EPIDEMIOLOGICAL SCIENCE

BNT162b2 mRNA COVID-19 vaccine and booster in patients with autoimmune rheumatic diseases: a national cohort study

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ABSTRACT

Introduction Emerging evidence supports the immunogenic response to mRNA COVID-19 vaccine in patients with autoimmune rheumatic diseases (ARD). However, large-scale data about the association between vaccination, and COVID-19 outcomes in patients with ARD is limited.

Methods We used data from Clalit Health Services, which covers more than half of the population in Israel. Patients with ARD older than 18 were included between 20 December 2021 and 30 September 2021, when the BNT162b2 mRNA COVID-19 vaccine, and later a third booster dose, were available. The primary outcome was a documented positive SARS-CoV-2 PCR test. We used a Cox regression models with vaccination status as time-dependent covariate and calculated the HR for the study outcome.

Results We included 127 928 patients with ARD, of whom, by the end of the study follow-up, there were 27 350 (21.3%) unvaccinated patients, 31 407 (24.5%) vaccinated patients and 69 171 (54.1%) patients who also received a third booster-dose. We identified 8470 (6.6%) patients with a positive SARS-CoV-2 PCR test during the study period. The HR for SARS-CoV-2 infection among the vaccination group was 0.143 (0.095 to 0.214, p<0.001), and among the booster group was 0.017 (0.009 to 0.035, p<0.001). Similar results were found regardless of the type of ARD group or antirheumatic therapy.

Conclusion Our results indicate that both the BNT162b2 mRNA COVID-19 vaccine and the booster are associated with better COVID-19 outcomes in patients with ARD.

Key messages

What is already known about this subject?

- COVID-19 vaccines were found to be immunogenic in most patients with autoimmune rheumatic diseases (ARD), with a comparable rate of adverse reactions. The effect of COVID-19 vaccination and booster in a large-scale setting is unknown.

What does this study add?

- This is the largest cohort so far demonstrating association between BNT162b2 mRNA COVID-19 vaccine and better COVID-19-related outcomes among patients with ARD.
- A third booster dose was associated with less SARS-CoV-2 infection among patients with ARD.
- Vaccination and booster were associated with better COVID-19-related outcomes regardless of the type of ARD diagnosis and the type of antirheumatic therapy.

How might this impact on clinical practice or future developments?

- Rheumatologists should encourage their patients to receive the BNT162b2 mRNA COVID-19 vaccine and booster.

BACKGROUND

The COVID-19 pandemic has devastating global implications. Patients with autoimmune rheumatic diseases (ARD) have an increased risk for hospitalisation and mortality compared with the general population, although it is unclear whether they are more susceptible to be infected with SARS-CoV-2.[1–3] In 2021, several COVID-19 vaccines have been approved and became available, though the majority of clinical trials have excluded patients with ARD and relevant treatments.[4]

Previous studies evaluated the influence of ARD and disease-modifying antirheumatic drugs (DMARDs) on vaccinations immunogenicity, as a surrogate for their clinical efficacy. COVID-19 vaccines were found to be immunogenic in the majority of patients with ARD, with a comparable rate of adverse reactions.[5 6] In addition, a flare in the baseline ARD was observed only in a minority of the patients following COVID-19 vaccination.[7] On the other hand, specific DMARDs (eg, rituximab, methotrexate and glucocorticoids) were found to impair vaccine immunogenicity.[8] The diminishing of the humoral response was observed as soon as 6 weeks after the use of the COVID-19 vaccine among patients with ARD.[9] Forty per cent of patients with BNT162b2 vaccine breakthrough occurred among immunocompromised.[10] Hence, it has been suggested that a booster dose of COVID-19 vaccine in ARD may increase the humoral response, and subsequently vaccine efficacy.[11]

This study aims to investigate the association between BNT162b2 mRNA COVID-19 vaccine and booster and related outcomes in a real-world cohort of patients with ARD. We wish to analyse the influence of this vaccine on patients with ARD risk to develop SARS-CoV-2 infection, hospitalisation and mortality.

METHODS

Study population

Clalit Health Services (CHS) is the largest Health Provider Organisation in Israel, with a membership of 4.5 million, about 52% of the country population.[12] CHS operates 14 medical centres. CHS has a centralised comprehensive computerised database of electronic healthcare records that receives continuous real-time input from the medical, laboratory, pharmaceutical, vaccination and hospitalisation operating systems, and can be accessed down to the individual patient. The dataset, based on reports from both hospitals and outpatients clinics, has been shown previously to have high validity and reliability.[13 14]

In this retrospective study, we included all CHS members diagnosed with ARD. We identified patients with ARD based on the International Classification of Disease, Ninth Revision (ICD-9) and similar ICD-9 based codes given before the study period of Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, psoriatic arthritis, ankylosing spondylitis, inflammatory autoimmune myopathies and systemic vasculitis (online supplemental table S1). Additional conditions such as antiphospholipids syndrome, Sjogren's and familial Mediterranean fever were also included.

Data extraction

We included all CHS patients with ARD older than 18 years, from 20 December 2020 to 30 September 2021. Patients with reported positive COVID-19 PCR before 20 December 2020 were excluded. During this period the BNT162b2 mRNA COVID-19 vaccine was available to the entire population in Israel of age 16 or older. A third BNT162b2 mRNA COVID-19 vaccine ('booster') was available from 29 July 2021, to persons older than 60 years and to special populations (such as patients with ARD), who received the second BNT162b2 mRNA COVID-19 vaccines more than 6 months ago. The booster became available to the entire population of Israel during August 2021. The dataset was extracted per patient per week. Each patient was considered as 'unvaccinated' if fulfilled any of these conditions: (1) Not receiving any BNT162b2 mRNA COVID-19 vaccine; (2) Receiving only one vaccine dose without prior infection; (3) Being infected after 20 December 2020, and receiving only one vaccine dose after this infection (as Israeli Ministry of Health allowed). Each patient was considered 'vaccinated' a week after the second BNT162b2 mRNA COVID-19 vaccine, and as a 'booster' a week after the third BNT162b2 mRNA COVID-19 vaccine. Patients who were infected after two vaccine doses, and also got the third vaccine dose were also defined as 'booster'. We extracted baseline demographic, medical and pharmaceutical variables. We obtained utilisation of glucocorticoids, conventional synthetic, biological and targeted synthetic DMARDs based on CHS prescription system if the regimen was issued during the 3 months before the study period (except for 6 months for rituximab).

The primary outcome was documented SARS-CoV-2 infection based on a positive PCR test. If additional SARS-CoV-2 infection or a positive PCR test were identified, we considered only the first event as a 'case'. Patients with ARD with a positive SARS-CoV-2 PCR test before 20 December were excluded from the analysis. Secondary outcomes were hospitalisation due to COVID-19, COVID-19-related death (identified after SARS-CoV-2 infection hospitalisation) and all-cause mortality. We analysed all-cause mortality as a sensitivity analysis to minimise the possibility of classification bias regarding the use of COVID-19-related death. Data were extracted from CHS using the Clalit Research Data sharing platform powered by MDClone (https://www.mdclone.com).

Statistical analysis

Descriptive statistics are reported as mean and SD, median and IQR, or number and percentage. To estimate the association of patient vaccination status with study outcomes, we used survival curves and Cox regression models with vaccination status as time-dependent covariate and calculated the HR. The incidence of SARS-CoV-2 infection and subsequent complications change across time and was strongly associated with receiving BNT162b2 mRNA COVID-19 Vaccine. Hence, we used a Cox regression models with vaccination status as time-dependent covariate which includes time-adjusted variables. The model included the vaccination status of each individual, which was ascertained on a weekly basis that could take one of the three scenarios: unvaccinated, partially vaccinated (for the period between receiving the first dose and a week after the second dose), and fully vaccinated. Thus, a person could theoretically contribute to several study groups, by being unvaccinated at the beginning, vaccinated later and covered by booster vaccination 6 months later. The model would reflect the effect of vaccination status averaged over the subjects with that certain status at each time point separately. We adjusted to Propensity Score (PS) to address a possible imbalance between subjects receiving vaccination/booster and those who did not.[15] For each person, we calculated the probability to receive vaccination, booster, or not using a multivariable multinomial logistic regression model. The PS model was adjusted for age, sex, ethnicity, type of ARD, smoking, hypertension, dementia, charlson index and current use of prednisone. In addition, we entered each set of covariates (demographic, medical history, pharmaceutical, etc as shown in table 1) meeting the proportionality assumption of the Cox model as a separate block of variables into the model. The final model was selected primarily based on their clinical relevance of the covariates and the model's discriminatory ability. We also considered the statistical significance of the coefficients as a secondary criterion in selecting the final list of covariates. The survival curves were adjusted for the same variables that were used in the Cox model of the primary analysis, except for the changing exposure over time .In addition, we created survival curves using vaccination status as a stratum, instead of separate models, to balance baseline covariates between vaccination groups (see online supplemental materials). We analysed the primary outcome for the entire cohort and then separately for each ARD diagnosis and relevant medical treatment. We conducted a sensitivity analysis only for the time period relevant to the booster (July–September 2021). Due to a short follow-up time, the sensitivity analysis evaluated only new cases of PCR and COVID-19 admissions. Finally, to handle the immunisation status changing over time, we conducted a sensitivity analysis by plotting Cox-adjusted survival curves for the entire follow-up time (December 2020–September 2021) and for the time relevant to the booster (July–September 2021) for new cases of the primary outcome (positive PCR). Data analysis was performed with SPSS V.25.0, IBM.

RESULTS

Baseline characteristics

The study cohort included 127 928 patients with ARD (4848 patients with a positive SARS-CoV-2 PCR test before 20 December were excluded from the final analysis). Overall, there were 27 350 unvaccinated patients, 31 407 vaccinated patients

Table 1 Demographic and clinical characteristics of vaccinated, unvaccinated and booster persons at baseline

	Unvaccinated (n=27 350)	Vaccinated (n=31 407)	Vaccinated and booster (n=69 171)	P value
Females (n,%)	18 163 (66.4)	20 868 (66.4)	45 435 (65.7)	0.020
Age (mean, ±SD)	55.3 (19.0)	51.6 (18.5)	65.1 (15.7)	<0.001
Jewish (n,%)	12 137 (75.0)	16 133 (71.4)	46 739 (92.3)	<0.001
Smoking (n,%)—never	20 921 (76.5)	21 214 (67.5)	45 971 (66.5)	<0.001
Past	2772 (10.1)	4542 (14.5)	14 750 (21.3)	
Current	3657 (13.4)	5651 (18.0)	8450 (12.2)	
ARD diagnosis (n,%)				
Rheumatoid arthritis	7615 (27.9)	7467 (23.8)	16 491 (23.8)	<0.001
Systemic lupus erythematosus	1063 (3.9)	695 (2.2)	1050 (1.5)	<0.001
Spondyloarthritis	6709 (24.5)	8685 (27.7)	15 868 (22.9)	<0.001
Scleroderma	876 (3.2)	1086 (3.5)	2181 (3.2)	0.04
Myositis	423 (1.5)	528 (1.7)	929 (1.3)	<0.001
Systemic vasculitis	5526 (20.2)	6384 (20.3)	17 357 (25.1)	<0.001
Other	5128 (18.8)	6562 (20.9)	15 295 (22.1)	<0.001
Medical history (n,%)				
Heart failure	1792 (6.6)	1815 (5.8)	5132 (7.4)	<0.001
Myocardial infarction	1329 (4.9)	1378 (4.4)	4703 (6.8)	<0.001
Hypertension	6330 (23.1)	6574 (20.9)	23 182 (33.5)	<0.001
Diabetes	4038 (14.8)	4522 (14.4)	14 646 (21.2)	<0.001
Obesity (BMI >30 kg/m^2)	7764 (28.4)	11 208 (35.7)	27 717 (40.1)	<0.001
COPD	1234 (4.5)	1394 (4.4)	4484 (6.5)	<0.001
Asthma	3298 (12.1)	4751 (15.1)	10 919 (15.8)	<0.001
Other lung disease	901 (3.3)	1152 (3.7)	3360 (4.9)	<0.001
CVA or TIA	3198 (11.7)	3777 (12.0)	12 480 (18.0)	<0.001
Malignancy	2070 (7.6)	2663 (8.5)	10 040 (14.5)	<0.001
Chronic kidney disease	1270 (4.6)	1229 (3.9)	3807 (5.5)	<0.001
Charlson comorbidity Index (median, IQR)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	4.0 (3.0–6.0)	<0.001
Charlson Comorbidity Index (mean, ±SD)	3.4 (2.8)	3.2 (2.8)	4.6 (2.8)	<0.001
Medical therapy (n,%)				
Prednisone <5 mg/day	108 (0.4)	236 (0.8)	1055 (1.5)	<0.001
5–20 mg/day	1224 (4.5)	2208 (7.0)	4976 (7.2)	
>20 mg/day	816 (3.0)	1729 (5.5)	2885 (4.2)	
Methotrexate	218 (0.8)	1899 (6.0)	4674 (6.8)	<0.001
csDMARDs	1102 (4.0)	3329 (10.6)	7384 (10.7)	<0.001
Colchicine	157 (0.6)	1517 (4.8)	2810 (4.1)	<0.001
Azathioprine	285 (1.0)	698 (2.2)	997 (1.4)	<0.001
Mycophenolate mofetil	104 (0.4	159 (0.5)	298 (0.4)	0.063
TNF alpha blockers	775 (2.8)	2140 (6.8)	3529 (5.1)	<0.001
IL-6 inhibitors	99 (0.4)	219 (0.7)	636 (0.9)	<0.001
IL-17 inhibitors	80 (0.3)	196 (0.6)	454 (0.7)	<0.001
IL 12/23 inhibitors	85 (0.3)	285 (0.9)	448 (0.6)	<0.001
Abatacept	21 (0.1)	62 (0.2)	156 (0.2)	<0.001
Rituximab	117 (0.4)	273 (0.9)	431 (0.6)	<0.001
JAK	127 (0.5)	316 (1.0)	676 (1.0)	<0.001
Calcineurin inhibitors	93 (0.3)	186 (0.6)	556 (0.8)	<0.001
Outcomes*				
Positive SARS-CoV-2 PCR	4202 (15.4)	3498 (11.1)	770 (1.1)	<0.001
COVID-19 hospitalisations	277 (1.0)	138 (0.4)	45 (0.1)	<0.001
COVID-19-related mortality	204 (0.7)	32 (0.1)	0 (0.0)	<0.001
All-cause mortality	1026 (3.8)	608 (1.9)	0 (0.0)	<0.001

*Outcome masseurs collected at end of follow-up.

ARD, autoimmune rheumatic diseases; BMI, body mass index; COPD, chronic obstructive pulmonary disease; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CVA, cerebro vascular accident; IL, interleukin; JAK, Janus kinase; TIA, transient ischaemic attack.

and 69 171 patients who received also a third booster dose. We identified 8470 (6.6%) patients with a positive SARS-CoV-2 PCR test during the study period, of whom 4202 (15.4%) were unvaccinated, 3498 (11.1%) were vaccinated and 770 (1.1%) were vaccinated and also received booster. The median follow-up time after receiving vaccination was 33.0 weeks (IQR 30.0–35.0) for the vaccination group and 5.0 weeks (IQR 2.0–7.0) for the booster group. The unvaccinated group had a

median follow-up of 45.0 weeks (IQR 45.0–45.0), during the overall study period

Table 1 presents the baseline characteristics of the patients according to vaccination groups. Compared with the unvaccinated and the vaccinated groups, the booster group was older (55.3 and 51.6 vs 65.1 respectively, p<0.001), with a higher rate of Jewish (75.0% and 71.4% vs 92.3%, respectively, p<0.001), and with a lower rate of current smokers (13.4% and 18.0% vs 12.2%, respectively, p<0.001). While RA and SLE were more common among the unvaccinated group, SPA was more common in the vaccinated group and systemic vasculitis was more common in the booster group (p<0.001 for all). The booster group had a significantly higher rate of almost every comorbidity and subsequently higher median Charlson's Comorbidity Index score compared with the unvaccinated and the vaccinated groups (4.0 vs 2.0 and 2.0 respectively, p<0.001). In addition, the unvaccinated group showed a significantly lower usage rate of almost every relevant medical therapy relevant to patients with ARD.

SARS-CoV-2 status

The baseline characteristics of patients according to their SARS-CoV-2 PCR status are presented in table 2. The positive SARS-CoV-2 patients were younger (54.2 vs 60.1, p<0.001), non-Jewish (77.7% vs 84.3%, p<0.001) while less current smokers (14.0% vs 11.7%, p<0.001). SPA was more common among the positive SARS-CoV-2 patients (26.0% vs 24.3%, p<0.001) and systemic vasculitis was less common (21.3% vs 23.0%, p<0.001). Obesity and asthma were the only comorbidities more common among the positive SARS-CoV-2 patients (40.2% vs 36.2%, p<0.001 and 15.8% vs 14.8%, p=0.01).

The positive SARS-CoV-2 patients showed higher usage rate of high dose prednisone (eg, for >20 mg/day 5.4% vs 4.2%, p<0.001 for the entire comparison), TNF alpha inhibitors (6.9% vs 4.9%, p=0.001), rituximab (1% vs 0.6%, p<0.001) and

Calcineurin inhibitors (0.7% vs 0.6%). The negative SARS-CoV-2 patients showed higher usage rate of Methotrexate (5.3% vs 4.9%, p=0.12), low dose prednisone (less than 5 mg/day, 1.1% vs 0.8%) and conventional synthetic DMARDs (9.2% vs9.8%, p=0.04).

Time-dependent analysis

Survival curves of SARS-CoV-2 infection, COVID-19 hospitalisation, COVID-19-related mortality and all-cause mortality are shown in figure 1. Patients who received the booster dose showed the best outcomes. Compared with the unvaccinated group, The HR for SARS-CoV-2 infection among the vaccinated group was 0.652 (95% CI 0.623 to 0.682) and among the booster groups was 0.064 (95% CI 0.060 to 0.070) (p<0.001). The HR for COVID-19 hospitalisation among vaccinated group was 0.456 (95% CI 0.371 to 0.560) and among the booster group was 0.050 (95% CI 0.036 to 0.069) (p<0.001). The HR for COVID-19-related mortality and all-cause mortality among the vaccinated group was 0.142 (95% CI 0.097 to 0.206, p<0.001) and 0.523 (95% CI 0.473 to 0.579, p<0.001), respectively. There were no COVID-19-related mortality and all-cause mortality among the booster group (table 1).

Cox regression models with vaccination status as time-dependent covariate for the entire cohort, per ARD subgroups and antirheumatic treatments, are presented in table 3. The HR for SARS-CoV-2 infection is presented compared with the unvaccinated group risk (defined as '1'). The HR for SARS-CoV-2 infection among the vaccination compared with unvaccinated group was 0.143 (95% CI 0.095 to 0.214, p<0.001), and among the booster compared with unvaccinated group was 0.017 (95% CI 0.009 to 0.035, p<0.001). Similar results were found regardless of the type of ARD group or therapy.

Table 2 Baseline demographic and clinical characteristics of positive and negative SARS-CoV-2 PCR*

	Negative PCR (n=119 458)	Positive PCR (n=8470)	P value
Females (n,%)	78 881 (66.0)	5585 (65.9)	0.85
Age (mean,±SD)	60.1 (18.1)	54.2 (18.1)	<0.001
Jewish (n, %)	70 524 (84.3)	4485 (77.7)	<0.001
Smoking (n, %)—never	82 039 (68.7)	6067 (71.6)	<0.001
Past	20 655 (17.3)	1409 (16.6)	
Current	16 764 (14.0)	994 (11.7)	
ARD diagnosis (n,%)			
Rheumatoid arthritis	29 571 (24.8)	2002 (23.6)	0.02
Systemic lupus erythematosus	2622 (2.2)	186 (2.2)	1.00
Spondyloarthritis	29 056 (24.3)	2206 (26.0)	<0.001
Scleroderma	3872 (3.2)	271 (3.2)	0.87
Myositis	1754 (1.5)	126 (1.5)	0.89
Systemic vasculitis	27 462 (23.0)	1805 (21.3)	<0.001
Other	25 111 (21.0)	1874 (22.1)	0.02
Medical history (n,%)			
Heart failure	8185 (6.9)	554 (6.5)	0.28
Myocardial infarction	7012 (5.9)	398 (4.7)	<0.001
Hypertension	33 985 (28.4)	2101 (24.8)	<0.001
Diabetes	21 652 (18.1)	1554 (18.3)	0.61
Obesity (BMI >30)	43 283 (36.2)	3406 (40.2)	<0.001
COPD	6720 (5.6)	392 (4.6)	<0.001
Asthma	17 626 (14.8)	1342 (15.8)	0.01
Other lung disease	5073 (4.2)	340 (4.0)	0.31
CVA or TIA	18 293 (15.3)	1162 (13.7)	<0.001
Malignancy	13 985 (11.7)	788 (9.3)	<0.001
Chronic kidney disease	5884 (4.9)	422 (5.0)	0.81
Charlson Comorbidity Index (median, IQR)	3.0 (1.0–6.0)	3.0 (1.0–5.0)	<0.001
Charlson comorbidity Index (mean, ±SD)	3.5 (2.8)	3.6 (2.8)	<0.001
Medical therapy (n,%)			
Prednisone <5 mg/day	1328 (1.1)	71 (0.8)	<0.001
5–20 mg/day	7690 (6.4)	718 (8.5)	
>20 mg/day	4974 (4.2)	456 (5.4)	
Methotrexate	6372 (5.3)	419 (4.9)	0.12
csDMARDs	10 981 (9.2)	834 (9.8)	0.04
Colchicine	4158 (3.5)	326 (3.8)	0.07
Azathioprine	1806 (1.5)	174 (2.1)	<0.001
Mycophenolate mofetil	507 (0.4)	54 (0.6)	0.01
TNF alpha blockers	5863 (4.9)	581 (6.9)	<0.001
IL-6 inhibitors	888 (0.7)	66 (0.8)	0.71
IL-17 inhibitors	684 (0.6)	46 (0.5)	0.81
IL 12/23 inhibitors	748 (0.6)	70 (0.8)	0.03
Abatacept	225 (0.2)	14 (0.2)	0.78
Rituximab	733 (0.6)	88 (1.0)	<0.001
JAK inhibitors	1040 (0.9)	79 (0.9)	0.55
Calcineurin inhibitors	772 (0.6)	63 (0.7)	0.28

*PCR positivity was collected at the end of follow-up.
ARD, autoimmune rheumatic diseases; BMI, body mass index; COPD, chronic obstructive pulmonary disease; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CVA, cerebro vascular accident; IL, interleukin; JAK, Janus kinase; TIA, transient ischaemic attack.

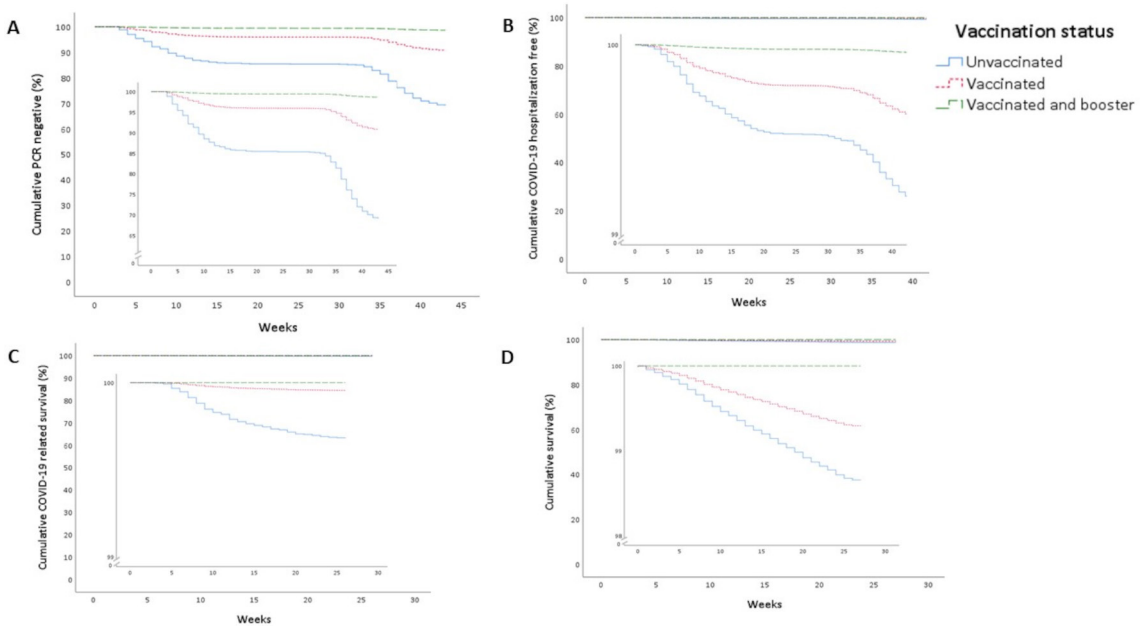

Figure 1 Multivariate adjusted survival curves of study outcomes from the initiation of the BNT162b2 mRNA Covid-19 vaccine: (A) Positive COVID-19 test. (B) COVID-19 related hospitalisation. (C) COVID-19 related mortality. (D) All-cause mortality. X axis – Week 0 first day is 27th of December 2020.

Figure 1 in the online supplemental material shows the results of a sensitivity analysis addressing the problem of immunisation status changing over time. Two survival plots: the first is for unvaccinated and vaccinated patients (regardless of booster) during the entire follow-up period (December 2020 to September 2021) and the second is for the three vaccinated groups following 31 July. The follow-up is also shifted by 1 week after the first vaccination took place. Both plots were

Table 3 Time-dependent Cox multivariate regression for COVID-19 positive PCR risk, in subgroups of comorbidity at baseline

	Unvaccinated (reference)	Vaccinated HR (95% CI)	Booster HR (95% CI)
All-cohort*	1.00	0.143 (0.095 to 0.214)	0.017 (0.009 to 0.035)
Rheumatoid arthritis*	1.00	0.133 (0.059 to 0.297)	0.024 (0.007 to 0.086)
Systemic lupus erythematosus*†	1.00	0.089 (0.037 to 0.216)	0.007 (0.002 to 0.020)
Spondyloarthritis	1.00	0.051 (0.015 to 0.170)	0.003 (0.001 to 0.020)
Scleroderma*	1.00	0.340 (0.070 to 1.662)	0.028 (0.001 to 0.552)
Myositis*	1.00	0.014 (0.001 to 1.245)	0.001 (0.001 to 1.469)
Systemic vasculitis*	1.00	0.185 (0.091 to 0.376)	0.023 (0.006 to 0.094)
Other*	1.00	0.040 (0.011 to 0.150)	0.004 (0.001 to 0.025)
Prednisone*<5 mg/day	1.00	0.143 (0.033 to 0.629)	0.005 (0.001 to 0.145)
5–20 mg/day	1.00	0.149 (0.084 to 0.266)	0.015 (0.006 to 0.043)
>20 mg/day	1.00	0.118 (0.047 to 0.299)	0.016 (0.004 to 0.063)
Methotrexate*	1.00	0.126 (0.053 to 0.298)	0.018 (0.004 to 0.076)
CsDMARDs*	1.00	0.136 (0.068 to 0.272)	0.018 (0.006 to 0.059)
Colchicine*	1.00	0.009 (0.001 to 0.168)	0.002 (0.001 to 0.078)
Azathioprine‡†	1.00	0.092 (0.051 to 0.166)	0.013 (0.006 to 0.027)
Mycophenolate mofetil‡†	1.00	0.155 (0.058 to 0.413)	0.020 (0.006 to 0.072)
TNF alpha blockers*	1.00	0.193 (0.029 to 1.273)	0.036 (0.004 to 0.341)
IL-6 inhibitors‡†	1.00	0.100 (0.034 to 0.291)	0.003 (0.001 to 0.012)
IL-17 inhibitors‡†	1.00	0.062 (0.018 to 0.216)	0.001 (0.000 to 0.009)
IL 12/23 inhibitors‡†	1.00	0.149 (0.059 to 0.379)	0.004 (0.001 to 0.017)
Rituximab‡†	1.00	0.055 (0.021 to 0.144)	0.016 (0.005-*0.046)
JAK inhibitors‡	1.00	0.013 (0.001 to 0.262)	0.001 (0.000 to 0.066)
Calcineurin inhibitors‡	1.00	0.050 (0.017 to 0.145)	0.004 (0.001 to 0.015)

Unvaccinated are reference group, ratio are given for vaccinated and booster dose completion.
*Adjusted for age, sex, smoking, obesity, hypertension, chronic obstructive pulmonary disease, Charlson's Comorbidity Index and propensity score.
†Due to convergence issues model was not adjusted for propensity score.
‡Adjusted for age, sex, Charlson's Comorbidity Index and propensity score.
CsDMARDs, conventional synthetic Disease-modifying antirheumatic drugs; IL, interleukin; JAK, Janus kinase; N/A, not available.

adjusted for the same variables as in the original analysis. The first survival plot shows that the vaccinated group had a lower risk for positive PCR during the entire study period (HR 0.675, 95% CI 0.642 to 0.711). The second survival plot shows that compared with the unvaccinated group the booster group had a lower risk for positive PCR (HR 0.436, 95% CI 0.374 to 0.508). The vaccinated group appeared to be at higher risk for positive PCR, although this difference was not statistically significant (HR 1.297, 95% CI 0.979 to 1.719).

DISCUSSION

This study demonstrated the association between important COVID-19-related outcomes and the BNT162b2 mRNA COVID-19 vaccine and booster dose, in patients with ARD. The BNT162b2 mRNA COVID-19 vaccine was found to be associated with a substantially lower rate of PCR positive proven COVID-19 infections, in addition to a lower rate of hospitalisations in COVID-19 units, COVID-19-related mortality and all-cause mortality.

We acknowledged that patients with ARD who chose to receive vaccination or booster might be different from those who did not. Our analysis could not be fully controlled for all aspects related to the protective effect of the vaccination. Yet, to minimise the possibility that our results may be confounded, we used PS in the primary outcome analysis. The positive association of vaccination and booster with the primary outcome remained significant in a PS adjusted model as well.

Several issues should be discussed following these results. Patients with ARDs and additional comorbidities tended to be more vaccinated, both in the booster dose and the first two vaccines (table 1). This reflects truly the tendency of patients with comorbidities to be vaccinated in order to be protected from COVID-19. Patients with RA were slightly more common among the unvaccinated group. It might be postulated that since RA is a disease with a higher prevalence in lower socioeconomic class, a higher smoking rate and less health-promoting behaviour, non-vaccination is a reflection of this kind of behaviour.[16 17] The American College of Rheumatology guidelines for vaccinating patients with ARD noted that patients with SLE are at a higher risk for severe COVID-19 outcomes and recommended vaccinating ARD including patients with SLE.[18] Nevertheless, our cohort showed a higher percentage of patients with SLE among non-vaccinated patients compared with the percentage receiving booster doses. Felten *et al* reported that patients with ARD do not perceive themselves as being at higher risk and that vaccination willingness was mainly influenced by their specialist.[19] This notion highlights the role played by the treating physicians, and the rheumatologists for promoting vaccination among this population.

A greater proportion of patients receiving antirheumatic drugs (table 1) received a booster dose, compared with non-vaccinated or two-dose vaccinated patients with ARD. In addition, we demonstrated a higher rate of PCR-negative patients with ARD suffering from hypertension, past myocardial infarction, chronic obstructive pulmonary disease, malignancies, stroke or transient ischaemic attack compared with PCR-positive patients with ARD at baseline (table 2). These two observations might reflect better health-promoting behaviour and/or better compliance for treatment in treated patients with ARD. Glintborg *et al* reported a higher medication compliance, increased fear and anxiety, and more self-isolation among >12 000 patients with ARD since the COVID-19 pandemic started.[20]

Studies addressing vaccination efficacy, revealed a lower immune response (measured by neutralising IgG) among patients with autoimmune disease, and patients receiving immunosuppression.[6 21] Some researchers suggested that vaccination response was explained by the comorbidity itself rather than by the immunosuppressant therapy given.[22] Lower antibody response was observed in both treated and untreated autoimmune diseases regardless of the treatment type. Most of other researchers searched for a correlation between immunosuppressants and immunogenicity. Rituximab is currently the most reported immunosuppressant to impair vaccine immune response.[23] Other studies reported lesser seroconversion among patients with ARD treated with mycophenolate mofetil (MMF), methotrexate and JAK-inhibitors, all tested after two doses vaccination regimen.[8 24] T-cell-mediated vaccination response in patients with ARD was also investigated, assuming that the humoral response does not show the whole vaccination immune response picture. Specific anti COVID-19 T cell response was observed in 58% of vaccinated rituximab treated patients both in positive or negative reconversion groups.[25] Our study presents data regarding different antirheumatic drugs, reported to be purchased by patients no more than 3 months before inclusion period. However, lower HRs for COVID-19 positive PCR in the vaccinated and booster group compared with non-vaccinated patients, regardless of the drug purchased suggests that immunosuppressants are just one variable which cannot by itself explain the whole picture. Additionally, this observation, might reflect not only the vaccine effect, but also proper behaviour of vaccinated patients. Further specific data are needed to deduct the specific contribution of the vaccination and booster to hazard risk reduction and the negative effect of antirheumatic treatments. Clinical outcomes were generally excellent for the BNT162b2 mRNA COVID-19 vaccine and boosted groups. An Israeli nationwide study of almost 600 thousands persons showed the efficacy of two doses vaccine on several clinical outcomes, that is—symptomatic COVID-19, hospitalisations, severe disease and death.[26] A following article about the booster dose a reporting information from more than 1.1 million Israelis persons aged more than 60 years, reported significantly less severe COVID-19 disease among persons receiving the booster.[27] Recently, Barda *et al* reported fewer hospitalisations, less severe COVID-19 disease and fewer COVID-19-related deaths among third dose vaccinated persons excluding immunocompromised patients.[28] To the best of our knowledge, our study this is the first study to report on BNT162b2 mRNA vaccine and booster and and COVID-19 associated clinical outcomes among patients with ARD in a real-world setting. The reported outcomes align with the mentioned data of the second and booster vaccination efficacy. Altogether, the heterogeneity of our cohort and possible un-controlled relations between variables, impede us from deducing causality effect. Connolly *et al* presented case series data of 18 patients with ARD. After receiving the third vaccine dose (mRNA-1273or BNT162b2), seroconversion was found in 80% of patient with negative or low antibody titre after the second dose.[29] The two patients with no humoral response after the third dose were treated with anti-CD-20 and MMF. Another small series of 17 patients with RA who remained seronegative after the second vaccine dose was offered to receive a third booster dose. Two weeks after the booster, antibodies above threshold were detected in 15 of those patients. Prednisone >5 mg/day was associated with a lower antibody titre, while temporary discontinuation of DMARDs was suggested to contribute to better immune response.[30] A recent study by Simon *et al* demonstrated the efficacy of booster dose for

non-responders patients with ARD, showing seroconversion or neutralising antibodies after booster in half of those patients.[31] Time since immunisation plays an important role in vaccination effectiveness due to the waning effect of the BNT162b2 mRNA -vaccine a few months after the second dose, implying that reports from longer follow-ups are needed.[32] After sensitivity analysis measuring outcomes from the first day of vaccination per patient (see online supplemental figure 1A), the differences between groups regarding SARS-CoV-2 infection seem smaller (HR 0.675 after sensitivity analysis vs 0.652 before). Measuring from the end of July 2021, compared with the unvaccinated group, the vaccinated group had increased numeric risk for SARS-CoV-2 infection, while decreased risk for COVID-19 hospitalisation. Booster group had lower risk for both outcomes (see online supplemental figure 1B).The most logical explanation for this phenomenon would be the dramatic change in the national policy towards the vaccinated populations that were allowed to visit public places, loosening the atmosphere in the general population in Israel, coupled with the summer vacations. More opportunities of exposure might have resulted in more infections.

Our study has some important limitations to take into consideration. This is a retrospective nationwide study which relies on medical data gathered from electronic medical records of patients with ARD. Due to security and privacy reasons, we could not validate the ICD-9 codes of this cohort. The prevalence of the majority of rheumatic diseases is higher in this cohort compared with Israeli and non-Israeli cohorts that were previously published.[33–38] The ARD population is heterogeneous in its demographics, rheumatic diseases feature and given treatments. Moreover, electronic computer medical records are almost always incomplete, hence some of the possible confounders may not be fully addressed in the multivariable analysis. Nevertheless, the data size consistency of the results, and valid outcomes such as PCR positivity, hospitalisations rate and mortality are reassuring about the effect of the vaccination. Another limitation is the relatively low number of patients who purchased immunemodulatory medications. This may be accounted for patients with non-active or past rheumatic diagnoses. Yet, the significantly lower HR for SARS-CoV-2 infection among the vaccinated and booster groups as compared with the unvaccinated group for those who did purchase antirheumatic medications, is an important finding considering immunogenicity issues in those patients (see table 3). Although statistically significant, our results are not adjusted to multiple testing, hence, the associations between each variable tested should be taken cautiously and in a larger context. Another limitation is that all-cause mortality might be influenced by death caused after non-reported or non-PCR tested COVID-19 infection. Also, it might be that late deadly sequelae of COVID-19 infection were not reported as COVID-19-related death. The follow-up period of the booster dose ended on 30 September, which may be too short to evaluate the booster effect. Also during the beginning of 2021, patients from the booster group, not yet boostered, were found PCR positive for COVID-19 after the second vaccine dose and got the booster dose 5–6 months later altogether (180 patients, data not shown). This observation is probably due to the Israeli Ministry of Health desk guidelines which recommended a booster dose 5–6 months after resolution from COVID-19 infection.

Due to the retrospective nature of this study, causality regarding the effectiveness of vaccination and booster among patients with ARD (especially regarding the effect of antirheumatic drugs) cannot be deducted. Yet, our results indicate better clinical outcomes in booster vaccinated patients with ARD in general. These findings support the notion that patients with ARD should be encouraged to receive the booster vaccination if available in their countries.

Notwithstanding these limitations, this is the first study that reports clinical outcomes of patients with ARD after the booster vaccine dose. This is also one of the few studies reporting clinical outcomes of vaccination and non-vaccination in patients with ARD in a real-world setting. Both the two doses of BNT162b2 mRNA COVID-19 vaccine and the booster appear to be associated with better prevention of SARS-CoV-2 infection among patients with ARD.

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