Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

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

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ABSTRACT

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.

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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**

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 symptom 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-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 χ^2 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

Table 1
Demographic, clinical and laboratory characteristics of hospitalized patients with COVID-19 after BNT162b2 vaccination

	Entire cohort				Patients admitted due to severe disease			
	All patients ($n = 152$)	Patients with favourable outcome ($n = 114$)	Patients with poor outcome ($n = 38$)	p value	All patients ($n = 93$)	Patients with favourable outcome ($n = 62$)	Patients with poor outcome ($n = 35$)	p value
Onset of infection (from second vaccine dose)								
to symptom onset, median (IQR)	35 (21–48) ($n = 125$)	36 (24–50) ($n = 91$)	31.5 (20–40.25) ($n = 34$)	0.09	34 (21–47) ($n = 89$)	36 (24.5–51.5)	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/m^2	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%)	0.98
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 (14.5%)	2 (5.5%)		9 (11%)	7 (14%)	2 (6%)	
Nosocomial transmission from another patient	15 (11%)	13 (13.5%)	2 (5.5%)		2 (2%)	1 (2%)	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%)		NA			
Medical condition unrelated to COVID-19	29 (19%)	26 (23%)	3 (8%)					
Late complication of COVID-19	2 (1%)	2 (2%)	0%					
Anti-Spike IgG testing								
Liaison, median (IQR)	9.7 (0–128.5) ($n = 25$)	30.4 (0–149) ($n = 21$)	1.5 (0–8) ($n = 4$)	0.11	9.7 (0–118)	30.4 (2.5–230)	0 (0–7.3)	0.06
* cutoff >15								
Abbot, median (IQR)	947.5 (29–13 129) ($n = 44$)	1623 (46.5–15 748) ($n = 32$)	644 (0–8276) ($n = 12$)	0.34	526 (1–15 748)	458 (14–39 485)	595 (0–3861)	0.38
* cutoff >50								
Positive serology (any assay), *n*/*N* (%)	44/69 (64%)	36/53 (68%)	8/16 (50%)	0.19	28/48 (58%)	21/33 (63%)	7/15 (47%)	0.27
Time from symptom onset to serological test (days), median (IQR)	7 (3-10)	6 (3-10.5)	8 (4.2-9)	0.43	8 (4-10.5)	8 (4-11)	8 (4-9)	0.77
First PCR done on admission								
Ct value, mean ± SD	22.7 ± 5.9 N = 103	23.4 ± 5.8 N = 76	20.5 ± 5.8 N = 27	0.02	22.4 ± 5.5 N = 66	23.6 ± 5 N = 42	20.4 ± 5.7 N = 24	0.02
Virus sequencing ($n = 32$), *n*/*N* (%)								
Wild-type	3/45 (7%)	1/36 (3%)	2/9 (22%)	0.13	1/26 (4%)	0 (0%)	1/7 (14%)	0.15
B.1.1.7	40/45 (89%)	33/36 (91%)	7/9 (78%)		23/26 (88%)	17/19 (89%)	6/7 (86%)	
B.1.351	2/45 (4%)	2/36 (6%)	0 (0%)		2/26 (8%)	2/19 (11%)	0 (0%)	
Treatment, *n* (%)								
Oxygen	97 (66%)	62 (56%)	35 (100%)	0.00	89 (96%)			
HFNC	46 (32%)	21 (19%)	25 (71%)	0.00	46 (52%)			
Mechanical ventilation	20 (13%)	0 (0%)	20 (53%)	0.00	19 (20%)			
Inotropic support	18 (12%)	0 (0%)	18 (47%)	0.00	17 (18%)			
Renal replacement therapy	16 (11%)	12 (11%)	4 (11%)	1.00	8 (8%)			
Corticosteroids[a]	101 (66%)	65 (58%)	35 (92%)	0.00	92 (95%)			
Remdesivir	35 (23%)	25 (22%)	10 (26%)	0.58	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.

[a] 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 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 ware 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%

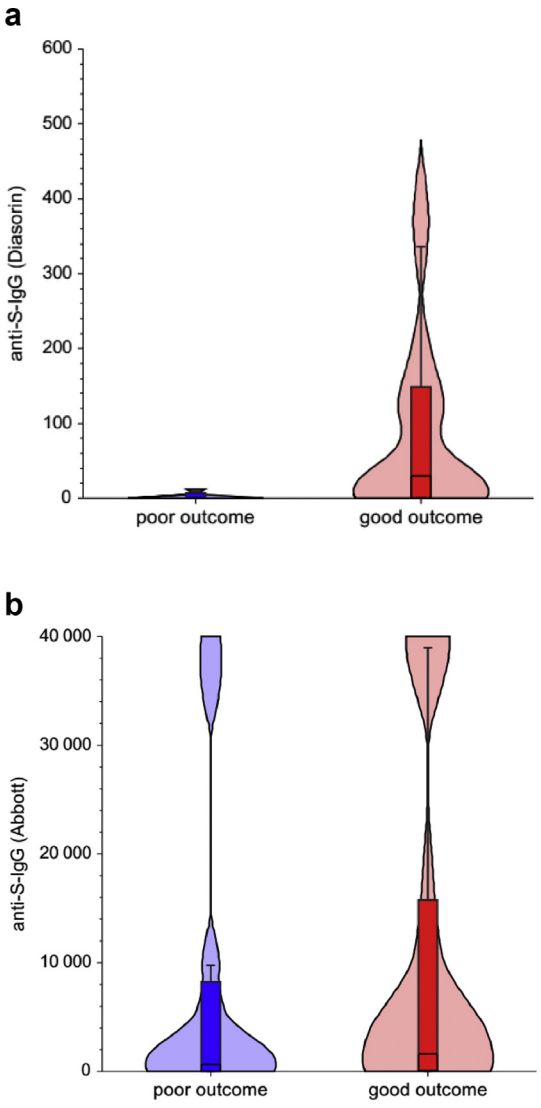

FIG. 1. Violin charts of results of anti-Spike-IgG testing for patients with favourable (good) and poor outcomes: (a) Diasorin's Liaison SARS-CoV-2 S1/S2 IgG (cut-off for positivity of >15 u/mL). One result was omitted from the chart as an outlier, of a patient with a favourable outcome, whose antibody titre was estimated to be 2650 u/mL using dilutions, as the upper limit of reporting for the assay is 400 u/mL. (b) Abbott's Architect AdviseDx SARS-CoV-2 IgG II, (cut-off for positivity of 50 u/mL). For both charts the horizontal line and box represent the median and the interquartile range, respectively. The width of the curved shape represents the proportion of patients.

Table 2
Comparison of the clinical characteristics of fully vaccinated and non-vaccinated hospitalized COVID-19 patients cohorts

	Fully vaccinated cohort	Non-vaccinated COVID-19 patients cohorts		
		Karagiannidis et al. [17]	Myers et al. [18]	Petrilli et al. [19]
No. of patients	152	10 021	377	2741
No. of hospitals	17	920	21	4
Time period	January–April 2021	February–April 2020	March 2020	March–April 2020
Country	Israel	Germany	California, USA	New York, USA
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	All 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	61 (50–73)	63 (51–74)
Hypertension	71%	55.6%	43.5	62%
Diabetes mellitus	48%	27.9%	31.3	34.7%
Heart failure	32%	19.6%	5.8	12.8%
Chronic lung disease	24%	13.6%	7.4	16.5%
Chronic kidney disease	27%	22.8%	12.7	21.2%
BMI >30 kg/m^2	32%	5.9%	NR	39.5%
Cancer	24%	NR	4.8	10.8%

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

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% versus 4%, p 0.12), but the small number of patients could preclude significant comparison of subgroups.

The mortality rate in the cohort was similar to that in unvaccinated hospitalized COVID-19 patients [20]. We could not find a statistically significant risk factor for a poor outcome, defined as mechanical ventilation or in-hospital death, except for a higher upper respiratory viral load, as represented by a lower Ct value. As our cohort included patients who were admitted for different reasons, an analysis including only patients whose reason for admission was severe COVID-19 was also performed, with similar findings.

Anti-Spike IgG assays were developed and validated for the diagnosis of SARS-CoV-2 infection. They can be used to measure the serological response to vaccination, although no correlate of protection has yet been identified. The two assays used in our cohort have a good correlation with neutralizing antibody titres [21,22]. Results of anti-Spike IgG were available for 69 patients, with two assays. These results do not represent titres achieved post-vaccination, as they were measured after SARS-CoV-2 infection, with a median of 7 days after symptom onset. Therefore, they might represent the host's ability for an early serological response to infection. Overall, results were variable, with titres ranging from below threshold to high titres beyond the assay's upper reporting limit. Patients with poor outcomes had a lower median titre in both assays, but these differences did not reach statistical significance.

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.

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