Vaccine coverage associated with ending a SARS-CoV-2 wave: a retrospective longitudinal analysis.

Aharona Glatman-Freedman¹,², Sarah F. Feldman³, Yael Hershkovitz¹, Zalman Kaufman¹, Rita Dichtiar¹, Lital Keinan-Boker¹,⁴, Michal Bromberg¹,²

Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel ¹

Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel ²

National Institute for Antibiotic Resistance and Infection Control, Ministry of Health, Tel Aviv, Israel ³

School of Public Health, Haifa University, Haifa, Israel ⁴

#Corresponding author: Aharona Glatman-Freedman, The Israel Center for Disease Control, Tel Hashomer; Ramat Gan, Israel. E mail: aharona.freedman@moh.gov.il

Running title: Vaccine-related end of SARS-CoV-2 wave
ABSTRACT

Background. Two SARS-CoV-2 waves in Israel ended while a substantial number of individuals remained unvaccinated or partially vaccinated. The indirect protective effect of the first BNT162b2 vaccination campaign in Israel was evaluated between 22 December 2020 and 18 May 2021.

Methods. The daily percentage of new PCR-confirmed SARS-CoV-2 cases among unvaccinated individuals was analyzed for trends. Major shifts were identified using piecewise linear regression analysis. At these shifts, the percentage of naturally vaccinated (past SARS-CoV-2 cases) and the percentage of actively vaccinated (by inoculation) individuals were weighted and summed to determine the percentage of natural and active vaccination (NAV).

Results. A first decline among unvaccinated individuals occurred during a lockdown period, when the percentage of NAV was 8.16%. The major decline occurred after the end of the lockdown when the percentage of NAV reached 52.05%. SARS-CoV-2 cases ultimately declined among unvaccinated individuals when the percentage of NAV reached 63.55%. During the study period, the Alpha variant was prevalent and the use of non-pharmaceutical intervention, including social distancing, existed to varying degrees.

Conclusions. The vaccination campaign played a major role in the decline of SARS-CoV-2 infection among unvaccinated individuals, leading to the end of the first 2021 SARS-CoV-2 wave (alpha variant) in Israel. The infection of unvaccinated individuals stopped when two thirds of the population were naturally or actively vaccinated. Any change in characteristics of the virus or the population can lead to a new outbreak.

Key words: Indirect protection; SARS-CoV-2; vaccination
INTRODUCTION

Large vaccination campaigns against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have been carried out around the world since the end of 2020. However, despite considerable efforts, pandemic control has not been achieved. By 1 December 2021, Israel underwent two SARS-CoV-2 waves since national vaccination efforts began. The end of these first and second waves was associated with increase in the second dose vaccine coverage, and with increase in the booster dose coverage, respectively. However, both waves subsided while a substantial number of individuals remained unvaccinated or partially vaccinated.

While direct protection consists of the reduction in infection among individuals vaccinated or naturally infected, indirect vaccine protection consists of the reduction of infection in the unvaccinated individuals of the same population (1). When a substantial share of the population becomes immune to an infectious disease through recovery from infection or through vaccination, and individuals who are not immune become indirectly protected, herd immunity occurs (2). Indirect vaccine protection exists when the vaccine protective effect in a population exceeds the expected protection, which depends on the level of vaccine coverage and protective efficacy (1).

The population vaccine coverage required to attain indirect protection varies by disease. While indirect protection for measles is attained once approximately 95% of the population ≤5 years old is vaccinated (3, 4), approximately 80% is required for mumps (5).

Israel SARS-CoV-2 vaccine campaign started on 20 December 2020 relying on the BNT162b2 vaccine, which was shown to have high vaccine efficacy and effectiveness in two-dose recipients (6-10). Substantial reduction of SARS-CoV-2 wave, predominated by the B.1.1.7 (Alpha) variant
(11), was observed following vaccine introduction. On 18 May 2021, only 19 new SARS-CoV-2 laboratory-confirmed cases were detected in Israel (2 cases per 1 million population), 4 SARS-CoV-2-positive patients were hospitalized and no death occurred. Thus, population-level protection from SARS-CoV-2 in Israel, was apparently achieved. The protective effect was short as a new SARS-CoV-2 wave, predominated by the B.1.617.2 (Delta) variant (11), started in the third week of June 2021, associated with waning of vaccine-induced protection (12, 13).

We sought to characterize the indirect effect of the BNT162b2 vaccine during the first SARS-CoV-2 wave (Alpha variant) that occurred while vaccines were available in Israel. Such characterization is important for understanding what percentage of the population needs to be ‘freshly’ vaccinated to end a SARS-CoV-2 wave.

METHODS

Study design and data collection

We performed a retrospective population-based analysis, using two national data repositories. The national SARS-CoV-2 Polymerase Chain Reaction (PCR) tests repository includes the following information for each individual: swab date, results date, and test result. The national SARS-CoV-2 vaccine repository includes the following information for each vaccinated individual: Vaccine name, lot number and administration date. Both repositories also include personal identifiers and demographic data.

The unique personal identity number (UPIN) of each Israeli resident was used to match the repositories. UPINs were twice encrypted. The number of Israeli residents (all ages n=9,053,200, and by age group) was based on the 2020 Central Bureau of Statistics statistical abstract(14).
Vaccination and SARS-CoV-2 status

Daily number of individuals vaccinated with one or two doses and individuals who were SARS-CoV-2-positive by PCR between 22 December 2020 and 18 May 2021, for the entire Israeli population and for the following age groups: 0-11, 12-15, 16-18, 19-34, 35-49, 50-59, 60-79 and ≥80 years old were retrieved from the repositories.

Individuals who received their first vaccine dose were considered to be one-dose recipients. Once they received a second dose, they were not considered one-dose recipients anymore, but second-dose recipients only.

Individuals were considered to be SARS-CoV-2-positive from the date of their first positive laboratory PCR result for SARS-CoV-2. A SARS-CoV-2-positive individual that previously received one or two vaccine doses was considered to be SARS-CoV-2-positive from the date of the positive PCR test result, and not considered anymore to be one- or two-dose recipient from this date. For individuals having more than one SARS-CoV-2-positive PCR test, only the first one was considered in the analysis. The number of unvaccinated individuals for each study date was calculated by omitting the number of Israeli residents who received the relevant (first or second) BNT162b2 vaccine dose from the total number of Israeli residents that did not have a documented SARS-CoV-2-positive test by that date.

Assessment of vaccination coverage

To assess the level of partial or full protection against SARS-CoV-2 of Israeli residents, we calculated the cumulative percentage of individuals who had received one BNT162b2 vaccine dose, two BNT162b2 vaccine doses, or who had a positive PCR test by the date of evaluation.
Dynamics of new SARS-CoV-2 cases

Daily percentages and seven-day moving average of percentages of new SARS-CoV-2 cases among individuals who received one vaccine dose, two vaccine doses or among unvaccinated individuals were calculated. Significant changes in daily percentage of new SARS-CoV-2 cases among unvaccinated individuals were detected using piecewise linear regression models (15). The date when a significant change occurred was called a breakpoint. The ‘first breakpoint’ was the breakpoint preceding the first significant change in slope. The ‘major decline breakpoint’ was the breakpoint preceding the steepest negative slope. The ‘End of decline’ was the last date before a negative value for the percentage of daily SARS-CoV-2 cases was fitted.

Determination of indirect protection

To determine the percentage of likely protected individuals due to natural and active vaccination (NAV) resulting from SARS-CoV-2 infection or vaccination, respectively, on a particular breakpoint date, we used the following parameters:

A. Percentage of individuals who had received two doses of the BNT162b2 vaccine at least 7 days prior to the particular breakpoint date. This percentage was based upon studies that demonstrated vaccine efficacy of 95% 7 days after receipt of the second dose (6).

B. Percentage of individuals who had received one dose of the BNT162b2 vaccine at least 14 days prior to the particular breakpoint date. This percentage was based upon studies that demonstrated vaccine effectiveness (VE) of around 50% 14-20 days after receipt of the first dose (9).
Percentage of individuals who had a positive SARS-CoV-2 PCR test at least 14 days prior to the particular breakpoint date. This percentage was based on the detection of robust neutralizing antibodies 14 days after the onset of symptoms (16).

Based on these parameters we designed a formula to determine the percentage of likely protected individuals due to NAV, on a particular date:

\[
%\text{NAV}(t) = %\text{VAC2}(t-7) + %\text{VAC1}(t-14)/2 + %\text{SARS-CoV-2-pos}(t-14)
\]

Where \( t \) represents the day of NAV determination, \( %\text{VAC2}(t-7) \) is the percentage of 2\textsuperscript{nd} dose recipients 7 days prior to day \( t \), \( %\text{VAC1}(t-14) \) is the percentage of 1\textsuperscript{st} dose recipients 14 days prior to day \( t \), \( %\text{SARS-CoV-2-pos}(t-14) \) is the percentage of SARS-CoV-2 PCR-positive individuals 14 days prior to day \( t \).

\( %\text{VAC1}(t-14) \) is divided by 2 to represent the fact-based assumption that a single BNT162b2 vaccine dose leads to about half of the two-dose VE (50%) against SARS-CoV-2 infection 14 days after administration (9).

Statistical analysis

SARS-CoV-2-positive individuals, one-dose recipients and two-dose recipients were expressed as daily cumulative percentage of total population. Seven-day moving average of daily percentage of SARS-CoV-2-positive cases was calculated among unvaccinated, one-dose and two-dose recipients. Seven-day moving average of percentage of hospitalization and death
among SARS-CoV-2-positive individuals was calculated for unvaccinated individuals and two-dose recipients.

Significant changes in daily percentage of confirmed SARS-CoV-2 cases among unvaccinated individuals throughout the study period were detected using Piecewise linear regression analysis (15) applied to the daily percentage (without smoothing) of new PCR-confirmed SARS-CoV-2-positive cases among unvaccinated individuals, using the R package segmented and R version 3.6.1. The number and positions of breakpoints were selected based on the Bayesian information criterion with a maximum of five breakpoints. The percentage of NAV was computed as described above, for each breakpoint and for the 'end of decline'.

The analyses were carried out for all Israeli residents and by age group.

**Ethical consideration**

The use of individual data from the two national data repositories was approved by the superior ethical committee of the Israel Ministry of Health (MOH).

**RESULTS**

**Progress of vaccination status**

Figure 1 demonstrates the evolution of percentage of vaccination coverage and percentage of SARS-CoV-2-positive individuals throughout the study period for the entire population and by age groups. Specifically, it shows the cumulative two-dose vaccination coverage and the cumulative percentage of SARS-CoV-2-positive individuals that increases over time. The one-
dose vaccination coverage is cumulative until one-dose recipients receive their second vaccine dose or became SARS-CoV-2-positive, at which point they are no longer counted as one-dose vaccine recipients.

By 18 May 2021, of the study population, only 35 individuals remained with only one vaccine dose (0.004%), and 36.4% were not vaccinated, nor had a past SARS-CoV-2 infection (Figure 1 panel A).

**Dynamics of SARS-CoV-2 cases**

Figure 2 demonstrates the seven-day moving average of the percentage of new SARS-CoV-2-positive cases (Figure 2A) and the seven-day moving average of the percentage of hospitalizations (Figure 2B) and deaths (Figure 3C) among SARS-CoV-2 positive individuals, by vaccination status. The percentages of cases, hospitalizations and deaths were higher among unvaccinated individuals as compared with two-dose vaccine recipients. The percentage of cases, hospitalizations and deaths reached a nadir by the end of the evaluation period, both among unvaccinated and two-dose vaccine recipients. Figure S1 of the supplementary material demonstrates the daily numbers of SARS-CoV-2 cases as well as hospitalizations and deaths among SARS-CoV-2-positive individuals of all ages, by vaccination status.

Figure 3 demonstrates the seven-day moving average of the percentage of new SARS-CoV-2-positive individuals by vaccination status, in all ages (Figure 3A), and by age group (Figure 3 B-I). The lowest SARS-CoV-2-positive percentage was observed among individuals who received two vaccine doses (Figure 3 A-G). The percentages among unvaccinated ≥19 year old individuals were higher as compared with one-dose and two-dose vaccine recipients (Figure 3 A-F).
Figure 4 shows the results of the piecewise regression analysis. Three breakpoints were identified in the all-ages analysis (Figure 4A), and two to three in the age group analyses. An end of decline was observed in all age groups prior to 18 May 2021 except for the 12-15 years-old group.

In all analyses, a substantial rise in the percentage of daily SARS-CoV-2 cases prior to the 'first breakpoint' was apparent. After the ‘first breakpoint’, the percentage of daily cases either plateaued, decreased or demonstrated a mild rise. All analyses demonstrated a ‘major decline breakpoint’ after which a steep decline was observed. This steep decline was followed by another breakpoint that led to the 'end of decline' (Figure 4).

For all ages and for each age group the 'first breakpoint' was different from the 'major decline breakpoint', with the exception of the 12-15 and the 16-18 age groups, where the 'first breakpoint' was also the 'major decline breakpoint'.

For all age groups, the ‘first breakpoint’ occurred between 7 January and 13 January 2021. For all age groups, with the exception of the 16-18 and the 12-15 age groups, the 'major decline breakpoint' occurred between 3 March and 10 March 2021. For all age groups, with the exception of the 12-15 age group, 'end of decline' occurred between 7 May and 13 May 2021. For specific dates, see Table 1.

**Determination of indirect protection**

Table 1 demonstrates the percentage of NAV in individuals of all ages and by age groups at the following points of interest: ‘first breakpoint’, ‘major decline breakpoint’ and ‘end of decline’. Specifically, it shows that in ‘all ages’ the first breakpoint occurred when the percentage of NAV was 8.16%, the ‘major decline breakpoint’ occurred when the percentage of NAV was 52.05%
and the ‘end of decline’ occurred when the percentage of NAV reached 63.55%. Figure S2 of the supplementary material shows daily NAV superimposed on the data presented in Figure 3.

**Use of non-pharmaceutical interventions during the study period**

Various non-pharmaceutical interventions (NPIs) were implemented during the vaccination campaign (Table 2). The vaccination campaign started during a rise in the number of SARS-CoV-2 cases, which resulted in lockdown on 27 December 2020 and its enhancement on 8 January 2021. As the rise in the number of cases was halted, gradual lifting of limitation occurred overtime. By 18 May 2021, several limitations were still in place (Table 2).

**DISCUSSION**

By 18 May 2021, only 19 new SARS-CoV-2 cases were identified in Israel. Our study suggests that indirect protection against SARS-CoV-2 was achieved by that point, as the number of new cases reached a very low level despite the fact that 36.4% of the population were not vaccinated, nor had a documented past SARS-CoV-2 infection.

Our study demonstrated that SARS-CoV-2 cases declined among unvaccinated individuals of all age groups. Furthermore, the key time points in which the SARS-CoV-2 pandemic wave shifted its course during the BNT162b2 vaccine campaign were demonstrated.

Although the role of lockdowns cannot be quantified, the ‘first breakpoint’ occurred during a lockdown period, when the percentage of NAV individuals of all ages was less than 10%, indicating that vaccination alone was most probably not the primary reason for the beginning of the shift in trend.
The ‘major decline breakpoint’ occurred after the lockdown ended and about half of the population of all ages was NAV, indicating that the vaccination campaign had a major role in the sustainable decline that started at this time point.

Of exception are the 12-15 and 16-18 years old age groups, for which the ‘major decline breakpoint’, which occurred on 11 January 2021, was also the ‘first breakpoint’. The vaccination campaign for the 16-18 years old age group started at the end of January 2021, and individuals aged 12-15 years old were vaccinated at that time only in extreme circumstances, with special MOH approval. Therefore, the early start of the sustainable decline among these age groups resulted, most likely, from vaccination of older individuals, with the addition of lockdown that lasted until 7 February 2021.

The end of decline was observed for all ages during the month of May 2021, when the NAV coverage was 63.55% for all ages.

The degree of the indirect vaccine effect can be affected by several factors: pathogen transmissibility, vaccine efficacy, pattern of population mixing, vaccine coverage and vaccine distribution in the population (5, 17-20).

The BNT162b2 vaccine efficacy was found to be 95% (6), thus providing this vaccine with an advantage towards reaching indirect vaccine effect. However, waning of the BNT162b2 vaccine-induced protection against infection (21) prevented the development of a long-standing herd protection and led into the Delta (B.1.617.2) variant wave that started in Israel at the end of June 2021(22, 21, 13, 12). A fresh BNT162b2 vaccine and a booster were found highly effective (10, 23, 24).
Transmissibility can vary among different SARS-CoV-2 variants (25-27). In this regard, the Omicron (B.1.1.529) variant, which was found to have increased transmissibility as compared to previous variants, was first detected in Israel at the end of November 2021 (28). It quickly became the predominant variant, reaching more than 90% of circulating SARS-CoV-2 viruses by 10 January, 2022 (11). Recent evaluations suggested a decreased BNT162b2 (including booster) VE against the Omicron variant (29, 30), thus affecting the potential to achieve vaccine indirect protection.

Pathogen transmissibility can be affected also by the use of NPIs, such as social distancing measures and the use of facial masks (26). In this regard, the early stages of the vaccine campaign took place while lockdown was in place. Furthermore, social distancing to various degrees was in effect in Israel until 31 May 2021, and the use of masks in closed spaces was in effect until 15 June 2021. Therefore, it is possible that the indirect protection achieved in Israel was aided by the use of NPI.

Basic mathematical models of pathogen transmission assume that populations mix homogeneously, and that disease transmission between any two individuals is equally probable, irrespective of their age, their residence or work location, their activity level, or other behavior characteristics (31). However, more recent pathogen transmission models take into consideration the heterogeneous mixing patterns of populations (31). In this regard, children are likely to have closer physical contact with their parents than other adults, and their ability to develop indirect protection can be strongly affected by their parents' vaccination (32). Therefore, some of the SARS-CoV-2 cases decline among Israeli children could have been driven by their parents' vaccination status.
Our study has several limitations. As this study addressed the development of indirect protection of the Israeli population, it did not address indirect protection in subpopulations other than age groups. A study in 177 communities in Israel during the first SARS-CoV-2 wave in which vaccine was available for ≥16 year old individuals, found that increase in vaccination rates in these communities was associated with infection rates decline among <16 years old individuals (33). However, that study did not take into account the natural immunity (which resulted from SARS-CoV-2 exposure) in these communities, nor did it establish the vaccination coverage required to reach the end of SARS-CoV-2 cases decline (33). A study from Spain suggested the development of indirect protection against SARS-CoV-2 in unvaccinated residents of long-term care facilities (34). Both studies were published before waning vaccine protection became evident.

An additional limitation stems from the fact that, despite our efforts, the real number of individuals who were infected with SARS-CoV-2 and developed natural immunity from SARS-CoV-2 exposure is unknown, and largely depends on the motivation to perform PCR testing, which may vary considerably among individuals. Two serological surveys from Israel showed that IgG antibodies against SARS-CoV-2-receptor binding domain were detected among 7.7% and 8.1% of samples from 0-15 and ≥16 year old individuals, respectively, in the month of December 2020 (35, 36), while 4.2% of Israeli residents of all ages were SARS-CoV-2-PCR-positive on day 1 of our study. Thus, our calculation of the percent NAV individuals required to achieve indirect protection may be underestimated.

In conclusion, indirect protection against SARS-CoV-2 was provided by the BNT162b2 vaccine and helped end the Alpha variant wave. However, the level of natural and active vaccination
required to achieve indirect protection depends on an equilibrium of factors including NPI use, circulating variants and waning immunity.

Contributors

AG-F conceived and designed the study, led data analysis and wrote the first draft of the manuscript. MB oversaw the study design and analysis. YH and RD retrieved the data. YH, SFF, ZK and RD performed data analysis. AG-F, SFF, LK-B and MB interpreted the data and edited the final manuscript. YH and RD verified the underlying data. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Declaration of interests

We declare no conflict of interest

Financial support: None.
REFERENCES

1. Clemens J, Shin S, Ali M. New approaches to the assessment of vaccine herd protection in clinical trials. The Lancet infectious diseases. 2011;11(6):482-7.

2. Desai AN, Majumder MS. What Is Herd Immunity? JAMA : the journal of the American Medical Association. 2020;324(20):2113.

3. Funk S, Knapp JK, Lebo E, Reef SE, Dabbagh AJ, Kretsinger K, et al. Combining serological and contact data to derive target immunity levels for achieving and maintaining measles elimination. BMC medicine. 2019;17(1):180.

4. van Boven M, Kretzschmar M, Wallinga J, O'Neill PD, Wichmann O, Hahné S. Estimation of measles vaccine efficacy and critical vaccination coverage in a highly vaccinated population. Journal of the Royal Society, Interface. 2010;7(52):1537-44.

5. Martinon-Torres F. Expected and unexpected effects of vaccination. In: P; VTVD, editor. Pediatric vaccines and vaccinations. Switzerland: Springer International Publishing 2017. p. 3-12.

6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. The New England journal of medicine. 2020;383(27):2603-15.

7. Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2022;74(3):472-8.

8. Dagan N, Barda N. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. 2021;384(15):1412-23.
9. Glatman-Freedman A, Bromberg M, Dichtiar R, Hershkovitz Y, L K-B. The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: a nation-wide retrospective longitudinal multiple cohort analysis using individualised data. EBioMedicine. 2021(72):103574.

10. Glatman-Freedman A, Hershkovitz Y, Kaufman Z, Dichtiar R, Keinan-Boker L, Bromberg M. Effectiveness of BNT162b2 Vaccine in Adolescents during Outbreak of SARS-CoV-2 Delta Variant Infection, Israel, 2021. Emerging Infectious Disease journal. 2021;27(11).

11. Our World in Data. SARS-CoV-2 variants in analyzed sequences, Israel. https://ourworldindata.org/grapher/covid-variants-area?country=~ISR 2021.

12. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ. Waning Immunity after the BNT162b2 Vaccine in Israel. N Engl J Med. 2021;385(24):e85.

13. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J Med. 2021;385(24):e84.

14. Central Bureau of Statistics. Population - statistical abstract of Israel - No. 71. https://www.cbs.gov.il/en/publications/Pages/2020/Population-Statistical-Abstract-of-Israel-2020-No-71.aspx. 2020 [13 February, 2021].

15. Muggeo VM. Estimating regression models with unknown break-points. Statistics in medicine. 2003;22(19):3055-71.

16. Pradenas E, Trinité B, Urrea V, Marfil S, Ávila-Nieto C, Rodríguez de la Concepción ML, et al. Stable neutralizing antibody levels 6 months after mild and severe COVID-19 episodes. Med (New York, NY). 2021;2(3):313-20.e4.
17. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52(7):911-6.

18. Bai F. Effect of population heterogeneity on herd immunity and on vaccination decision making process. Journal of theoretical biology. 2021:110795.

19. Hodgson D, Flasche S, Jit M, Kucharski AJ. The potential for vaccination-induced herd immunity against the SARS-CoV-2 B.1.1.7 variant. Euro Surveill. 2021;26(20).

20. Rashid H, Khandaker G, Booy R. Vaccination and herd immunity: what more do we know? Current opinion in infectious diseases. 2012;25(3):243-9.

21. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021;398(10309):1407-16.

22. Bayart JL, Douxfils J. Waning of IgG, Total and Neutralizing Antibodies 6 Months Post-Vaccination with BNT162b2 in Healthcare Workers. Vaccines. 2021;9(10).

23. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. The New England journal of medicine. 2021;385(26):2421-30.

24. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. The New England journal of medicine. 2021;385(15):1393-400.

25. Volz E, Mishra S. Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. Nature. 2021;593(7858):266-9.
26. Graham MS, Sudre CH, May A, Antonelli M, Murray B, Varsavsky T, et al. Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. The Lancet Public health. 2021;6(5):e335-e45.

27. Davies NG, Abbott S. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. 2021;372(6538).

28. Israel Ministry of Health. As of Today, 27/11/2021, One Confirmed Case of the Omicron Variant Was Detected in Israel. https://www.gov.il/en/departments/news/27112021-01 [press release]. 2021.

29. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. The New England journal of medicine. 2022;386.

30. Glatman-Freedman A, Bromberg M, Hershkovitz Y, Sefty H, Kaufman Z, Dichtiar R, et al. Effectiveness of BNT162b2 Vaccine Booster against SARS-CoV-2 Infection and Breakthrough Complications, Israel. Emerging infectious diseases. 2022;28(5):948-56.

31. Del Valle SY, Hyman JM, Chitnis N. Mathematical models of contact patterns between age groups for predicting the spread of infectious diseases. Mathematical biosciences and engineering : MBE. 2013;10(5-6):1475-97.

32. Hayek S, Shaham G, Ben-Shlomo Y, Kepten E, Dagan N, Nevo D, et al. Indirect protection of children from SARS-CoV-2 infection through parental vaccination. Science (New York, NY). 2022;375(6585):1155-9.

33. Milman O, Yelin I. Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. 2021.
34. Monge S, Olmedo C, Alejos B, Lapeña MF, Sierra MJ, Limia A. Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain. Emerging infectious diseases. 2021;27(10).

35. Indenbaum V, Lustig Y, Mendelson E, Hershkovitz Y, Glatman-Freedman A, Keinan-Boker L, et al. Under-diagnosis of SARS-CoV-2 infections among children aged 0-15 years, a nationwide seroprevalence study, Israel, January 2020 to March 2021. Euro Surveill. 2021;26(48).

36. Israel Center for Disease Control, Ministry of Health. Serological survey of SARS-CoV-2 antibodies among adults in Israel, January 2020-July 2021 [Hebrew]. https://www.gov.il/he/departments/publications/reports/icdc-410. 2022.
FIGURE LEGENDS

Figure 1. Progress of the percentage of vaccination coverage (actively vaccinated population) and the percentage of SARS-CoV-2-positive cases (naturally vaccinated population) for all ages (Panel A) and by age groups (Panels B-I). The panels show the cumulative two-dose vaccination coverage (green bars) and the cumulative percentage of SARS-CoV-2-positive individuals (blue bars). The one-dose vaccination coverage (orange bars) shown is cumulative until one-dose recipients receive their second vaccine dose or became SARS-CoV-2 positive, at which point they are no longer counted as one-dose vaccine recipients. The non-colored area above the bars represents the daily percentage of Israeli residents who were neither vaccinated nor having been documented by that date to be SARS-COV-2 infected. yo - years old.

Figure 2. Seven-day moving average of the percentage of new PCR-confirmed SARS-CoV-2-positive cases (Panel A), hospitalizations (Panel B) and deaths (Panel C) of individuals of all ages among two-dose vaccine recipients and unvaccinated individuals.

Figure 3. Seven-day moving average of the percentage of new PCR-confirmed SARS-CoV-2-positive cases out of individuals of all ages (Panel A), and individuals belonging to specific age groups (Panels B-I) by vaccination status. yo - years old.

Figure 4. Piecewise regression analysis applied to the daily percentage of new PCR-confirmed SARS-CoV-2-positive cases among unvaccinated individuals of all ages (Panel A) and by age groups (Panels B-I). The 'first breakpoint', the 'major decline breakpoint' and the 'end of decline' are marked in Panel A. yo - years old.
**Table 1.** Calculation of the percentage of naturally and actively vaccinated individuals in the population and by age groups at points of interest, Israel, December 2020 – May 2021.

| Age group (years) | 2nd dose coverage -7d (%) | 1st dose coverage -14d (%) | SARS-CoV-2+ by PCR -14d (%) | Naturally and actively vaccinated (NAV) (%) |
|------------------|--------------------------|---------------------------|-----------------------------|-------------------------------------------|
| **First breakpoint (Date)** | | | | |
| All ages | 0.00 | 7.26 | 4.53 | 8.16 |
| ≥80 | 0.00 | 28.08 | 3.37 | 17.41 |
| 50-59 | 0.00 | 8.27 | 4.83 | 8.96 |
| 35-49 | 0.00 | 3.63 | 4.75 | 6.56 |
| 19-34 | 0.00 | 0.72 | 6.29 | 6.65 |
| 16-18 | 0.00 | 0.18 | 4.75 | 4.84 |
| 12-15* | 0.00 | 0.00 | 4.87 | 4.87 |
| 0-11 | 0.00 | 0.00 | 2.83 | 2.83 |
| **Major decline breakpoint (Date)** | | | | |
| All ages | 8 March 2021 | 37.03 | 13.49 | 8.27 | 52.05 |
| ≥80 | 3 March 2021 | 76.68 | 5.11 | 5.58 | 84.82 |
In rare cases, individuals 12-15 received the BNT162b2 vaccine prior to FDA approval for this age group. These individuals received the vaccine due to the presence of underlying diseases or due to being household members of immunocompromised patients. Special approvals for their vaccination were granted on a case-by-case basis.
Table 2. Timeline of non-pharmaceutical interventions during the COVID-19 vaccination campaign, Israel December 2020 to June 2021.

| Milestone                        | Date               | Main directives                                                                                                                                 |
|----------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Start of vaccination campaign    | 20 December, 2020  |                                                                                                                                             |
| Initial lockdown                 | 27 December, 2020  | 1,000 meter mobility limit, gathering restrictions; private sector workplace attendance at 50% capacity (except essential workers); schools remain open (except for grades 5-10) |
| Enhanced lockdown                | 8 January, 2021    | Addition of: school closure (except special education and no re-entry boarding schools), no workplace attendance (except essential workers), enhanced gathering restrictions |
| Stage 1 reopening                | 7 February, 2021   | Mobility limit lifted                                                                                                                       |
| Stage 2 reopening                | 21 February, 2021  | Beginning of non-essential commerce and activities for the public, under the 'green pass' (entry to fully vaccinated and recovered individuals) regulations; gradual school reopening; |
| Stage 3 reopening                | 7 March, 2021      | Additional school reopening; additional non-essential commerce reopening.                                                                     |
| Stage 4 reopening                | 19 March, 2021     | 5000 people allowed in open sports events; children allowed in open swimming pools.                                                           |
| Stage 5 reopening | 18 April, 2021 | No obligation to wear masks in outdoors except for gatherings. |
|--------------------|----------------|---------------------------------------------------------------|
| Stage 6 reopening  | 27 May, 2021   | Movie theaters re-open.                                       |
| Stage 7 reopening  | 1 June, 2021   | 'Green pass' and 'Purple pass' (social distancing guidelines indoors) use cancelled |
| Stage 8 reopening  | 15 June, 2021  | No obligation to wear masks in closed spaces, except for medical facilities, nursing homes and airplanes |
Figure 1

147x82 mm (.25 x DPI)
Figure 2

A. SARS-CoV-2-positive cases

B. Hospitalization

C. Death

Figure 2
147x207 mm (.25 x DPI)
Figure 3
147x82 mm (.25 x DPI)

Figure 4
147x101 mm (.25 x DPI)