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BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel

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A B S T R A C T

Objectives: The mRNA coronavirus disease 2019 (COVID-19) vaccines have shown high effectiveness in the prevention of symptomatic COVID-19, hospitalization, severe disease and death. Nevertheless, a minority of vaccinated individuals might become infected and experience significant morbidity. Characteristics of vaccine breakthrough infections have not been studied. We sought to portray the population of Israeli patients, who were hospitalized with COVID-19 despite full vaccination.

Methods: A retrospective multicentre cohort study of 17 hospitals included patients fully vaccinated with Pfizer/BioNTech’s BNT162b2 vaccine who developed COVID-19 more than 7 days after the second vaccine dose and required hospitalization. The risk for poor outcome, defined as a composite of mechanical ventilation or death, was assessed.

Results: A total of 152 patients were included, accounting for half of hospitalized fully vaccinated patients in Israel. Poor outcome was noted in 38 patients and mortality rate reached 22% (34/152). Notably, the cohort was characterized by a high rate of co-morbidities predisposing to severe COVID-19, including hypertension (108; 71%), diabetes (73; 48%), congestive heart failure (41; 27%), chronic kidney and lung diseases (37; 24% each), dementia (29; 19%) and cancer (36; 24%), and only six (4%) had no co-morbidities. Sixty (40%) of the patients were immunocompromised. Higher viral load was associated with a significant risk for poor outcome. Risk also appeared higher in patients receiving anti-CD20 treatment and in patients with low titres of anti-Spike IgG, but these differences did not reach statistical significance.
Conclusions: We found that severe COVID-19 infection, associated with a high mortality rate, might develop in a minority of fully vaccinated individuals with multiple co-morbidities. Our patients had a higher rate of co-morbidities and immunosuppression compared with previously reported non-vaccinated hospitalized individuals with COVID-19. Further characterization of this vulnerable population may help to develop guidance to augment their protection, either by continued social distancing, or by additional active or passive vaccinations. Tal Brosh-Nissimov, Clin Microbiol Infect 2021;27:1652 © 2021 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Introduction

The mRNA coronavirus disease 2019 (COVID-19) vaccines, Pfizer/BioNTech’s BNT162b2 and Moderna’s mRNA-1273, were 94%–95% effective in preventing symptomatic COVID-19 in phase III studies, showing similar efficacy in different age groups, including persons older than 75 years, and persons with co-morbidities [1,2]. In Israel, 839 162 cumulative COVID-19 cases (9269/100 000) and 6396 deaths (70/100 000) were reported due to COVID-19 by 20 May 2021 [3]. The Israeli vaccination campaign began on 19 December 2020 and relied exclusively on BNT162b2. By 20 May 2021, more than 5.4 million had received two doses, reaching a coverage of 55% of the population, and about 88% for people older than 50 years [3]. The real-life vaccine effectiveness of BNT162b2 was similar to the efficacy reported in the phase III studies [4,5], and had a significant impact on the local dynamics of COVID-19 [6], with cases declining to 30 new cases/week (0.3/ 100 000) by 20 May 2021. Vaccine effectiveness was shown to be somewhat lower in people older than 70 years and in those with multiple co-morbidities [7]. The vaccine effectiveness for the prevention of hospitalization due to COVID-19 was found to be 87% after the second dose in an early case–control study [4], and 96% in a later comparison of person-time incidence rates from a national registry in Israel [5]. Currently, reports from other countries include a US study showing 94% effectiveness after two doses of any mRNA vaccine [8], and two UK studies that measured an 80%–91% effectiveness for prevention of hospitalization of a single dose of BNT162b2 [9,10].

Data are lacking on the nature of breakthrough infections with COVID-19 vaccines. No data were published on the clinical characteristics and serological correlates of protection of study participants who were hospitalized with COVID-19 after vaccination. Immunocompromised individuals were not included in those pivotal studies. Recent studies measured the immunogenicity of BNT162b2 in immunocompromised patients, showing significantly lower seroconversion rates and lower anti-Spike IgG titres in kidney and liver transplant recipients [11,12] and in patients with chronic lymphocytic leukaemia [13], and lower antibody titres in haemodialysis patients [14,15].

According to the Israeli Ministry of Health registry, by 26 April 2021, 397 fully vaccinated patients were hospitalized in Israel with PCR-proven COVID-19 after their second vaccine dose, 234 of them had severe COVID-19 and 90 died (Dr Eric Haas, Israeli Ministry of Health, personal communication). Using a sample of hospitalized patients, we aimed to characterize vaccinated patients with breakthrough COVID-19 requiring hospitalization and define the main risk factors associated with poor outcomes in this group.

Materials and methods

This was a multicentre cohort study of patients admitted to any of the 17 participating hospitals. Included were patients who received two doses of BNT162b2, had a PCR-confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and were hospitalized in a COVID-19–dedicated unit. As effectiveness of BNT162b2 was studied in patients more than 7 days after the second dose in most clinical studies [2,4,5], either symptomatic onset, the first positive PCR test or the date of admission, whichever happened first, had to be more than 7 days after the second dose. Women in labor admitted to maternity wards were excluded.

Clinical data were retrieved from patients’ records according to a predefined questionnaire and were entered into a de-identified database. SARS-CoV-2 PCR testing was performed using various assays at participating centres, and cycle threshold (Ct) values were reported according to specific gene targets but were analysed together with the lowest Ct value of any gene target chosen to represent a surrogate for the viral load. Anti-Spike antibody tests were performed locally using two available commercial kits: the Liaison SARS-CoV-2-2-S1/S2-IgG (Diasorin, Saluggia, Italy), with a positive cut-off of >15 units/mL; and the Architect AdviseDx SARS-CoV-2-IgG-II (Abbot, Lake Forest, IL, USA), with a positive cut-off of >50 u/mL. Viral genomic sequencing was performed to identify variants of concern on available samples, with results categorized as wild-type, B.1.1.7, B.1.351 or other variants of concern. COVID-19 severity was categorized according to the US National Institutes of Health criteria [16].

The primary outcome was a composite of mechanical ventilation or in-hospital death, referred to as poor outcome. Favourable outcome was defined as patients who were either discharged or were still hospitalized and not ventilated at the end of the study. For statistical analysis, categorical variables were compared between patients with favourable and poor outcomes using χ² and Fisher’s exact tests, and continuous variables were compared using independent samples t test or Mann–Whitney U test. NCSS 2021 v21.0.2 software was used for analyses.

The study was approved by the institutional research ethics boards of each participating hospital. Due to the retrospective design, informed consent was not required.

Results

During the study period (18 January to 20 April 2021) data were reported for 152 patients from 17 general hospitals across Israel. The epidemic curve of new cases is shown in the Supplementary material (Appendix S1, Fig. S1). The clinical data of the patients are shown in Table 1. The median time elapsed from the second dose to admission was 39.5 days (range 8–97 days), and 125/152 (82%) patients were admitted 21 days or more after vaccination, supporting the assumption that they were not infected before vaccination. The median age was 71.1 years (range 22–98 years); most were male (107, 70%) and 38 (25%) were residents of a long-term care facility. Only six patients (4%) had no co-morbidity. Immunosuppression was present in 60 patients (40%). Common causes of
| Indication for admission, n (%) | Entire cohort | Patients with favourable outcome | Patients with poor outcome | p value | Entire cohort | Patients with favourable outcome | Patients with poor outcome | p value |
|--------------------------------|---------------|----------------------------------|---------------------------|---------|---------------|----------------------------------|---------------------------|---------|
| Onset of infection (from second vaccine dose) | | | | | | | | |
| to symptom onset, median (IQR) | 35 (21–48) (n = 125) | 36 (24–50) (n = 114) | 31.5 (20–40–25) (n = 38) | 0.09 | 34 (21–47) (n = 91) | 36 (24.5–51.5) (n = 89) | 31.5 (20–40) | 0.095 |
| to hospital admission, median (IQR) | 39.5 (25.5–52) | 40.5 (28–53) | 35 (22–48) | 0.19 | 40 (28–53) | 41.5 (30–59) | 34 (21–46) | 0.04 |
| Age (years), mean ± SD | 71.1 ± 14.3 | 70 ± 15.2 | 74.7 ± 10.5 | 0.13 | 72 ± 12 | 70.8 ± 12.6 | 74.2 ± 10.5 | 0.19 |
| Male gender, n (%) | 107 (70%) | 80 (70%) | 27 (71%) | 0.92 | 71 (73%) | 47 (76%) | 24 (69%) | 0.44 |
| LTCF residence, n (%) | 38 (25%) | 29 (25%) | 9 (24%) | 0.83 | 23 (24%) | 14 (23%) | 9 (26%) | 0.73 |
| Co-morbidities, n (%) | | | | | | | | |
| Hypertension | 108 (71%) | 78 (68%) | 30 (79%) | 0.22 | 72 (74%) | 44 (71%) | 28 (80%) | 0.33 |
| Diabetes mellitus | 73 (48%) | 56 (49%) | 17 (45%) | 0.64 | 52 (54%) | 35 (56%) | 17 (49%) | 0.45 |
| BMI >30 kg/m² | 47/149 (32%) | 36 (32%) | 11 (30%) | 0.78 | 31 (33%) | 19 (32%) | 12 (34%) | 0.79 |
| Chronic renal failure | 48 (32%) | 38 (34%) | 10 (26%) | 0.34 | 30 (31%) | 21 (34%) | 9 (26%) | 0.40 |
| Ischaemic heart disease | 43 (28%) | 32 (28%) | 11 (29%) | 0.92 | 28 (29%) | 18 (29%) | 10 (29%) | 0.96 |
| Congestive heart failure | 41 (27%) | 28 (25%) | 13 (34%) | 0.25 | 27 (28%) | 14 (23%) | 13 (37%) | 0.12 |
| Chronic lung disease | 37 (24%) | 28 (25%) | 9 (24%) | 0.91 | 22 (23%) | 15 (24%) | 7 (20%) | 0.64 |
| Cancer | 36 (24%) | 25 (22%) | 12 (32%) | 0.23 | 31 (32%) | 21 (34%) | 10 (29%) | 0.59 |
| Dementia | 29 (19%) | 19 (17%) | 10 (26%) | 0.19 | 18 (19%) | 9 (15%) | 9 (26%) | 0.19 |
| Chronic liver disease | 7 (5%) | 6 (5%) | 1 (3%) | 0.68 | 4 (4%) | 3 (5%) | 1 (3%) | 1.0 |
| Immunosuppression, n (%) | | | | | | | | |
| Any type | 60 (40%) | 42 (37%) | 18 (47%) | 0.25 | 50 (52%) | 32 (52%) | 18 (51%) | 0.99 |
| Chemotherapy or anti-metabolite | 27 (18%) | 20 (18%) | 7 (18%) | 0.90 | 23 (24%) | 16 (26%) | 7 (20%) | 0.52 |
| Corticosteroids | 29 (19%) | 21 (18%) | 8 (21%) | 0.72 | 22 (23%) | 14 (23%) | 8 (23%) | 0.96 |
| Anti-CD20 | 10 (7%) | 5 (4%) | 5 (13%) | 0.12 | 10 (10%) | 5 (8%) | 5 (14%) | 0.49 |
| Solid organ transplantation | 16 (11%) | 13 (11%) | 3 (8%) | 0.76 | 13 (13%) | 10 (16%) | 3 (9%) | 0.37 |
| Exposure leading to infection, n (%) | | | | | | | | |
| Unknown | 95 (73%) | 68 (71%) | 27 (77%) | 0.03 | 68 (81%) | 42 (82%) | 26 (79%) | 0.23 |
| Household | 16 (12%) | 14 (15%) | 2 (5.5%) | 0.14 | 9 (11%) | 7 (14%) | 2 (5%) | 0.65 |
| Nosocomial transmission from another patient | 15 (11%) | 13 (13.5%) | 2 (5.5%) | 2 (25%) | 1 (23%) | 1 (3%) |
| Nosocomial transmission from a HCW | 1 (1%) | 0 (0%) | 1 (3%) | 1 (1%) | 0 (0%) | 1 (3%) |
| Other | 4 (3%) | 1 (1%) | 3 (9%) | 4 (5%) | 1 (2%) | 3 (9%) |
| Indication for admission, n (%) | | | | | | | | |
| Severe COVID-19 | 97 (64%) | 63 (55%) | 34 (89%) | 0.00 | 97 (100%) | |
| Non-severe COVID-19 necessitating hospital isolation | 24 (16%) | 23 (20%) | 1 (3%) | 3 (9%) |
| Medical condition unrelated to COVID-19 | 29 (19%) | 26 (23%) | 3 (8%) |
| Late complication of COVID-19 | 2 (1%) | 2 (2%) | 0% |
| First PCR done on admission | | | | | | | | |
| Ct value, mean ± SD | 22.7 ± 5.9 | 23.4 ± 5.8 | 20.5 ± 5.8 | 0.02 | 22.4 ± 5.5 | 23.6 ± 5 | 20.4 ± 5.7 | 0.02 |
| Virus sequencing (n = 32), n/N (%) | | | | | | | | |
| Wild-type | 3 (45%) | 1 (36%) | 2 (29%) | 0.13 | 1 (26%) | 0 | 17 (14%) | 0.15 |
| B.1.1.7 | 40/45 (89%) | 31/36 (91%) | 7 (98%) | 0.03 | 23/26 (88%) | 17/19 (90%) | 6/7 (86%) | 0.77 |
| B.1.351 | 2/35 (2%) | 2/22 (9%) | 0% | 0% | 2/21 (10%) | 2/19 (11%) | 0% |
| Treatment, n (%) | | | | | | | | |
| Oxygen | 97 (66%) | 62 (58%) | 35 (100%) | 0.00 | 89 (86%) |
| HFNC | 46 (32%) | 21 (19%) | 25 (71%) | 0.00 | 46 (52%) |
| Mechanical ventilation | 20 (13%) | 0 (0%) | 20 (53%) | 0.00 | 19 (20%) |
| Insotropic support | 18 (12%) | 0 (0%) | 18 (47%) | 0.00 | 17 (18%) |
| Renal replacement therapy | 16 (11%) | 12 (11%) | 4 (13%) | 1.00 | 10 (8%) |
| Corticosteroids | 101 (66%) | 65 (38%) | 35 (82%) | 0.00 | 92 (95%) |
| Remdesivir | 35 (23%) | 25 (22%) | 10 (26%) | 0.05 | 34 (35%) |
| Convalescent plasma/ hyperimmune serum | 26 (17%) | 17 (15%) | 9 (24%) | 0.22 | 25 (26%) |
| Tocilizumab | 8 (5%) | 3 (3%) | 5 (13%) | 0.02 | 7 (7%) |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HCW, health-care worker; HFNC, high-flow nasal cannula; IQR, interquartile range; LTCF, long-term care facility; SD, standard deviation; NA, not applicable.

Corticosteroids were given for treatment of severe COVID-19, as a part of maintenance treatment for patients on chronic steroid treatment, or to treat immunological complications (e.g. vestibular neuritis).
immunosuppression were chronic corticosteroid treatment, chemotherapy or anti-metabolite treatment, solid organ transplantation and anti-CD20 treatment.

In most cases the source of the patient’s infection was unknown. Sixteen patients (12%) were exposed to an infected household member, 15 (11%) were exposed in health-care settings to another patient (most in a long-term care facility), and 1 (1%) was exposed to an infected health-care worker.

For most patients, the indication for admission was severe COVID-19 (97%; 64%). For 24 (16%) patients the severity of COVID-19 did not necessitate admission, and the patients were admitted to provide means of isolation (e.g. need for dialysis in a COVID-19 patient that could not be arranged outside the hospital; a resident of a long-term care facility with no isolation capacity). In 29 patients (19%) there was a medical problem unrelated to COVID-19 that necessitated admission, and in two (1%) there was a late complication of COVID-19 (thromboembolism), with an incidental in-hospital diagnosis of COVID-19.

Most (93%; 61%) of the patients in this cohort had severe or critical illness. The mortality rate was 22% (34/152). At the end of the study period, 12 patients were still hospitalized and not ventilated, and were categorized as a favourable outcome. Overall, the primary outcome of mechanical ventilation or death occurred in 38 patients (25%). A comparison of baseline risk factors between the primary outcome of mechanical ventilation or death occurred in 38 patients (25%). A comparison of baseline risk factors between the groups did not identify any statistically significant differences. Some non-significant differences of note between favourable and poor outcomes included a higher rate of anti-CD20 treatment (13% versus 4%, p 0.12), cancer (32% versus 22%, p 0.23), congestive heart failure (34% versus 25%, p 0.25) and dementia (26% versus 17%, p 0.19) in the poor outcome group.

Anti-Spike IgG titres after admission were available for 69 patients, using two different kits. In both, the median titre was lower for patients with a poor outcome: Diasorin 1.5 (interquartile range (IQR) 0–8) versus 30.4 (IQR 0–149); Abbott 644 (IQR 0–8276) versus 1623 (IQR 46.5–15 748). In both analyses these differences did not reach statistical significance (p values 0.11 and 0.34, respectively). Serology results are shown in Fig. 1.

Results of PCR testing including analysis of Ct values appear in the Supplementary material (Appendix S1). Sequencing results of SARS-CoV-2 RNA were available for 45 patients, with most (40; 89%) found to be B.1.1.7, three (7%) wild-type and two (4%) B.1.351. The distribution of variants of concern between the groups showed that both had a majority of B.1.1.7, whereas the two B.1.351 variants were from patients with a favourable outcome, although one of the B.1.351 patients required a high-flow nasal cannula.

Six patients had no co-morbidities. Their average age was 60 years (range 42–85 years), and none were long-term care facility residents. Three of them presented with severe COVID-19 but had a good outcome after treatment with oxygen and corticosteroids. Two were admitted for vestibular neuritis, and one for chest pain. Viral sequencing was performed on five of them, with B.1.1.7 detected.

A repeat comparative analysis between the favourable and poor outcome groups including only individuals who were admitted with severe COVID-19, excluding other reasons for hospitalization, yielded similar findings (Table 1).

**Discussion**

This study includes a detailed description of 152 mRNA COVID-19-vaccinated individuals who presented with a significant breakthrough infection leading to hospitalization. All these patients had their disease onset 8 days or more after their second vaccine dose, and in most much later, with a median time to admission exceeding 1 month.

The clinical profile of the patients is typical of other COVID-19 hospitalized patients, being elderly males and having high rates of co-morbidities linked to COVID-19 severity. Nevertheless, co-morbidities were more common in patients with vaccine breakthrough infections compared with large case series on unvaccinated hospitalized patients (see Table 2), including diabetes (48% versus 27.9%–34.7%), hypertension (71% versus 43.5%–62%), heart failure (28% versus 5.8%–12.8%), chronic lung diseases (24% versus 7.4%–16.5%), chronic kidney disease (32% versus 12.7%–22.8%) and cancer (24% versus 4.8%–10.8%) [17–19]. Furthermore, 96% of the patients had at least one co-morbidity. Of six patients with no co-morbidity, only three had severe COVID-19, all with a favourable outcome. The high rate of co-morbidities might be explained by a lower vaccine effectiveness in patients with co-morbidities, by the risk of co-morbidity exacerbation after breakthrough infection, or by both. Immunosuppression in our cohort was common, with 40%
of patients having any type, including corticosteroid therapy, chemotherapy and anti-CD20 treatments, and recipients of organ transplants. This fact is both expected, and in agreement with the lower immunogenicity findings of immunocompromised individuals after vaccination. Immunosuppression was not associated with a worse outcome, except for anti-CD20 treatment, which had a threefold higher odds ratio to be in the poor outcome group (13% with a worse outcome, except for anti-CD20 treatment, which had a

| No. of patients | Fully vaccinated cohort | Non-vaccinated COVID-19 patients cohorts |
|-----------------|------------------------|----------------------------------------|
| No. of hospitals | 152                    | 10 021                                 |
| Country         | Israel                 | 920                                    |
| Time period     | January–April 2021     | February–April 2020                    |
| Inclusion       | All fully vaccinated patients with PCR-confirmed COVID-19 and admitted to hospital | All patients with PCR-confirmed COVID-19 and admitted to hospital |
| Age (years), mean ± SD or median (IQR) | 71 ± 14.3 | 68 ± 17.3 |
| Hypertension    | 71%                    | 55.6%                                  |
| Diabetes mellitus| 48%                    | 27.9%                                  |
| Heart failure   | 32%                    | 19.6%                                  |
| Chronic kidney disease | 27%   | 13.6%                                  |
| BMI >30 kg/m²   | 32%                    | 5.9%                                   |
| Cancer          | 24%                    | NR                                     |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; NR, not reported; SD, standard deviation.

BNT162b2, as most COVID-19 vaccines, is based on the SARS-CoV-2 spike antigen, and therefore its efficacy might be influenced by antigen change. Mutants with significant changes have emerged around the world, with some exhibiting reduced neutralization by sera from convalescent or immunized individuals [23]. These variants of concern, such as B.1.1.7 (20I/501Y.V1), B.1.351 (20H/501Y.V2) and P.1 (20J/501Y.V3), are being monitored in Israel and worldwide. During this study, the dominant circulating strain in Israel was B.1.1.7, with an overwhelming percentage of new infections with this strain beginning in November–December 2020 [17]. The B.1.351 variant of concern exhibited decreased neutralization and a lower vaccine efficacy for the NVX-CoV2373 vaccine in Novavax's phase III study in South Africa [23,24]. A recent case–control study from Israel showed a disproportionate risk for BNT162b2-vaccinated individuals to be infected with B.1.351, with an odds ratio of 8:1 compared with unvaccinated individuals, while B.1.1.7 did not seem to have more breakthrough infections in vaccinees [25]. Despite that, the absolute number of B.1.351 variants in that study was low (nine cases overall). National surveillance in Israel has not identified an emergence of B.1.351 or any other vaccine-escape mutants so far, despite a steady rate of approximately 1% of all samples found to be B.1.351 [26]. In our cohort only a limited number of isolates were sequenced, with 2/45 (4%) found as B.1.351. Although this rate, which is above the reported rate of this variant of concern, may support its vaccine-escape capability, the two patients with B.1.351 were reported from the same hospital within a few days and belonged to a community with a high B.1.351 prevalence in unvaccinated individuals. Therefore, this might represent a local outbreak rather than vaccine breakthrough. Most samples were found to be B.1.1.7, as this became the most common strain in Israel.

This study has some limitations. This cohort of 152 patients from 17 of 26 public general hospitals in Israel represents about half of fully vaccinated patients with COVID-19 requiring hospitalization in the country. As patients admitted to long-term geriatric hospitals were not included, the data are representative of patients admitted to general hospitals. A third of the patients did not have severe COVID-19, and therefore might not truly represent the failure of the vaccine to prevent significant morbidity and mortality, although many had another significant medical indication for admission that might be related to SARS-CoV-2 infection, such as thromboembolism, neurological problems and exacerbation of their underlying co-morbidities. The study was not designed to estimate risk factors for vaccine failure, because patients were identified after hospitalization and were not compared with uninfected controls. Specifically, our findings concerning anti-Spike-antibody titres do not necessarily represent titres achieved by vaccination or before infection and cannot be used to estimate any correlate of protection. The number of patients in the cohort was too small for some of the comparisons between favourable and poor outcomes, specifically for some risk factors that seemed to be more common in
patients with poor outcome such as different co-morbidities, types of immunosuppression and antibody titres. In view of the impact of the successful Israeli vaccination campaign, it is not expected that a significant additional number of vaccinated patients with similar severe breakthrough infection will be available for analysis soon. More data from countries with ongoing COVID-19 might be needed.

Conclusions

A small minority of fully vaccinated BNT162b2 recipients might still develop severe SARS-CoV-2 infection despite the vaccine’s high effectiveness, with need for in-patient care. This representative cohort of hospitalized patients is characterized by older age, high rate of co-morbidities predisposing for progression to severe COVID-19 and a high rate of immunosuppression. The outcome of these patients was similar to that of non-vaccinated hospitalized COVID-19 patients. Additional prospective longitudinal studies are urgently needed to identify predictors for vaccine breakthrough infection and simple correlates of vaccine protection, to enable identification of individuals at higher risk, who would require continued strict precautions, and possibly repeated active vaccination or other prophylactic measures, such as passive vaccination. Furthermore, indirect protection of vulnerable individuals is best achieved by mass vaccination leading to herd immunity.

Author contributions

TBN conceived the study, analysed the data and prepared the manuscript. EO, MC, ME, LN, MS, YM, RC, KH, MW, OZ, BC, RN, HZ, GR and YWW collected patient data and made significant contributions to the manuscript. All authors approved the manuscript for publication.

Transparency declaration

TBN reports a contract with the Israeli Institute of Biological Research for the conduction of a clinical trial on a novel COVID-19 vaccine. GR reports consulting fees from MSD and Gilead, travel fees from MSD, and honoraria from Pfizer, MSD and Astellas, none related to vaccine products. The other authors report no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.06.036.

References

[1] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
[2] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603–15.
[3] Ministry of Health. COVID-19 dashboard 2021. Available at: https://covid19.health.gov.il/COVID-19/general/.
[4] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412–23.
[5] Haas E, Angulo A, McLaughlin J, Anis E, Singer S, FK K, et al. Nationwide vaccination campaign with BNT162b2 in Israel demonstrates high vaccine effectiveness and marked declines in incidence of SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths. Lancet 2021. epub ahead of print.
[6] Rossman H, Shilo S, Meir T, Cofrine M, Shalti UI, Segal E. COVID-19 dynamics after a national immunization program in Israel. Nat Med 2021. https://doi.org/10.1038/s41591-021-01337-2. epub ahead of print.
[7] Barda N, Dagan N, Balicer R. Correspondence: BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination campaign. N Engl J Med 2021. https://doi.org/10.1056/NEJMct2104281. epub ahead of print.
[8] Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell C, Steinbugl J, et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 among hospitalized aged adults ≥ 65 years—United States, January–March 2021. MMWR Morb Mortal Wkly Rep 2021;70. https://doi.org/10.15585/mmwrr.mm7018e1.
[9] Vasilieou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021;397:1646–57.
[10] Bernal J, Andrews N, Gower C, Stowe J, Roberson C, Tessier E, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenosine vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. MedRxiv 2021. https://doi.org/10.1101/2021.03.01.21252652.
[11] Gruppler A, Rabinowitch L, Schwartz D, Schwartz F, Ben-Yehoyada M, Shashar M, et al. Reduced humoral response to mRNA-SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant 2021. https://doi.org/10.1111/ajt.16615. epub ahead of print.
[12] Rezapourchi L, Gruppler A, Baruch R, Ben-Yehoyada M, Halperin T, Tucker D, et al. Low immunogenicity to SARS-COV-2 vaccination among liver transplant recipients. J Hepatol 2021. https://doi.org/10.1016/j.jhep.2020.04.020. epub ahead of print.
[13] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021. https://doi.org/10.1182/blood.2021011568. epub ahead of print.
[14] Agur T, Ben-Dor N, Goldman S, Lichtenberg D, Herman-Edelstein M, Yahav D, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—a prospective cohort study. Nephrol Dial Transplant 2021. https://doi.org/10.1093/ndt/gfab15. epub ahead of print.
[15] Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbara A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol 2021;16. https://doi.org/10.2215/ jcasn.035012. CJN.0350121.
[16] NIH. COVID-19 treatment guidelines: clinical spectrum of SARS-CoV-2 Infection 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. [Accessed 30 April 2021].
[17] Karagiannidou C, Mosteri C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med 2020;8:853–63.
[18] Myers LC, Parodi SM, Escolar G, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA 2020;323:2195–8.
[19] Petrelli CM, Jones SA, Yang J, Rajagopal H, O’Dellon L, Chrenyuk V, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
[20] Petrelli CM, Jones SA, Yang J, Rajagopal H, O’Dellon L, Chrenyuk V, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
[21] Diasorin. LIAISON® SARS-CoV-2 S1/S2 IgG Factsheet. n.d. Available at: https://www.diasorin.com/sites/default/files/allegati/liaison_sars_cov_2_s1s2_igg_brochure.pdf.pdf.
[22] Ng DL, Goldgof GM, Shy BR, Levine AG, Balcerek J, Bapat SP, et al. SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood from the San Francisco Bay Area. MedRxiv 2020. https://doi.org/10.1101/2020.05.19.20107482.
[23] Donnell L, Chernyak Y, et al. Increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 phase-3. [Accessed 27 April 2021].
[24] Novavax. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK Phase 3 trial, 3; 2021. Available at: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3. [Accessed 27 April 2021].
[25] Kurtin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. MedRxiv 2021. https://doi.org/10.1101/2021.04.06.21254882. 2021.04.06.21254882.
[26] Ministry of Health. South African variant found in about 1% of all positive tests 2021. Available at: https://www.gov.il/en/departments/news/22022021-01. [Accessed 27 April 2021].