 years of age and individuals with previous laboratory-confirmed SARS-CoV-2 infection (i.e., excluded from both the susceptible population and the counts of outcomes). Then, we calculated daily, age-specific (16–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years, based on 2021 census data) incidence rates for persons who were unvaccinated and for those who were at least partially vaccinated for each of our four outcomes. We then calculated, for each day in the analysis period, rate differences between these two groups with 95% confidence intervals (CI). Then, we multiplied daily rate differences (and, separately, corresponding lower and upper bounds of the 95% CI of the rate difference) by the size of the susceptible population (i.e., no previous evidence of laboratory-confirmed SARS-CoV-2 infection) and by the proportion that was at least partially vaccinated. This process was repeated for and summed across all days in the analysis period for each of the four SARS-CoV-2 outcomes to estimate the total burden (with 95% uncertainty range [UR]) of SARS-CoV-2 averted and is summarized with the formula below:

$$SARS\text{–}CoV\text{–}2\ averted = \sum_{age\ stratum\ =\ 1}^{8} \sum_{Jan\ 3,\ 2021}^{Apr\ 10,\ 2021} N * Vx_{\geq 1dose}(COVID_{UnVx} - COVID_{\geq 1dose})$$

where N = daily total susceptible population size for each age stratum (i.e., excluding those with previous evidence of laboratory-confirmed SARS-CoV-2 infection); $Vx_{\geq 1dose}$ = daily cumulative proportion of persons (within each age stratum) vaccinated with ≥1 dose of BNT162b2 with ≥14 days after the first dose; $COVID_{UnVx}$ = daily rate of SARS-CoV-2 infections and COVID-19-related hospitalizations, severe

or critical hospitalizations, or deaths in the unvaccinated group; $COVID_{\geq 1\ dose}$ = daily rate of SARS-CoV-2 infections and COVID-19-related hospitalizations, severe or critical hospitalizations, or deaths among persons who received ≥1 dose with ≥14 days after the first dose.

Similar to our previous analysis,[3] when calculating incidence rates, person-days for vaccinated individuals were determined each day by multiplying the proportion of persons who were at least partially vaccinated by population size estimates for each age stratum. Person-days for unvaccinated individuals were determined each day by subtracting the number of person-days contributed by those who were ever vaccinated from the total census population for each age stratum. Individuals with prior SARS-CoV-2 infection were excluded from person-day estimates. Finally, using the same methodology, we also determined the cases averted among those who were fully vaccinated. The number of cases averted among the partially vaccinated was estimated by subtracting the number of cases averted among the fully vaccinated from the total number of cases averted among all persons who were at least partially vaccinated. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Role of the funding source

The Israel MoH and Pfizer separately provided in-kind support to this study. No funding was exchanged between the Israel MoH and Pfizer. MoH and Pfizer were involved in the study design and writing of the report, and approved the decision to submit for publication.

Results

By the end of the follow-up period (Apr 10, 2021), 79.8% of Israelis ≥16 years of age were at least partially vaccinated. Most (92.4%) who were at least partially vaccinated were fully vaccinated, corresponding to 73.8% of Israelis ≥16 years of age being fully vaccinated by the end of the follow-up period. Vaccine coverage was higher and occurred earlier and more rapidly in older age groups (**Figure 1**). For example, among persons ≥75 years, >98% and >94% were at least partially vaccinated and fully vaccinated, respectively, at the end of the analysis period.

During the analysis period, there were 269,459 cases, 13,338 hospitalizations (of which 63.2%; 8,429/13,338 were severe or critical), and 2,859 deaths among persons ≥16 years of age. Median daily rate differences between persons who were at least partially vaccinated and unvaccinated individuals were 71.8 per 100,000 (interquartile range [IQR]: 34.3–91.2) for SARS-CoV-2 infections, 3.0 per 100,000 (1.3–4.5) for COVID-19-related hospitalizations, 1.5 per 100,000 (0.5–2.7) for severe and critical COVID-19-related hospitalizations, and 0.3 per 100,000 (0.0–0.6) for COVID-19-related deaths. Stratified results revealed that rate differences varied considerably over time and were highest in January and February (when SARS-CoV-2 activity was at its peak) and that the largest rate differences in hospitalizations and deaths between unvaccinated and vaccinated were observed among persons ≥65 years of age (**Tables 1 and 2**).

We estimated that 158,665 (95% UR: 115,899–201,431) SARS-CoV-2 infections, 24,597 (6,622–42,571) hospitalizations, 17,432 (3,065–31,799) severe and critical hospitalizations, and 5,533 (-1,146–12,213) deaths were averted by the nationwide vaccination program through Apr 10, 2020 (**Table 3 and Figure 2**). Although adults ≥65 years of age made up only 17.3% (1,127,965/6,538,911) of the total population ≥16 years of age, they accounted for 65.9% (16,213/24,597) of hospitalizations, 72.3% (12,611/17,432) of severe or critical hospitalizations, and 91.0% (5,035/5,533) of deaths averted (**Table 3**). Fully vaccinated persons, who constituted the majority of the adult population by the end of the analysis period, accounted for most of the averted SARS-CoV-2 infections (73.1%; 116,000/158,665) and averted COVID-19-related hospitalizations (79.1%; 19,467/24,597), severe or critical hospitalizations (79.9%; 13,927/17,432), and deaths (78.6%; 4,350/5,533) (**Table 3**).

Discussion

COVID-19 vaccine uptake in Israel occurred faster than anywhere else in the world.[12] Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine was first made available in Israel on Dec 20, 2020 and was used exclusively during the pandemic. The MoH initially prioritized vaccination for healthcare workers, adults in long-term care facilities, immunocompromised persons, and the elderly. By Feb 4,

2021 the vaccine was made widely available to all Israelis ≥16 years of age. By the end of the follow-up period, Apr 10, 2021, Israel had administered >2 million doses per month, resulting in 80% of its population ≥16 years of age being at least partially vaccinated and 74% being fully vaccinated. More than 90% of adults ≥65 years of age had received two doses. The start of Israel's nationwide vaccination campaign coincided with the beginning of Israel's largest wave of COVID-19 to date. Against this backdrop of disease activity and the initiation of a vaccination program, studies from Israel have already emerged to i) confirm high real-world effectiveness of the vaccine against COVID-19 cases, hospitalizations, and deaths,[3,4] and ii) record dramatic declines in SARS-CoV-2 activity corresponding with the introduction of the vaccine.[3,5] The true public health impact of the nationwide vaccination program, however, has not yet been described, and Israel represents the first setting where early estimates of this type of impact can be comprehensively evaluated.

Since the beginning of the pandemic, Israel has recorded a total of 835,811 SARS-CoV-2 infections and 6,292 COVID-19-related deaths through Apr 10, 2021 in a population of approximately 9.2 million. Of these, 269,459 SARS-CoV-2 infections, 13,338 COVID-19-related hospitalizations, 8,429 severe or critical COVID-19-related hospitalizations, and 2,859 COVID-19-related deaths occurred during the analysis period from Jan 3, 2021 through Apr 10, 2021 among persons ≥16 years of age (6.5 million of 9.2 million total population). Through Apr 10, 2021, a period of 112 days from the start of the nationwide vaccination campaign, we estimated that vaccination averted 158,665 (95% UR: 115,899–201,431) SARS-CoV-2 infections, 24,597 (6,622–42,571) hospitalizations, 17,432 (3,065–31,799) severe and critical hospitalizations, and 5,533 (-1,146–12,213) deaths. Thus, our results suggest that Israel would have experienced at least three times as many hospitalizations and deaths than actually occurred between the start of the vaccination program through Apr 10, 2021 but for the rapid implementation of the nationwide vaccination campaign. Based on our estimates, the vaccination campaign averted almost as many deaths as occurred in Israel during the entire pandemic. URs were wide, especially for deaths, given variability in day-to-day COVID-19-related mortality rate differences and low numbers of deaths following the rollout of the vaccination program.

Israel's strategy of prioritizing vaccination of the elderly according to schedule (2 doses, 21 days apart) seemed to have notable impact on directly averting hospitalizations and deaths, and contributed to the relatively high proportion of severe outcomes averted. For example, although adults ≥65 years of age made up only 17% of the total vaccine-eligible population ≥16 years of age, this same age group accounted for 66% of hospitalizations, 72% of severe or critical hospitalizations, and 91% of deaths averted by the vaccination campaign. In adults ≥75 years of age, vaccination was especially efficient, averting approximately three hospitalizations and one death per 100 persons in this age group during the first 112 days of the vaccination campaign.

Although we modeled the impact of being at least partially vaccinated, most (92%) of these individuals were fully vaccinated. Thus, our results largely reflect the impact of a nationwide vaccination campaign that rapidly achieved high two-dose coverage. Overall, 73% of SARS-CoV-2 infections and 79% of COVID-19-related hospitalizations and deaths averted stemmed from fully vaccinated persons. These data highlight the direct impact of the recommended two-dose schedule, but also elucidate the additional, incremental benefit of protection after only one dose while awaiting completion of the full two-dose schedule. These findings complement our previous VE evaluation in Israel showing significant protection 14-21 days after the first dose of BNT162b2, albeit lower than that ≥7 days after the second dose.[3]

Our cases-averted model has limitations. First, rate differences between vaccinated and unvaccinated groups were based on observational data. We stratified our analysis by age and by day of the pandemic to control for key potential confounders but did not have information describing rates by other factors such as comorbidities, socioeconomic status, and likelihood of seeking SARS-CoV-2 testing—which, as previously described,[3] may vary by vaccination status. Real-world VE results in Israel based on these same national surveillance data, however, were recently shown[3] to be consistent with estimates of efficacy from the RCT.[6] A second limitation is that our analysis does not include potential indirect effects that could have reduced disease burden among the unvaccinated, including children <16 years of age who were not eligible for vaccination and were excluded from the analysis. If indirect effects

stemming from the vaccination program were substantial, our results would likely underestimate the impact of the nationwide vaccination program. The potential for indirect effects seems probable based on preliminary evidence suggesting effectiveness of BNT162b2 against asymptomatic infections[3] and that the vaccine reduces infectivity[13,14] and provides indirect effects[15,16]—suggesting the vaccine would likely contribute to breaking chains of transmission in the population. Additionally, the long-term impact of high vaccine coverage/pressure on keeping the pandemic under control was also not accounted for in this model. Future studies should attempt to estimate indirect effects of Israel's COVID-19 vaccination program, which would be additive to our analysis. We also assumed no impact of the vaccine <14 days after the first dose. This is consistent with the clinical trial experience[6] and assumptions made in our previous analyses of VE. However, if BNT162b2 provided any protection during this period our cases-averted calculations would be underestimated. In addition, given our cases-averted calculations excluded those with prior SARS-CoV-2 infection, our analysis assumes no impact of vaccination in this group. The RCT showed similar efficacy when previously-infected individuals were included,[6] however, and if vaccination confers better, broader, or longer effectiveness than does natural infection,[17] our estimates of SARS-CoV-2 outcomes averted via direct effects of vaccine introduction (only) would be conservative. Given differences between countries in how vaccines are rolled out, population-level vaccine coverage achieved, and pandemic activity at the time of vaccination, caution should be used in extrapolating our findings to other populations and health-delivery systems. Another limitation is that a national lockdown occurred at approximately the same time that the vaccination program began, making it difficult to tease apart the impacts of the vaccination program from lockdown restrictions. However, we compared daily incidence rates in vaccinated and unvaccinated individuals to account for day-to-day effects of the lockdown and changes in SARS-CoV-2 activity. Moreover, previous evaluations of Israel's nationwide surveillance data have suggested that vaccine introduction impacted the pandemic independently of the lockdown.[3,13] Finally, while we estimated the public-health impact of the vaccination program in terms of COVID-19 cases, hospitalizations, and deaths averted, future analyses should outline the economic benefit of the vaccination program, including both the direct medical costs of our estimated averted

COVID-19 outcomes, as well as broader macroeconomic benefits of being able to re-open society, schools, the workplace, and the broader economy.

In conclusion, Israel's nationwide vaccination campaign, which was rolled out during a surge in SARS-CoV-2 infections, averted an estimated 158,665 SARS-CoV-2 infections, 24,597 hospitalizations (of which 17,432 would have been severe or critical), and 5,533 deaths in the population of 6.5 million vaccine-eligible persons ≥16 years in the first 112 days of the vaccination campaign. Of these, 66% of hospitalizations and 91% of deaths averted were among those ≥65 years of age. Without vaccination, Israel would have likely experienced approximately three times the number of hospitalizations and deaths compared to what actually occurred during their largest wave of SARS-CoV-2 experienced to date, which would have likely overwhelmed the healthcare system. Indirect effects and long-term benefits of the program, which could be substantial, were not included in these estimates and warrant future research.

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Data sharing

No individual-level or sensitive data were used in this analysis. Requests for data should be made to the Ministry of Health of Israel. Aggregated surveillance data are freely available online at https://data.gov.il/dataset/covid-19.

Contributors

JM and EH conceived this study, conducted the analysis, and edited the final manuscript. JM, EH, FA, FK, and DS wrote the first draft of the protocol. JM, EH, FK, and KP cleaned and analyzed the data. All authors contributed to the study design. All authors contributed to drafting the protocol and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published.

Declaration of interests

John McLaughlin, Frederick Angulo, Farid Khan, Gabriel Mircus, Kaijie Pan, Jo Southern, David Swerdlow, and Luis Jodar hold stock and stock options in Pfizer Inc. Marc Lipsitch has provided advice on COVID-19 free of charge to Janssen, Astra-Zeneca, Pfizer, and COVAXX (United Biomedical), as well as to the nonprofit One Day Sooner and has received consulting income or honoraria from Merck, Bristol Meyers Squibb, and Sanofi, and institutional research support from Pfizer. All other authors report no conflicts.

Role of the funding source

The Israel MoH and Pfizer separately provided in-kind support to this study. No funding was exchanged between the Israel MoH and Pfizer. No individual-level or sensitive data was exchanged between parties. MoH and Pfizer were involved in the study design and writing of the report and approved the decision to submit for publication.

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Table 1. Median daily rate differences and interquartile ranges (IQR) in SARS-CoV-2 outcomes by month, age group, and outcome comparing unvaccinated individuals to persons who were at least partially vaccinated* in Israel, Jan 3, 2021 – Apr 10, 2021.

	Median Daily Rate Difference per 100 000 (IQR) by Month			
	Jan 3, 2021* – Jan 31, 2021	Feb 1, 2021 – Feb 28, 2021	Mar 1, 2021 – Mar 31, 2021	Apr 1, 2021 – Apr 10, 2021†
Age group in years	*SARS-CoV-2 Infections*			
16–24	85.7 (52.7, 119.3)	103.8 (77.9, 115.5)	35.5 (18.0, 83.2)	8.4 (8.2, 11.3)
25–34	72.3 (47.9, 80.4)	96.0 (74.8, 108.3)	48.6 (20.9, 82.4)	16.5 (10.8, 18.8)
35–44	61.8 (32.3, 71.3)	82.6 (69.9, 98.8)	45.3 (30.5, 79.1)	12.2 (7.1, 17.5)
45–54	52.4 (32.0, 64.2)	86.0 (73.2, 96.5)	52.2 (30.6, 84.5)	13.3 (9.4, 17.7)
55–64	58.3 (49.1, 70.9)	83.5 (66.7, 91.5)	49.3 (22.3, 74.4)	10.2 (5.6, 15.0)
65–74	51.5 (42.0, 63.2)	61.4 (48.2, 72.0)	31.4 (19.1, 45.8)	12.2 (10.3, 20.6)
75–84	62.8 (51.0, 70.2)	86.7 (61.7, 97.7)	65.6 (38.8, 78.5)	25.4 (14.7, 35.7)
≥85	94.0 (75.5, 118.3)	82.9 (64.0, 140.7)	79.5 (44.8, 101.9)	18.5 (17.7, 34.6)
All ≥16	74.2 (56.3, 85.1)	96.7 (73.4, 108.2)	44.1 (24.6, 81.1)	13.1 (10.4, 15.9)
	COVID-19-related hospitalizations			
16–24	0.8 (0.5, 0.8)	1.2 (0.9, 1.5)	1.2 (0.7, 1.5)	0.4 (0.0, 0.9)
25–34	1.8 (1.2, 2.1)	2.6 (2.0, 3.8)	2.4 (1.6, 3.1)	1.0 (0.5, 1.5)
35–44	2.0 (1.5, 2.5)	3.7 (2.4, 4.9)	3.7 (1.1, 4.6)	0.7 (0.0, 1.3)
45–54	3.4 (2.4, 4.1)	6.6 (5.6, 7.7)	5.8 (3.8, 8.5)	1.2 (1.1, 2.4)
55–64	5.9 (4.1, 7.6)	10.6 (8.3, 12.0)	6.9 (4.1, 10.5)	0.7 (0.0, 1.5)
65–74	11.0 (9.5, 14.1)	13.7 (9.5, 16.3)	7.9 (5.0, 13.1)	4.0 (2.1, 4.1)
75–84	22.6 (18.3, 27.8)	32.4 (27.4, 42.4)	32.8 (20.1, 38.9)	15.5 (14.1, 21.8)
≥85	46.9 (32.4, 57.8)	48.0 (39.3, 69.8)	46.3 (28.9, 71.7)	0.0 (0.0, 0.0)
All ≥16	1.1 (0.4, 1.5)	4.3 (3.4, 5.3)	3.8 (2.9, 5.4)	1.3 (1.1, 1.7)
	Severe and critical COVID-19-related hospitalizations			
16–24	0.1 (0.0, 0.1)	0.2 (0.1, 0.4)	0.0 (0.0, 0.4)	0.0 (0.0, 0.0)
25–34	0.3 (0.1, 0.4)	0.7 (0.6, 1.2)	0.6 (0.0, 1.2)	0.0 (0.0, 0.0)
35–44	0.7 (0.5, 1.0)	1.5 (1.0, 2.2)	1.2 (0.5, 2.6)	0.0 (0.0, 0.0)
45–54	2.0 (1.6, 2.4)	4.2 (3.3, 5.0)	3.7 (1.9, 5.7)	0.6 (0.0, 1.2)
55–64	3.9 (2.3, 5.7)	7.3 (5.9, 8.8)	4.1 (2.8, 7.8)	0.0 (0.0, 0.0)
65–74	7.9 (6.4, 11.0)	10.5 (6.5, 13.6)	6.5 (2.0, 11.2)	1.1 (-0.2, 2.2)
75–84	18.0 (12.9, 23.4)	27.1 (20.5, 30.5)	25.8 (13.9, 33.4)	7.7 (0.0, 14.6)
≥85	35.8 (25.0, 56.5)	44.0 (27.9, 53.6)	31.5 (22.9, 62.1)	0.0 (0.0, 0.0)
All ≥16	0.4 (-0.3, 0.6)	2.4 (1.8, 3.2)	2.5 (1.5, 3.4)	0.4 (0.2, 0.6)
	COVID-19-related deaths			
16–24	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
25–34	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
35–44	0.0 (0.0, 0.1)	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
45–54	0.2 (0.1, 0.3)	0.1 (0.0, 0.6)	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)
55–64	0.7 (0.2, 1.2)	0.7 (0.4, 1.8)	0.0 (0.0, 1.4)	0.0 (0.0, 0.0)
65–74	2.5 (1.5, 3.7)	2.6 (1.2, 3.9)	2.0 (0.0, 3.6)	0.0 (0.0, 0.0)
75–84	7.7 (6.6, 12.3)	10.1 (6.6, 15.5)	6.5 (0.0, 13.1)	0.0 (0.0, 0.0)
≥85	22.6 (15.8, 29.5)	23.4 (16.7, 35.3)	15.2 (0.0, 38.9)	0.0 (0.0, 0.0)
All ≥16	-0.2 (-0.5, 0.0)	0.4 (0.3, 0.6)	0.6 (0.3, 0.7)	0.0 (0.0, 0.1)

*Jan 3, 2021 corresponds to the first day on which persons could have been at least partially vaccinated (defined as individuals who received at least one dose of BNT162b2 with ≥14 days after the first dose).

†Apr 10, 2021 is the last day of the analysis period.

Table 2. Median daily rate differences and interquartile ranges (IQR) in SARS-CoV-2 outcomes by month, age group, and outcome comparing unvaccinated individuals and fully vaccinated‡ individuals in Israel, Jan 3, 2021 – Apr 10, 2021.

	Median Daily Rate Difference per 100 000 (IQR) by Month			
	Jan 3, 2021* – Jan 31, 2021	Feb 1, 2021 – Feb 28, 2021	Mar 1, 2021 – Mar 31, 2021	Apr 1, 2021 – Apr 10, 2021†
Age group in years	*SARS-CoV-2 Infections*			
16–24	137.2 (95.2, 145.4)	114.6 (89.2, 134.4)	38.8 (18.4, 88.8)	8.5 (8.3, 11.5)
25–34	99.1 (73.2, 108.6)	106.4 (80.6, 118.1)	53.2 (22.3, 89.6)	16.6 (11.0, 19.0)
35–44	88.4 (71.5, 97.7)	91.7 (77.0, 107.7)	48.3 (31.0, 87.6)	12.6 (7.3, 17.4)
45–54	91.4 (71.5, 104.8)	99.6 (81.9, 108.1)	54.3 (30.7, 88.6)	13.5 (9.4, 17.8)
55–64	92.6 (71.2, 107.7)	87.9 (70.2, 101.7)	50.4 (23.1, 77.9)	10.3 (5.6, 15.5)
65–74	76.0 (59.8, 88.8)	64.3 (49.5, 79.1)	32.7 (19.7, 47.2)	12.3 (10.5, 20.8)
75–84	75.9 (68.1, 93.2)	90.9 (63.5, 99.6)	67.3 (38.7, 82.3)	25.4 (14.7, 36.0)
≥85	116.3 (91.5, 156.5)	83.6 (65.4, 144.7)	80.1 (46.6, 102.5)	18.4 (17.7, 34.5)
All ≥16	105.6 (79.4, 112.1)	103.6 (78.8, 118.8)	47.1 (24.9, 86.2)	13.2 (10.5, 16.1)
	COVID-19-related hospitalizations			
16–24	0.8 (0.7, 1.0)	1.2 (1.0, 1.6)	1.2 (0.7, 1.7)	0.4 (0.0, 0.9)
25–34	1.8 (1.4, 2.1)	3.0 (2.1, 3.8)	2.4 (1.7, 3.5)	1.0 (0.5, 1.5)
35–44	2.2 (1.9, 2.9)	3.6 (2.5, 4.8)	3.6 (1.2, 4.8)	0.7 (0.0, 1.3)
45–54	3.6 (3.1, 4.6)	6.7 (5.7, 7.6)	6.0 (3.8, 9.0)	1.2 (1.2, 2.4)
55–64	7.3 (6.3, 8.7)	10.7 (8.8, 12.1)	7.2 (4.1, 10.5)	0.8 (0.0, 1.6)
65–74	13.3 (10.2, 15.3)	13.9 (9.9, 17.2)	8.3 (5.1, 13.3)	4.1 (2.1, 4.2)
75–84	28.7 (23.7, 32.8)	33.3 (27.7, 42.9)	32.7 (20.4, 38.9)	15.5 (14.1, 21.8)
≥85	56.6 (44.7, 70.8)	51.8 (40.0, 71.4)	46.2 (28.8, 72.6)	0.0 (0.0, 0.0)
All ≥16	3.2 (2.5, 3.8)	4.6 (3.4, 5.5)	3.9 (2.9, 5.6)	1.3 (1.2, 1.7)
	Severe and critical COVID-19-related hospitalizations			
16–24	0.1 (0.0, 0.1)	0.2 (0.1, 0.4)	0.0 (0.0, 0.4)	0.0 (0.0, 0.0)
25–34	0.3 (0.2, 0.4)	0.7 (0.6, 1.2)	0.6 (0.0, 1.2)	0.0 (0.0, 0.0)
35–44	0.8 (0.6, 1.2)	1.5 (0.9, 2.2)	1.2 (0.6, 2.6)	0.0 (0.0, 0.0)
45–54	2.3 (1.9, 3.0)	4.2 (3.5, 5.0)	3.8 (1.8, 5.7)	0.6 (0.0, 1.2)
55–64	4.4 (3.3, 5.9)	7.4 (6.0, 8.8)	4.1 (2.9, 7.8)	0.0 (0.0, 0.0)
65–74	9.0 (7.6, 11.1)	10.8 (6.6, 13.7)	6.9 (2.0, 11.2)	1.1 (0.0, 2.2)
75–84	21.7 (18.0, 27.0)	28.5 (21.2, 31.4)	26.5 (13.9, 34.1)	7.7 (0.0, 14.6)
≥85	43.3 (32.5, 61.4)	44.5 (30.1, 55.4)	31.5 (22.9, 62.1)	0.0 (0.0, 0.0)
All ≥16	1.7 (1.4, 2.1)	2.6 (2.0, 3.3)	2.6 (1.5, 3.4)	0.4 (0.2, 0.6)
	COVID-19-related deaths			
16–24	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
25–34	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
35–44	0.0 (0.0, 0.1)	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
45–54	0.2 (0.1, 0.3)	0.2 (0.0, 0.6)	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)
55–64	0.8 (0.5, 1.4)	0.7 (0.5, 1.7)	0.0 (0.0, 1.4)	0.0 (0.0, 0.0)
65–74	3.0 (2.3, 4.5)	2.7 (1.2, 4.0)	2.0 (0.0, 3.6)	0.0 (0.0, 0.0)
75–84	10.6 (7.4, 13.6)	10.5 (6.7, 15.7)	6.5 (0.0, 13.5)	0.0 (0.0, 0.0)
≥85	29.1 (20.8, 37.3)	24.1 (17.3, 35.7)	15.2 (0.0, 38.9)	0.0 (0.0, 0.0)
All ≥16	0.6 (0.4, 0.7)	0.5 (0.3, 0.6)	0.6 (0.3, 0.7)	0.0 (0.0, 0.1)

*Jan 3, 2021 corresponds to the first day on which persons could be at least partially vaccinated (defined as individuals who received at least one dose of BNT162b2 with ≥14 days after the first dose).

†Apr 10, 2021 is the last day of the analysis period.

‡Fully vaccinated individuals are persons who received two doses of Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine with ≥7 days after the second dose.

Table 3. Estimated SARS-CoV-2 infections and COVID-19-related hospitalizations, severe or critical hospitalizations, and deaths averted with Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine with 95% uncertainty range (UR) by number of doses received in Israel, Jan 3, 2021 – Apr 10, 2021*.

	SARS-CoV-2 cases averted (95% UR)				
	Population size	SARS-CoV-2 infections	COVID-19-related hospitalizations	Severe or critical COVID-19-related hospitalizations	COVID-19-related deaths
Age group in years	*overall total averted by individuals who were at least partially vaccinated**				
16–24	1,258,389	17,443 (14,839 – 20,047)	347 (-6 – 699)	57 (-34 – 149)	5 (-5 – 15)
25–34	1,231,583	20,762 (17,393 – 24,131)	904 (222 – 1,586)	229 (-35 – 493)	10 (-11 – 32)
35–44	1,156,876	24,255 (19,821 – 28,690)	1,273 (339 – 2,207)	579 (8 – 1,150)	26 (-28 – 81)
45–54	981,651	28,634 (22,440 – 34,828)	2,544 (785 – 4,303)	1,595 (283 – 2,907)	130 (-117 – 377)
55–64	782,447	24,421 (18,141 – 30,701)	3,316 (1,169 – 5,463)	2,361 (601 – 4,120)	326 (-198 – 850)
65–74	675,369	20,332 (13,242 – 27,422)	4,908 (1,551 – 8,265)	3,575 (835 – 6,315)	1,045 (-282 – 2,373)
75–84	319,285	15,025 (7,456 – 22,594)	6,868 (1,828 – 11,908)	5,461 (1,085 – 9,838)	2,070 (-262 – 4,402)
≥85	133,311	7,793 (2,567 – 13,018)	4,437 (733 – 8,141)	3,575 (322 – 6,828)	1,920 (-242 – 4,083)
All ≥16	6,538,911	158,665 (115,899 – 201,431)	24,597 (6,622 – 42,571)	17,432 (3,065 – 31,799)	5,533 (-1,146 – 12,213)
	subtotal averted by fully vaccinated†				
16–24	1,258,389	10,282 (8,755 – 11,810)	220 (-8 – 448)	33 (-19 – 86)	4 (-3 – 11)
25–34	1,231,583	12,919 (10,842 – 14,997)	580 (128 – 1,032)	140 (-24 – 305)	6 (-4 – 16)
35–44	1,156,876	17,063 (13,983 – 20,144)	877 (211 – 1,543)	398 (-0.4 – 797)	18 (-16 – 52)
45–54	981,651	21,698 (17,112 – 26,283)	1,931 (568 – 3,293)	1,199 (193 – 2,205)	101 (-79 – 281)
55–64	782,447	19,219 (14,384 – 24,053)	2,598 (899 – 4,297)	1,844 (455 – 3,234)	253 (-143 – 649)
65–74	675,369	16,337 (10,694 – 21,981)	3,954 (1,221 – 6,687)	2,865 (653 – 5,078)	831 (-213 – 1,874)
75–84	319,285	12,390 (6,121 – 18,659)	5,762 (1,504 – 10,020)	4,599 (906 – 8,291)	1,669 (-227 – 3,565)
≥85	133,311	6,092 (1,886 – 10,297)	3,545 (544 – 6,546)	2,847 (223 – 5,472)	1,469 (-217 – 3,154)
All ≥16	6,538,911	116,000 (83,777 – 148,223)	19,467 (5,067 – 33,867)	13,927 (2,386 – 25,468)	4,350 (-902 – 9,601)
	subtotal averted by partially vaccinated‡				
16–24	1,258,389	7,161 (6,084 – 8,238)	127 (2 – 251)	24 (-15 – 63)	1 (-1 – 4)
25–34	1,231,583	7,843 (6,551 – 9,134)	324 (94 – 554)	89 (-11 – 188)	5 (-6 – 16)
35–44	1,156,876	7,192 (5,838 – 8,546)	396 (129 – 663)	181 (9 – 353)	8 (-13 – 30)
45–54	981,651	6,936 (5,328 – 8,545)	613 (216 – 1,010)	396 (89 – 702)	29 (-39 – 97)
55–64	782,447	5,203 (3,757 – 6,648)	718 (270 – 1,166)	516 (146 – 886)	73 (-56 – 201)
65–74	675,369	3,995 (2,549 – 5,441)	954 (330 – 1,577)	709 (182 – 1,237)	215 (-70 – 499)
75–84	319,285	2,635 (1,335 – 3,935)	1,106 (324 – 1,888)	863 (179 – 1,547)	401 (-34 – 837)
≥85	133,311	1,701 (681 – 2,721)	892 (190 – 1,595)	728 (99 – 1,356)	452 (-25 – 928)
All ≥16	6,538,911	42,665 (32,122 – 53,207)	5,130 (1,555 – 8,704)	3,505 (679 – 6,331)	1,184 (-244 – 2,612)

*Jan 3, 2021 corresponds to the first day on which individuals could have been at least partially vaccinated (defined as persons who received at least one dose of BNT162b2 with ≥14 days after the first dose). Apr 10, 2021 is the last day of the analysis period. We calculated, for each day in the analysis period, rate differences between the unvaccinated and vaccinated groups with 95% confidence intervals (CI). To extrapolate these rate differences and 95% CIs to the estimated number of cases averted (with 95% uncertainty ranges [UR]) by vaccination each day across the four outcomes, we multiplied daily rate differences (and, separately, corresponding lower and upper bounds of the 95% CI of the rate difference) by the size of the susceptible (i.e., no previous evidence of laboratory-confirmed SARS-CoV-2 infection) population and by the proportion that was at least partially vaccinated. This process was repeated for and summed across all days in the analysis period for each of the four SARS-CoV-2 outcomes to estimate the total burden (with 95% URs) of SARS-CoV-2 averted.

†Fully vaccinated individuals are persons who received two doses of Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine with ≥7 days after the second dose.

‡Partially vaccinated individuals are persons who received only one dose with ≥14 days after the first dose or two doses with <7 days after the second dose.

Figure 1. Cumulative uptake of Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel by number of doses received and time since last vaccination among persons ≥16 years of age, Jan 3, 2021 – Apr 10, 2021. Dec 20, 2020 was the start of the Israel's nationwide BNT162b2 vaccination campaign. Jan 3, 2021 corresponds to the first day on which persons could be at least partially vaccinated (defined as individuals who received at least one dose of BNT162b2 with ≥14 days after the first dose). Fully vaccinated individuals are persons who received two doses of Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine with ≥7 days after the second dose.

(see separate attachment)

Figure 2. Cumulative number of SARS-CoV-2 outcomes over time comparing observed cases with nationwide BNT162b2 vaccination and predicted cases without vaccination by outcome, Dec 20, 2020 – Apr 10, 2021. *Note:* Y-axes vary across outcomes. Dec 20, 2020 corresponds to the start of Israel's nationwide BNT162b2 vaccination program. Jan 3, 2021 corresponds to the first day in which persons received at least one dose of BNT162b2 with ≥14 days after the first dose.

(see separate attachment)