Quantifying the Population-level Effect of the COVID-19 Mass Vaccination Campaign in Israel: a Modeling Study

Ido Somekh[1,2*] M.D.,

Wasiur R. KhudaBukhsh[3*] PhD.,

Elisabeth Dowling Root[4*] PhD.,

Lital Keinan Boker [5,6] MD, PhD.,

Grzegorz Rempala[7#] PhD.,

Eric A.F. Simões[8#] MB, BS, DCH, MD.,

Eli Somekh[2,9#] MD

***These authors contributed equally.**
#These authors contributed equally.

[1]Department of Pediatric Hematology Oncology, Schneider Children's Medical Center of Israel, Petah Tikva, Israel.
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
[3]School of Mathematical Sciences, University of Nottingham, Nottingham, United Kingdom
[4]Department of Geography and Division of Epidemiology, The Ohio State University, and Translational Data Analytics Institute Columbus, Columbus, OH, USA.
[5]Israel Center for Disease Control, Israel Ministry of Health, Israel.
[6]School of Public Health, University of Haifa, Haifa, Israel.
[7] Department of Mathematics, The Ohio State University, Columbus, OH, USA.
[8] University of Colorado School of Medicine, Aurora, CO, USA.
[9] Department of Pediatrics, Mayanei Hayeshuah Medical Center, Bnei Brak, Israel.

Correspondence:
Eli Somekh, MD,
Mayanei Hayeshuah Medical Center,
17 Povarski St, Bnei Brak, Israel.
E-mail: esomekh@gmail.com
Phone: +972523683481

Alternative Correspondence: Eric A. F. Simões, MD
University of Colorado School of Medicine, Aurora, CO, USA
12123 E 16th Ave, Aurora, Colorado 80045
E-mail: ERIC.SIMOES@cuanschutz.edu
Phone: +13039190500

© The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Summary:
The BNT162b2 mRNA COVID-19 vaccination campaign prevented over 500,000 COVID-19 cases, 15,000 hospitalizations and 5,000 deaths in Israel in 2 months. In addition, the campaign indirectly, prevented over 150,000 SARS-CoV-2 infections among unvaccinated children.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

ABSTRACT:

Background: Estimating real-world vaccine effectiveness is challenging since a variety of population factors can impact vaccine effectiveness.

We aimed to assess the population-level reduction in cumulative SARS-CoV-2 cases, hospitalizations and mortality due to the BNT162b2 mRNA COVID-19 vaccination campaign in Israel during January-February, 2021.

Methods: An SIR model and a Dynamic Survival Analysis (DSA) statistical approach was used. Daily counts of tested positive and of vaccine doses administered obtained from the Israeli Ministry of Health, were used to calibrate the model. The model was parameterized using values derived from a previous phase of the pandemic during which similar lockdown and other preventive measures were implemented in order to take into account the effect of these preventing measures on COVID-19 spread.

Results: Our model predicts for the total population a reduction of 648,585 SARS-CoV-2 cases (75% confidence interval [CI]: 25,877–1,396,963) during the first 2 months of the vaccination campaign. The number of averted hospitalizations for moderate – severe conditions were 16,101 (75 % CI: 2,010–33,035) and reduction of death was estimated as 5,123 (CI: 388–10,815) fatalities.

Among children aged 0-19 years, we estimated a reduction of 163,436 (CI: 0–433,233) SARS-CoV-2 cases which we consider as an indirect effect of the vaccine.

Conclusions: Our results suggest that the rapid vaccination campaign prevented hundreds of thousands of new cases as well as thousands of hospitalizations and fatalities and has probably averted a major health care crisis.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Introduction

During the second half of December 2020, Israel launched a national vaccination campaign to promote COVID-19 vaccine use. This campaign was based on the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech, Mainz, Germany) and was planned to include a large proportion of the Israeli adult population in a short time interval.[1]

Vaccine effectiveness against symptomatic SARS-CoV-2 infection at days 14 through 20 after the first dose and at 7 days following the second dose were 47% - 57% and 92% - 94% , respectively.[3-7] Post-licensure effectiveness studies are crucial to determine the population-level impact of a vaccine and determine the total impact of direct and indirect effects of the vaccine.[8,9] But these studies are prone to limitations derived from their observational design and potential bias introduced by case ascertainment, surveillance, and data quality.[10]

Estimating real-world vaccine effectiveness is challenging. A variety of population factors can impact vaccine effectiveness, including differences between vaccinated and unvaccinated individuals related to health-seeking behaviors and access to health care, prior health conditions, or demographic characteristics.[11] Effectiveness studies are not randomized, meaning vaccinated and unvaccinated individuals may be fundamentally different across these demographic and socioeconomic factors. Potential selection bias in the administration of the vaccine is typically unknowable and careful statistical controls must be included to account for confounding.[12] Population differences may also bias observational studies because of differential exposure to infection or differences in access to care and health seeking behaviors. Observational studies are not blinded, so vaccinated individuals may change behaviors which mitigate the probability of infection. Cases of disease reported to a surveillance system are not random and may reflect any number of biases.[12]

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Challenges related to delays in case reporting, weekend effects, censoring and truncation, and uneven geographic or population vaccination roll out can all impact estimates of effectiveness that rely on high quality surveillance data.

Equally crucial is understanding the indirect effects of the vaccine. Indirect effects occur through two main mechanisms. First, vaccination can reduce symptoms and viral shedding, rendering infected individuals less infectious than unvaccinated individuals.[13] The recent SIREN study clearly demonstrated this effect with the BNT162b2 mRNA COVID-19 vaccine.[10] Second, vaccination can reduce the number of infected people in the population, thereby reducing the risk of infection among susceptible individuals. Effectiveness studies typically compare outcomes of vaccinated and non-vaccinated individuals, and systematically underestimate the combined direct and indirect protective benefits to vaccinees.[14,15] Quantifying the indirect effects of vaccination typically requires more time, innovative study design, and higher quality data collection.[13]

Though much has been written on methods for evaluating vaccine effectiveness,[8,16] most observational studies continue to use traditional statistical approaches which compare incidence rates in the vaccinated vs. unvaccinated population. Studies do not account for confounding caused by other population-level mitigation strategies like lockdowns, business and school closures, or travel restrictions which fundamentally alter the epidemiology of the disease under study. However, no matter how many potential confounding variables are controlled for, traditional statistical models cannot usually fully account for the dynamically changing biases and complex interactions/uncertainties present in any particular study. They also cannot fix problems with poor quality or incomplete surveillance data. Mathematical models[17,18] are another avenue by which to explore the population-level impact of the vaccine, including both direct and indirect effects.[15] Building a valid vaccination model for SARS-CoV-2 is particularly challenging because the changing dynamics of both infection

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

and vaccination must be accounted for, reflecting the race between continuous spread of infection, and the vaccination efforts restricted by logistics and supply limitations.

The viable mathematical model of SARS-CoV-2 vaccination has to take into account various complex interactions between multiple factors effecting the epidemic dynamics, like the initial disease prevalence, the compliance with non-pharmaceutical interventions (NPIs) and the rate of growth or decay of infection at various times, the speed of the vaccine rollout as well as its targeting and uptake.[19] In addition, it is important to assess the effect of vaccination not only in terms of efficacy and effectiveness, but also in estimations of the averted SARS-CoV-2 infections and COVID-19 related hospitalizations and fatalities, both in the vaccinated and the unvaccinated population. The magnitude of averted cases depends not only on the efficacy, but also on other factors such as disease incidence, degree of implementation of NPIs, compliance with vaccination recommendations, etc. Estimation of direct and indirect COVID-19 related burden averted following vaccination roll-out, may better characterize the benefit of the vaccination campaign beyond what randomized controlled trials and observational studies provide.

Due to a lack of data of randomized longitudinal trials, we develop a mathematical model that is used with observational data to quantify the effect of vaccination as the infection spreads and the public health countermeasures (e.g., lockdowns and social distancing) are implemented.

Using an extended version of the standard compartmental susceptible-infected-recovered/removed (SIR) model and a Dynamic Survival Analysis (DSA) statistical approach[20] to estimate its parameters, we aimed to assess the population-level reduction in cumulative SARS-CoV-2 cases due to the BNT162b2 mRNA COVID-19 vaccination campaign in Israel. We used the SIR model[21] for disease transmission with two additional

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

compartments for individuals vaccinated with only one dose and those vaccinated with two doses. Data on daily counts of individuals who tested positive and daily numbers of vaccine doses administered were used to calibrate the model. The statistical methodology to infer the parameters of the compartmental model is based on the DSA approach,[20,22,23] which combines classical dynamical systems theory and survival analysis. The DSA approach applies a simple algebraic manipulation to the SIR equations and allows us to apply tools from survival analysis to population-level epidemic data. The DSA approach accounts for changes in SARS-CoV-2 infections due to confounding effects of lockdown and other mitigation strategies, while, simultaneously accounting for data-related challenges. This approach is particularly appropriate for the Israeli context since the effect of the vaccination campaign was slowed by a resurgence of COVID-19 cases, largely due to the rapid circulation of the B.1.1.7 variant.[1,24] Consequently, January and February 2021 saw the highest rates of COVID-19 related fatalities and hospitalization of patients with severe condition.

The full effect of the vaccine has been difficult to estimate because it was launched simultaneously with non-pharmacological measures such as school closure and national lockdown. One of our model parameters accounts for the effective removal of individuals from the susceptible pool due to vaccination and NPIs such as lockdown. This parameter is learned empirically using the DSA method. The population-level effect of vaccines is then computed by setting this specific parameter to zero. This approach provides an objective and standardized way of the population-level effect of vaccination in that it can be generalized to other populations.

Here, we use the DSA method to estimate the number of cases, hospitalizations and fatalities prevented during the first two months of the mass vaccination campaign in Israel. We also estimate the indirect effect of vaccination in the adult population on the incidence of

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

new SARS-CoV-2 cases in unvaccinated children. We used two methods to quantify the population-level impact on the reduction in cumulative SARS-CoV-2 infections due to rapid vaccination. Approach 1 simulates population-level daily counts of positive tests based on the model and known testing patterns when no vaccines are administered. We then compare this simulated number to the actual number of known positive tests to estimate the vaccine attributable reduction in cases. We expect these simulated estimates to be higher because they assume no mitigation measures were enacted except for vaccination. However, this approach fails to separate the effect of vaccination from the confounding effect of lockdown and other preventive measures which occurred simultaneously, to the vaccine rollout in Israel. Approach 2 parameterizes the model using values derived from a phase of the pandemic during which similar lockdown and other measures were implemented. In this second approach, we used the daily case counts from September 1, 2020 to November 1, 2020, a time window that saw a surge in cases followed by a strict lockdown. We expect these simulated estimates to be lower because the NPIs are explicitly incorporated into the model through parameterization, thereby reducing the estimated overall cumulative cases and attributing a smaller reduction in cumulative cases to the vaccine.

Methods

Surveillance and data

COVID-19 Cases: Daily counts of COVID-19 cases and fatalities attributed to COVID-19 were obtained from Ministry of Health reports and sites.[25,26]

COVID-19 Vaccinees: Daily counts of COVID-19 vaccinees (BNT162b2 mRNA COVID-19 vaccine) were obtained from the Ministry of Health reports and sites.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Population: The age specific breakdown of the Israeli population was obtained from the Israel Central Bureau of Statistics.[27]

Setting and population

The vaccination campaign was launched on December 20, 2020. A Timetable of the vaccination campaign and the relevant non-pharmacologic measures used to slow COVID-19 spread are detailed in Panel A in the Supplementary Appendix.

Mathematical model

We used the standard SIR compartmental model for disease transmission along with two additional compartments for individuals vaccinated with only one dose and those vaccinated with two doses. A detailed description is provided in the Supplementary Appendix and Supplementary table 1.

Patient Consent Statement: The design of this work conforms to standards currently applied in Israel, and according to the guideline of the Ministry of Health guidelines, this study is considered exempt from IRB approval since de-identified data from public sources were used.

Results

Figure 1 shows the SARS-CoV-2 epidemic curve from March 1, 2020 through the end of the study period (February 28, 2021). There was a significant outbreak beginning in late August 2020, which was controlled through the second national lockdown. An additional large outbreak ("third wave") began in December and coincided with the beginning of the mass vaccination campaign (Figure 2B). Since the start of the mass vaccination of the Israeli population (December 20, 2020) through the end of the study period (February 28, 2021), a total of 399,565 individuals contracted SARS-CoV-2 infection in Israel, with 7,217 COVID-

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

19 associated hospitalizations for moderate –severe conditions, and 2,681 COVID-19 associated deaths. During the study period a gradual decline in weekly number of COVID-19 associated hospitalizations was observed (beginning on January 17, 2021) as well as a gradual decline of weekly fatalities (Figure 2A& 2B) associated with SARS-CoV-2 infections beginning on January 24, 2021 (Figure 2B).

Figure 3(A) compares the actual number of cumulative SARS-CoV-2 cases in the entire Israeli population, and the estimated number of cumulative cases under the no vaccination scenarios following the two approaches described above. The actual and estimated cumulative cases and 75% confidence bounds are shown in Table 1. Given the huge amount of uncertainty (as seen in the figures), we have used 75% confidence bounds because 90% or 95% confidence bounds, which are more standard, would be too wide to be useful for our purpose. The purple dotted line (and the blue shaded regions indicating 75% confidence bounds) show the no-intervention scenario (Approach 1) while the black dashed lines (and the grey shaded region indicating 75% confidence bounds) correspond to the no vaccination scenario in which the parameters are trained on data from September 1, 2020 to November 1, 2020 (Approach 2). The solid red line indicates the actual number of cumulative cases in the population over the study period. Table 1 indicates for the total population, a reduction of 913,057 (CI: 128,043-1,442,984) SARS-CoV-2 infections under approach 1 and 648,585 (CI: 25,877 - 1,396,963) under approach 2. The corresponding values per 1 million populations were 98,708 and 70,117 averted SARS-CoV-2 infections under approach 1 and 2 respectively.

Figure 3(B) and Table 1 show the actual number of cumulative SARS-CoV-2 infections in the population less than 20 years of age, and the estimated number of cumulative cases under the two simulation approaches. We consider this to be an indirect effect of the vaccine since the population under 20 years was not eligible for vaccination until the end of

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

February. Again, the solid red line indicates the actual number of cumulative cases in this population (500,286). The indirect effect of the vaccine equates to an estimated reduction of 654,719 (CI: 114,109 – 1,022,195) under Approach 1 and 163,436 under Approach 2 (CI: 0 – 433,233). The corresponding values per 1 million pediatric populations (aged 0-19 years) were 198,400 and 49,526 SARS-CoV-2 infections averted under approach 1 and 2, respectively. The simulated daily SARS-CoV-2 positive tests in entire population and among the younger population (less than 20 years of age) under no interventions and no vaccination regimes are shown in Supplementary figure 1 (Supplementary Appendix).

Figure 3(C) and Table 1 show the effect of vaccination on COVID-19 related moderate – severe hospitalizations. As of February 28, 2021 the cumulative number of hospitalizations was 16,941 (red line). Under Approach 1 (purple dotted line), the reduction in hospitalizations was estimated at 22,843 (CI: 4,909 - 35,306) and under Approach 2, 16,101 (CI: 2,010 – 33,035). The corresponding values per 1 million populations were 2,470 and 1,741 averted hospitalizations under approach 1 and 2, respectively.

Figure 3(D) and Table 1 show the effect of vaccination on the cumulative number of COVID-19 related fatalities. Approach 1 estimates a reduction of 7,389 deaths (CI: 1,362 – 11,578) while approach 2 estimates a reduction of 5,123 deaths (CI: 388 – 10,815).

The corresponding values per 1 million populations were 799 and 554 averted deaths associated with SARS-CoV-2 infections under approach 1 and 2, respectively. The simulated population-level Daily SARS-CoV-2 hospitalizations and mortality under no intervention and no vaccination regimes are shown in Supplementary figure 2 (Supplementary Appendix).

Comparison of simulated cumulative count of positive tests and daily counts of positive tests with true daily counts is shown in Figure 4. In the following figure, the solid red

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

lines show the actual trajectories. The means of the simulated trajectories are shown as broken line in purple.

As of January 8, 2021, the cumulative count of positive tests was 480,338. As seen in Figure 4, the simulated trajectories lie close to the true counts of cumulative positive tests (Figure 4A) and daily counts of positive tests (Figure 4B). The true trajectory lies entirely within the 75% confidence bounds (shaded blue regions) indicating a good fit of the model to the data. This comparison demonstrates good matching between the simulated to the actual curves of daily counts. Further comparisons are provided in the Supplementary Appendix (Figures S3-S10).

Discussion

This study evaluated the impact of the BNT162b2 mRNA vaccine in the Israeli population utilizing a mathematical model which enumerated the number of averted COVID-19 cases as a result of the mass vaccination in Israel. Under approach 2 that parameterizes the model using values derived from a phase of the pandemic during which similar lockdown and other preventive measures were implemented, the estimated number of cases averted during the study period was 70,117/1,000,000 population with estimated prevention of 1741 /1,000,000 population hospitalizations for moderate-severe conditions and 554 fatalities per 1 million population. We also evaluated the indirect effect in children, who during the study period were not yet vaccinated but would be offered protection from widespread vaccination of adults. As children may be less susceptible to COVID-19 infection and less infectious than adults (at least with the pre B.1.1.7 circulating SARS-CoV-2 variants), interaction with adults may have been a major driver to SARS-CoV-2 infection among children, and we therefore hypothesized that the prevention of SARS-CoV-2 infections in adults would be accompanied by a decline in pediatric COVID-19 cases.[28–30] In line with this hypothesis, the results of the

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

study revealed that under approach 2, a total of 163,436 COVID-19 cases in children aged 0-19 were averted (averted rate : 49,526 cases per 1 million pediatric population) due to vaccination of the adult population.

Our study adds another important avenue for understanding BNT162b2 mRNA vaccine effectiveness and its impact on population-level infection rates. . It should be pointed out that the use of a highly effective vaccine does not necessarily result in the prevention of many new cases, since if new cases could have been prevented by other means such as altered public behavior, the effect of the vaccine may not be apparent. Traditional observational studies, which use the same type of surveillance data we use here, are sensitive to problems with data quality, and often cannot adequately account for changes in SARS-CoV-2 infection due to confounding effects of mitigation strategies. The DSA modeling approach, directly accounts for the impact of additional mitigation measures in the parameterization of the model (especially in approach 2), thereby providing a novel method for enumerating the effectiveness of the vaccine in reducing excess morbidity. This approach also provides estimates of uncertainty, which can strengthen inferences when data quality is an issue. Moreover, despite being relative, the lockdown measures introduced at different phases of the pandemic will have different effects on the overall rate of infection. [29] However, this can be properly captured by a modeling-based analysis such as ours but not necessarily by empirical studies.

One of the major lessons of this study has been the vast importance of a rapid vaccination campaign as results suggests that a slower pace of vaccination in Israel could have resulted in the addition of hundreds of thousands of new cases as well as thousands of hospitalizations and fatalities. Such a large number of hospitalizations would have resulted in a major health care crisis that was actually seen in other countries.[32-33]

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

There are several limitations that should be mentioned. This study is based on a mathematical model that is sensitive to initial parameterization and therefore prone to inherent errors in assumptions. Another limitation is that the concurrent non-pharmacologic measures implemented during the vaccination campaign could have potentially averted some and even most of these cases without the vaccination campaign. However, the parameters used in approach 2 were derived from a phase of the pandemic during which similar mitigation measures were implemented – e.g., September 2020 when there was a national lockdown and school closure. When we assessed model fit for this early segment of the time series, the close match between the actual trajectories of positive cases and the simulated ones indicated a very good fit of the model to the observed data. Thus, extrapolation of the model into a later time period and comparing these estimates with real-world data demonstrated its reliability.

We assume a "mass-action" mode of disease transmission in this study. The empirical analysis (Figure 4) confirms that this assumption is acceptable for our current purpose. In a sense one may think about our analysis as a way of averaging the agent-based dynamics, which despite being more realistic is also difficult to calibrate from empirical data. Since we are concerned with an overall population-level effect, the use of average transmission network appears acceptable in our case. [34-38]

The main strength of our study is that it is based on a reliable national database and is in line with the recent data that show the real-life vaccine effectiveness in the Israeli population. This report illustrates the effect of the rapid implementation of COVID-19 vaccination at a national scale and suggests that the accompanying models serve as a paradigm for other national COVID vaccination programs.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Acknowledgements:

We wish to thank Dr. Eric Haas for the great help in data collection.

Author Contributions:

I.S., E.D.R., E.A.F.S. and E.S. conceptualized the study. W.R.K. conducted the mathematical analysis and was supervised by E.D.R., and G.R. I.S., W.R.K., E.D.R., G.R., E.A.F.S. and E.S. analyzed the data. I.S., L.K.B., and E.S. participated in the data collection. I.S., W.R.K., E.D.R., G.R., E.A.F.S. and E.S wrote the manuscript. All co-authors reviewed and approved the manuscript.

Potential conflict of interest:

I.S., W.R.K., E.D.R., L.K.B., G.R., and E.S. declare no conflict of interest. E.A.F.S. reports grants, personal fees and non-financial support from Astra Zeneca Inc, grants, personal fees and non-financial support from Merck & Co., grants, personal fees and non-financial support from Regeneron Inc, grants, personal fees and non-financial support from Pfizer Inc, personal fees, non-financial support and other from Abbvie Inc, personal fees from Alere Inc, grants, personal fees and non-financial support from Roche Inc, other from GSK Inc, grants from Johnson and Johnson, grants and non-financial support from Novavax Inc, outside the submitted work.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

References

1. 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; 397:1819–1829.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N. Engl. J. Med. 2020; 383: 2603–2615.
3. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N. Engl. J. Med. 2021; 384: 1412–1423.
4. Chodick G, Tene L, Patalon T, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv 2021.01.27.21250612 (2021) doi:10.1101/2021.01.27.21250612.
5. 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, 20201; 397: 875–877.
6. Hall VJ, Foulkes S, Saei A, et al. Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study). Lancet. 2021; 397:1725-1735. doi: 10.1016/S0140-6736(21)00790-X.7.
7. Robertson JFR, Sewell HF, Stewart M. Delayed second dose of the BNT162b2 vaccine: innovation or misguided conjecture? The Lancet 2021: 397: 879–880.
8. Clemens J. Evaluating New Vaccines for Developing Countries: Efficacy or Effectiveness? JAMA JAMA. 1996; 275:390-7.
9. Concato J, Shah N, Horwitz RI. Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs. N. Engl. J. Med. 2000; 342:1887–1892.
10. de Bruyn G. Cofactors that may influence vaccine responses: Curr. Opin. HIV AIDS. 2021; 5: 404–408.
11. Clemens JD, Van Loon FFPL, Rao M, et al. Nonparticipation as a Determinant of Adverse Health Outcomes in a Field Trial of Oral Cholera Vaccines. Am. J. Epidemiol. 1992;135: 865–874.
12. Chen RT, Orenstein WA. Epidemiologic Methods in Immunization Programs. Epidemiol. Rev. 1996;18: 99–117.
13. 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. 2021; 27:790–792.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

14. Halloran ME, Haber M, Longini IM, Struchiner CJ. Direct and Indirect Effects in Vaccine Efficacy and Effectiveness. Am. J. Epidemiol. 1991;133: 323–331.

15. Gallagher ME, Sieben AJ, Nelson, KN, et al. Indirect benefits are a crucial consideration when evaluating SARS-CoV-2 vaccine candidates. Nat. Med. 2021; 27: 4–5.

16. Donauer S, Payne DC, Edwards KM, et al. Determining the effectiveness of the pentavalent rotavirus vaccine against rotavirus hospitalizations and emergency department visits using two study designs. Vaccine 2013; 31:2692–7.

17. Moore S, Hill, EM, Dyson L, Tildesley MJ, Keeling MJ. Modelling optimal vaccination strategy for SARS-CoV-2 in the UK. PLoS Comput Biol. 2021;17:e1008849. doi: 10.1371/journal.pcbi.1008849. PMID: 33956791.

18. Bubar KM, Reinholt K, Kissler SM, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. Science 2021; 371: 916–921.

19. Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. Lancet Infect. Dis. 2021;21:793-802.

20. KhudaBukhsh WR, Choi B, Kenah E, Rempała GA. Survival dynamical systems: individual-level survival analysis from population-level epidemic models. Interface Focus 2020; 10:20190048. doi: 10.1098/rsfs.2019.0048.

21. Andersson, H, Britton T. in: Stochastic Epidemic Models and Their Statistical Analysis.pp:3-125. Springer, ,Berlin, Germany, 2000.

22. KhudaBukhsh WR, Khalsa SK, Kenah E, Rempala GA, Tien JH. COVID-19 dynamics in an Ohio prison. medRxiv 2021.01.14.21249782 (2021) doi:10.1101/2021.01.14.21249782.

23. KhudaBukhsh, W. R., Choi, B., Kenah, E., Rempała, G. A. Survival dynamical systems: individual-level survival analysis from population-level epidemic models. Interface focus, 2020; 10:20190048. doi: 10.1098/rsfs.2019.0048.

24. Somekh I, Sharabi A, Dory Y, Simões EAF, Somekh E. Intrafamilial spread and altered symptomatology of sars-cov-2, during predominant circulation of lineage b.1.1.7 variant in Israel. Pediatr Infect Dis J. 2021; 40:e310-e311.

25. Corona Virus national Information Center. https://www.gov.il/he/departments/corona-national-information-and- knowledge-center.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

26. The Novel Corona virus, State of Israel Ministry of Health. https://data.gov.il/dataset/covid-19.

27. CBS. Population Estimates. https://old.cbs.gov.il/shnaton69/st02_03.pdf.

28. Somekh I, Yakub Hanna H, Heller E, Bibi H, Somekh E. Age-Dependent Sensory Impairment in COVID-19 Infection and its Correlation with ACE2 Expression. Pediatr. Infect. Dis. J. 2020; 39:, e270–e272.

29. Somekh I, Shohat T, Boker LK, Simões EAF, Somekh E. Reopening Schools and the Dynamics of SARS-CoV-2 Infections in Israel: A Nationwide Study. Clin Infect Dis. 2021; 73:2265-2275.

30. Somekh I, Boker LK, Shohat T, Pettoello-Mantovani M, Simões EAF, Somekh E. Comparison of COVID-19 Incidence Rates Before and After School Reopening in Israel. JAMA Netw Open. 2021;4:e217105. doi: 10.1001/jamanetworkopen.2021.7105.

31. Giordano G, Blanchini F, Bruno R, et al. M. Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy. Nat Med. 2020;26:855-860.

32. Marinho PRD, Cordeiro GM, Coelho HFC, Brandão SCS. COVID-19 in Brazil: A sad scenario. Cytokine Growth Factor Rev.2021; 58:51–54.

33. JHU & Center for Systems Science and Engineering. COVID-19 Dashboard. COVID-19 Dashboard. https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6.

34. OSU COVID-19 Response Team (2020). "Predicting COVID-19 Cases and Subsequent Hospital Burden in Ohio". 2020; In: https://tinyurl.com/2e42s4wy.

35. Bubar, K. M., Reinholt, K., Kissler, S. M., et al. D. B. (2021). Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. Science 2021; 371: 916-21.

36. Chen, Y. C., Lu, P. E., Chang, C. S., & Liu, T. H. A time-dependent SIR model for COVID-19 with undetectable infected persons. IEEE Transactions on Network Science and Engineering 2020; 7: 3279-94.

37. Last, M. (2020). The first wave of COVID-19 in Israel—Initial analysis of publicly available data. PLoS One. 2020; 15:e0240393

38. COVID-19 Hospital Impact Model for Epidemics (CHIME).2020; https://penn-chime.phl.io/

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Estimate	Actual cumulative number as of 2/28/2021	Approach 1		Approach 2	
		Estimated cumulative positive tests under no intervention	Estimated reduction in cases with vaccination	Estimated cumulative positive tests under no intervention	Estimated reduction in cases with vaccination
Total population	774,045	1,687,102 (CI: 902,088 - 2,217,029)	913,057 (CI: 128,043 - 1,442,984)	1,422,630 (CI: 799,922 – 2,171,008)	648,585 (CI: 25,877 - 1,396,963)
Children (<20 years of age)	500,286	1,155,005 (CI: 614,395 - 1,522,481)	654,719 (CI: 114,109 – 1,022,195)	663,722 (CI: 439,237 – 933,509)	163,436 (CI: 0 – 433,233)
Hospitalization	16,941	39,784 (CI: 21,850 - 52,247)	22,843 (CI: 4,909 - 35,306)	33,042 (CI: 18,951 – 49,976)	16,101 (CI: 2,010 – 33,035)
Mortality	5,778	13,167 (CI: 7,140 - 17,356)	7,389 (CI: 1,362 - 11,578)	10901 (CI: 6,165, 16,593)	5,123 (CI: 388 – 10,815)

Table 1. *Actual cumulative number of COVID-19 cases in the total population, in the population <20 years of age, hospitalizations and mortality and the population-level effect of vaccination on the estimated cumulative positive tests under no intervention and the estimated reduction in cases with vaccination, following two different simulation approaches.*

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Figure Legends:

Figure 1. Daily Case Counts of SARS-CoV-2 Positive Tests. Daily numbers of SARS-CoV-2 positive samples tested during March 2020 – February 2021 are shown. The "epidemic waves" of COVID-19 in Israel are depicted; Major time points, including lockdown periods, social restrictions, and the start of vaccinations are noted.

Figure 2. SARS-CoV-2 Infections, Hospitalizations, Fatalities and Vaccinations, by Date. (A) Daily counts of positive SARS-CoV-2 tests. (B) Time series and counts of the BNT162b2-mRNA COVID-19 vaccine first dose administered. Vaccinations began on December 19, 2020. (C) Daily counts of COVID-19 moderate-severely ill hospitalizations. In order to account for potential changes in the definition of moderate, severe and critical cases, we have combined the counts. (D) Daily counts of COVID-19 fatalities.

Figure 3. Actual Cumulative Numbers, and Calculated Numbers Under the 'No Vaccination' Scenario, of SARS-CoV-2 Infections, Hospitalizations and Fatalities. Weekly numbers of SARS-CoV-2 infections, hospitalizations and deaths are shown during January – February, 2021, including the actual numbers and the calculated numbers of the no vaccination scenario utilizing the two different approaches. (A) The actual and the calculated numbers of the 'no vaccination' scenario of SARS-CoV-2 weekly positive tests are shown for the whole population. (B) The actual and the calculated numbers of the 'no vaccination' scenario of weekly SARS-CoV-2 positive tests are shown for children aged 0-19 years, demonstrating the indirect effect of vaccination on the young population (less than 20 years of age). (C) The actual and the calculated numbers of the 'no vaccination' scenario of weekly SARS-CoV-2 hospitalizations are shown, demonstrating the effect of vaccination on hospitalizations for moderate to severe conditions. (D) The actual and the calculated numbers of the 'no vaccination' scenario of weekly SARS-CoV-2 deaths are shown demonstrating the effect of vaccination on cumulative fatality. The solid red curve corresponds to actual case counts. The purple dotted line (and blue shaded regions indicating 75% confidence bounds) show the no intervention scenario modeled under Approach 1. The black dashed line (and grey shaded region indicating 75% confidence bounds) correspond to the 'no vaccination' scenario modeled under Approach 2.

Accepted Manuscript

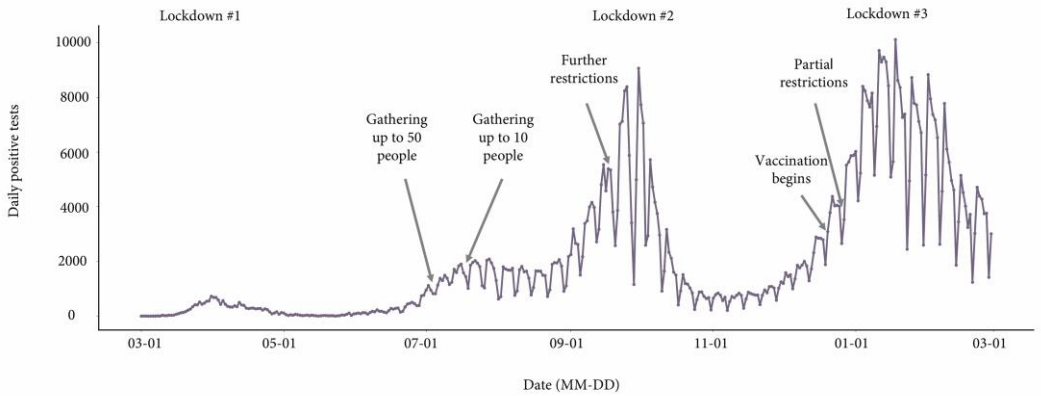
Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Figure 4. Comparison of Actual SARS-CoV-2 Infections and Simulated Counts, during January 8 – January 28, 2021. Comparison of simulated cumulative counts of positive counts and daily counts of positive tests with true counts is shown. As of January 8, 2021, the cumulative count of positive tests was 480,338. As demonstrated in the figure, the simulated trajectories lie close to the true counts of cumulative positive tests. The solid red line shows the actual trajectories. The means of the simulated trajectories are shown as broken line in purple. The shaded blue regions indicate 75% confidence around the mean trajectory. (A) Comparison of the cumulative counts of positive counts against the true counts. (B) Comparison of the fitted daily counts of positive tests against true counts of daily positive tests. The dips in the counts are due to weekend effects. Even though the true trajectory of daily counts of positive tests is unsmooth, the simulated counts of daily positive tests are generally close to it. In particular, the true trajectory lies entirely within the 75% confidence bounds indicating a good fit of the model to the data.

Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

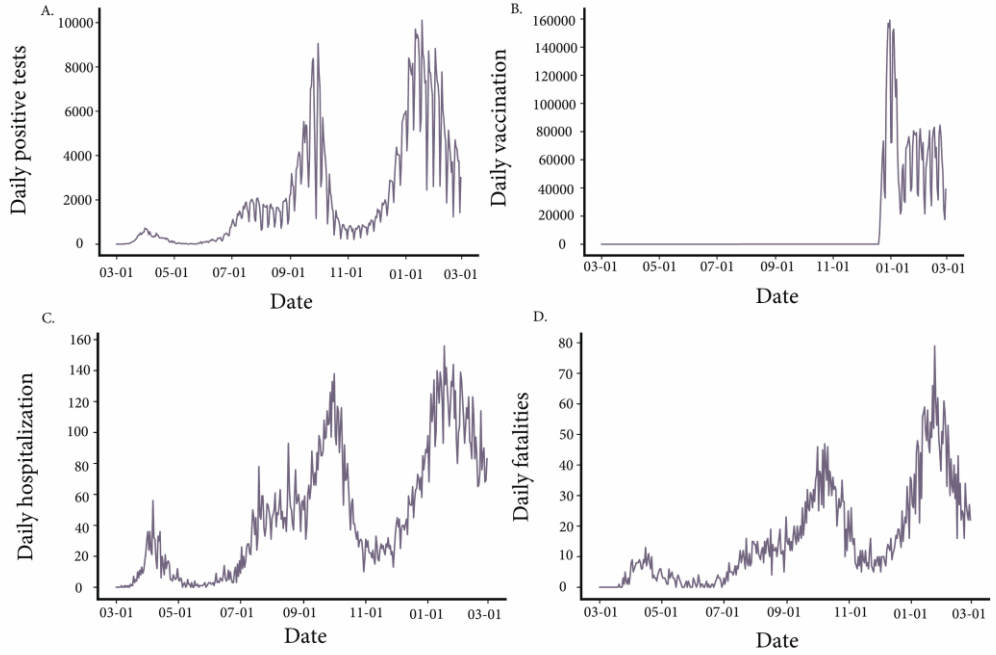
Figure 1



Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

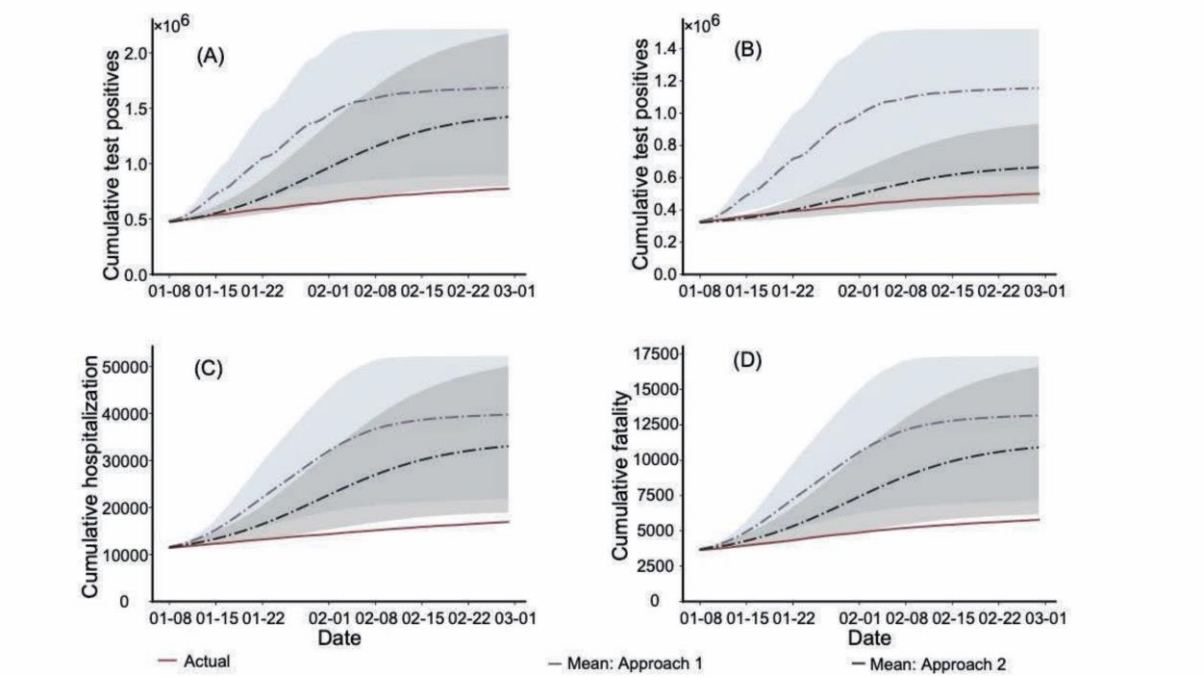
Figure 2



Accepted Manuscript

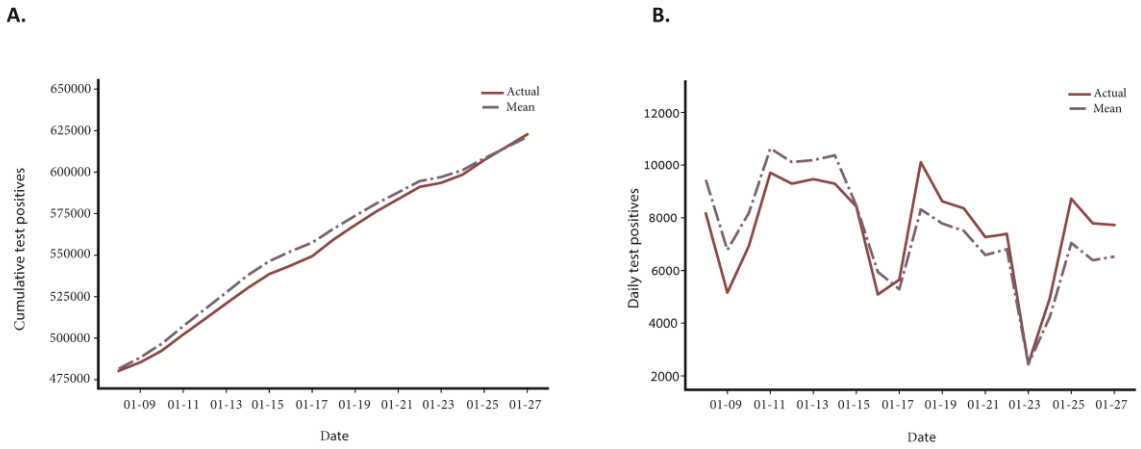
Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Figure 3



Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022

Figure 4



Accepted Manuscript

Downloaded from https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofac087/6530634 by guest on 11 April 2022