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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Boekel L, Stalman EW, Wieske L, et al. Breakthrough SARS-CoV-2 infections with the delta (B.1.617.2) variant in vaccinated patients with immune-mediated inflammatory diseases using immunosuppressants: a substudy of two prospective cohort studies. *Lancet Rheumatol* 2022; published online April 29. https://doi.org/10.1016/S2665-9913(22)00102-3.

Supplementary appendix:

"COVID-19 breakthrough infections in patients with immune-mediated inflammatory disorders and immunosuppressants – data from two prospective cohort studies"

Boekel L, Stalman EW, et al.

Contents

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Supplementary methods

T2B! study

Recruiting centers
Participants treated in out-patient clinics at the Amsterdam UMC (locations AMC and VUmc), Erasmus MC Rotterdam, Leiden University Medical Centre, University Medical Centre Groningen, Maastricht University Medical Centre), Utrecht University Medical Centre, and one Rheumatology treatment center (Reade, Amsterdam Rheumatology & immunology Centre, Amsterdam). Additional participants were recruited from two cohort studies on COVID-19 related disease severity in patients with auto-immune diseases, the ARC, and COMS-19 studies (Trial ID NL8513 and NCT04498286).

Pre-defined immune mediated inflammatory disorders
Rheumatological: rheumatoid arthritis, spondyloarthritis, SLE, giant cell arteritis, Sjogren syndrome, vasculitis, other immune-mediated rheumatologic conditions.
Neurological: multiple sclerosis, neuromyelitis optica spectrum disorder, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, inflammatory myositis
Gastro-enterological: Crohn's disease, ulcerative colitis, auto-immune hepatitis, other inflammatory bowel disorders
Dermatological: atopic dermatitis, psoriasis, pemphigus, other immune-mediated dermatologic conditions

Definitions of active treatment, types of immunosuppressants and combination therapies
We defined immunosuppressants (ISPs) as either immunosuppressive or immunomodulatory treatment. Active treatment was defined as treatment with a particular ISP in the last three moments prior to the first vaccination or if treatment was started between the first and second vaccination (when applicable). For antiCD20 therapies, cladribine, or cyclophosphamide active treatment was defined as a last administration within 12 months prior to first vaccination or between the first and second vaccination. Subdivision was made between monotherapy or as part of combination therapy. The following treatments were not regarded as systemic immunosuppressants in this study: any topical, inhaled, or rectal administered immunosuppressant, mesalazine, sulfasalazine, and budesonide.

Eligible participants
Patients were eligible if diagnosed with any of the pre-defined immune mediated inflammatory disorders, and control participants were eligible if no active or previous autoimmune, oncological or hematological disease and no current or previous treatment with systemic immunosuppressive medication in the last year. All participants were > 18 years old and able to complete a questionnaire in Dutch. Participants with immunosuppressant therapy for cancer (i.e. chemotherapy) or organ transplantation (incl. stem-cell transplantation) and participants with known pregnancy were excluded.

Further details on methodology of the T2B! study have been described before (*study accepted for publication in the Lancet Rheumatology, reference not yet available*)

ARC study

Study design
Between April, 2020 and March, 2021, all adult patients with rheumatic IMIDs from the Amsterdam Rheumatology & immunology Center were invited to participate in this study. All patients were asked, but not obliged, to recruit their own control subject of the same sex, comparable age (age difference of < 5 years) and without a rheumatic IMID. Clinical data prior to SARS-CoV-2 vaccination were collected at baseline and up to two times during follow-up via online questionnaires distributed by email. Prior to SARS-CoV-2 vaccination, serum samples were collected up to two times via regular blood withdrawal at the local research institutes or via a finger prick that could be performed at home, prior to COVID-19 vaccination. After SARS-CoV-2 vaccination, serum samples were collected up to three times. All participants gave written informed consent.

Procedures
Data collection on the incidence and disease severity of COVID-19 ended on April 30, 2021, due to the start of the Dutch national COVID-19 vaccination program. The baseline questionnaire was sent to participants when they were included in the study. The first and second follow-up questionnaires were sent to participants 1-4 and 5-9 months after completion of the baseline questionnaire

Between May and November 2020, all included patients were invited for their first blood draw at the local research institute of Reade, preferably at the time of completion of the first follow-up survey. Between October and December 2020, a self-administered finger prick test kit was sent to healthy controls and patients who were unable to visit the research institute. Between January and March 2021, all participants were invited for a first or second blood draw at the research institute, again preferably at the time of completing a follow-up survey. A test kit was sent to participants who had indicated their preference for the finger prick method in a previous survey or via direct contact with the researchers. From April 1, 2021, serum samples were collected after the first and/or second SARS-CoV-2 vaccine dose. Between October 1 and December 31, 2021, serum samples were collected cross-sectionally to investigate the serum prevalence of nucleocapsid antibodies.

Data sharing
Aggregated data and code for reproducing the results of this analysis can be shared upon reasonable request.

Table S1 Missing data

Table showing the number of missings in variables with missing data. Variables not included in the table had no missings. The number of missings in comorbidity data in healthy controls is relatively high due to inability to access healthcare records to verify diagnoses of healthy controls included in the T2B! study.

	IMID patients with immunosuppressants (n = 3207)		**IMID patients without immunosuppressants (n = 985)**		**Healthy controls (n = 822)**	
	With breakthrough infection (n= 148)	**Without breakthrough infection (n=3059)**	**With breakthrough infection (n=52)**	**Without breakthrough infection (n=933)**	**With breakthrough infection (n=33)**	**Without breakthrough infection (n=789)**
Comorbidities – no. (%)						
Cardiovascular disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	82 (10)
Chronic pulmonary disease	0 (0)	0 (0)	0 (0)	0 (0)	5 (15)	82 (10)
Diabetes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	82 (10)
Obesity	0 (0)	5 (0.2)	0 (0)	5 (0.5)	0 (0)	10 (1)
T2B-study serology – no. (%)	n = 84	n = 1572	n = 22	n = 452	n = 7	n = 167
Sample available – no. (%)	9 (11)	187 (12)	3 (14)	54 (12)	0 (0)	16 (10)

IMID = immune mediated inflammatory disease.

Table S2. Baseline characteristics for the two cohorts separately

Table showing baseline characteristics of immune-mediated inflammatory disorder (IMID) patients with immunosuppressants and controls (IMID patients without immunosuppressants and healthy controls) for the two cohort studies.

	ARC-cohort (n = 2444)			T2B-cohort (n = 2573)		
	IMID with IST (n = 1355)	IMID without IST (n = 454)	Healthy controls (n = 632)	IMID with IST (n = 1852)	IMID without IST (n = 531)	Healthy controls (n = 190)
Patient characteristics						
Age, years – mean (SD)	59 (13)	58 (14)	60 (12)	50 (13)	51 (13)	48 (11)
Female sex – no. (%)	908 (67)	258 (57)	423 (67)	1134 (61)	340 (64)	126 (66)
Male sex – no. (%)	447 (33)	196 (43)	209 (33)	718 (39)	191 (36)	63 (34)
Comorbidities – no. (%)						
Cardiovascular disease	180 (13)	69 (15)	59 (9)	167 (9)	41 (8)	1 (0.5)
Chronic pulmonary disease	167 (12)	67 (15)	40 (6)	126 (7)	26 (5)	2 (1)
Diabetes	81 (6)	30 (7)	25 (4)	80 (4)	19 (4)	0 (0)
Obesity	218 (16)	89 (20)	63 (10)	300 (16)	66 (12)	22 (12)
COVID-19 infections prior to first vaccination – no. (%)						
Total confirmed COVID-19 diagnoses*	128 (9)	44 (10)	65 (10)	274 (15)	82 (15)	65 (34)
PCR-confirmed diagnosis only	0 (0)	0 (0)	0 (0)	79 (4)	22 (4)	4 (2)
Serological confirmed diagnosis only	58 (4)	20 (4)	37 (6)	113 (6)	31 (6)	21 (11)
PCR and serological confirmed diagnosis	70 (5)	24 (5)	28 (4)	82 (4)	29 (6)	40 (21)
Immune mediated inflammatory disorders– no. (%)						
Rheumatic disease [a]	1355 (100)	454 (100)	-	634 (34)	88 (17)	-
Neurological [b]	0 (0)	0 (0)	-	492 (27)	183 (34)	-
Gastro-enterological [c]	0 (0)	0 (0)	-	484 (26)	121 (23)	-
Dermatological [d]	0 (0)	0 (0)	-	242 (13)	139 (26)	-
Immunosuppressants – no. (%)[#]						
MTX	671 (50)	-	-	321 (17)	-	-
monotherapy	288 (21)			154 (8)		
TNF-inhibitor	482 (36)	-	-	447 (24)	-	-
monotherapy	240 (18)			283 (15)		
Anti-CD20	54 (4)	-	-	212 (11)	-	-
monotherapy	15 (1)			155 (8)		
MMF	9 (0.7)	-	-	96 (5)	-	-
monotherapy	3 (0.2)			66 (4)		
S1P modulator	0 (0)	-	-	66 (4)	-	-
monotherapy	0 (0)			66 (4)		
Other immunosuppressants [e]	653 (48)	-	-	1066 (58)	-	-
monotherapy	252 (19)			705 (38)		
SARS-CoV-2 vaccination types – no. (%)						
AstraZeneca	265 (20)	72 (16)	170 (27)	204 (11)	60 (11)	2 (1)
Pfizer/BioNTech	924 (68)	332 (73)	376 (60)	1095 (59)	266 (50)	70 (37)
Moderna	92 (7)	34 (8)	43 (7)	471 (25)	169 (32)	104 (55)
Janssen	27 (2)	4 (0.9)	29 (5)	38 (2)	22 (4)	11 (6)
Mix	47 (4)	12 (3)	14 (2)	44 (2)	14 (3)	3 (2)
Time since full vaccination, days – mean (SD)	189 (41)	187 (42)	189 (43)	164 (30)	163 (32)	170 (27)
Additional vaccine dose during follow-up	365 (27)	94 (21)	130 (21)	592 (32)	72 (14)	12 (6)
Additional vaccine dose received prior to breakthrough infection	2 (0.1)	2 (0.4)	2 (0.3)	14 (0.8)	0 (0)	0 (0)

[a]: Including rheumatoid arthritis, spondylarthritis, systemic lupus erythematosus and Sjögren syndrome, Vasculitis (small, medium and large vessel vasculitis and other forms of vasculitis except giant cell arteriti),Other rheumatological (giant-cell arteritis, polymyalgia rheumatica and others);
[b]: Multiple sclerosis and neuromyelitis optica spectrum disorder, Inflammatory neuropathies and myopathies (chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and inflammatory myositis), Myasthenia gravis;

[c]: *Gastro-enterological: Crohn's disease, ulcerative colitis, auto-immune hepatitis, other inflammatory bowel disorders (auto-immune hepatitis, auto-immune sclerosing cholangitis);*

[d]: *Dermatological: atopic dermatitis, psoriasis, pemphigus, other dermatological (vitiligo, pemphigus, psoriasis and others)*

[e]: *Other immunosuppressants include abatacept, belimumab, calcineurin inhibitors, cladribine, corticosteroids, DHODH inhibitors, dimethylfumarate, dupilumab, eculizumab, glatiramer, hydroxychloroquine, IL-17A antagonists, IL-23 antagonists, immunoglobulin, interferon-bèta, JAK inhibitors, natalizumab, omalizumab, purine antagonists, tocilizumab, ustekinumab, vedolizumab, cyclophosphamide, anakinra, ixekizumab, sarilumab, sulfasalazine, leflunomide and azathioprine.*

**In the T2B-COVID study, healthy controls with a primary COVID-19 infection were actively recruited.*

Patients could be treated with multiple non-mutually exclusive immunosuppressants.

IMID: immune-mediated inflammatory disorder; MTX: methotrexate; TNF-inhibitor: tumor necrosis factor inhibitor; a-CD20: anti-CD20 therapy; MMF: mycophenolate mofetil; S1P: sphingosine-1-phosphate receptor modulators.

Table S3. Baseline characteristics of all participants with and without breakthrough infections of both cohorts combined

Table showing baseline characteristics of participants of T2B! cohort and ARC-COVID cohort combined, divided in to immune-mediated inflammatory disorder (IMID) patients with immunosuppressants and controls (IMID patients without immunosuppressants and healthy controls), with and without a COVID-19 breakthrough infection.

	IMID patients with immunosuppressants (n = 3207)		**IMID patients without immunosuppressants (n = 985)**		**Healthy controls (n = 822)**	
	With breakthrough infection (n= 148)	**Without breakthrough infection (n=3059)**	**With breakthrough infection (n=52)**	**Without breakthrough infection (n=933)**	**With breakthrough infection (n=33)**	**Without breakthrough infection (n=789)**
SARS-CoV-2 breakthrough infection						
Cumulative incidence - %	4.6 (5)	-	5.5 (5)	-	4.0 (4)	-
Incidence rate – no. events per 1000 person months	8.0	-	9.2	-	6.6	-
Time at risk, days – median (IQR)	136 (115-162)	179 (161-199)	138 (87-164)	175 (157-196)	153 (111-173)	184 (166-202)
Patient characteristics						
Age, years – mean (SD)	50 (13)	54 (14)	50 (15)	55 (14)	57 (12)	57 (13)
Female sex – no. (%)	89 (60)	1953 (64)	32 (62)	566 (61)	24 (73)	525 (67)
Male sex – no. (%)	59 (40)	1106 (36)	20 (38)	367 (39)	9 (27)	264 (33)
Comorbidities – no. (%)						
Cardiovascular disease	14 (9)	333 (11)	5 (10)	105 (11)	3 (9)	57 (7)
Chronic pulmonary disease	12 (8)	281 (9)	5 (10)	88 (9)	4 (12)	38 (5)
Diabetes	10 (7)	151 (5)	6 (12)	43 (5)	2 (6)	23 (3)
Obesity	27 (18)	491 (16)	7 (14)	148 (16)	4 (12)	81 (10)
SARS-CoV-2 infections prior to first vaccination– no. (%)						
Total confirmed diagnoses	10 (7)	392 (13)	3 (6)	123 (13)	2 (6)	128 (16)
PCR confirmed diagnosis	4 (3)	75 (2)	0 (0)	48 (5)	0 (0)	4 (1)
Serological confirmed diagnosis	6 (4)	165 (5)	3 (6)	22 (2)	2 (6)	56 (7)
PCR and serological confirmed	0 (0)	152 (5)	0 (0)	53 (6)	0 (0)	68 (9)
Immune-mediated inflammatory disorders – no. (%)						
Rheumatic disease [a]	84 (57)	1902 (62)	31 (60)	511 (55)	-	-
Neurological [b]	22 (15)	470 (15)	5 (10)	178 (19)	-	-
Gastro-enterological [c]	32 (21)	452 (15)	5 (10)	116 (12)	-	-
Dermatological [d]	10 (7)	232 (8)	11 (21)	128 (14)	-	-
Immunosuppressants– no. (%)*						
MTX	37 (25)	955 (31)	-	-	-	-
monotherapy	15 (10)	427 (14)				
TNF-inhibitor	49 (33)	880 (29)	-	-	-	-
monotherapy	30 (20)	493 (16)				
Anti-CD20	16 (11)	250 (8)	-	-	-	-
monotherapy	12 (8)	158 (5)				
MMF	3 (2)	102 (3)	-	-	-	-
monotherapy	0 (0)	35 (1)				
S1P modulator	5 (3)	61 (2)	-	-	-	-
monotherapy	5 (3)	61 (2)				
Other immunosuppressants [e]	73 (49)	1646 (54)	-	-	-	-
monotherapy	42 (28)	915 (30)				
SARS-CoV-2 vaccine types – no. (%)						
AstraZeneca	19 (13)	450 (15)	6 (12)	126 (14)	11 (33)	161 (20)
Pfizer/BioNTech	99 (66)	1920 (63)	34 (65)	564 (61)	18 (55)	428 (54)
Moderna	27 (18)	536 (18)	10 (19)	193 (21)	4 (12)	143 (18)

Janssen	1	(0.7)	64	(2)	2	(4)	24	(3)	0 (0)	40 (5)
Mix	3	(2)	88	(3)	0	(0)	26	(3)	0 (0)	17 (2)
Additional vaccine dose during follow-up	23	(15)	934	(31)	2	(4)	164	(18)	3 (9)	139 (18)
Additional vaccine received prior to breakthrough	16	(11)	-		1	(2)	-		1 (3)	-
Post-vaccination antibody response	n = 84		n = 1572		n = 22		n = 452		n = 7	n = 167
Seroconversion – no. (%)	66	(79)	1361	(87)	22	(100)	439	(97)	7 (100)	165 (99)
Median IgG titer (IQR), all groups	61	(13 - 131)	86	(19 - 201)	90	(42-219)	157	(65 - 283)	135 (86 - 223)	233 (143-367)
Poor responders [f]	0.1	(0.1 – 2.3)	3.8	(0.1 – 25)	-		-		-	-
Other immunosuppressants	88	(50 – 146)	111	(46 – 227)	-		-		-	-

[a]: *Including rheumatoid arthritis, spondylarthritis, systemic lupus erythematosus and Sjogren's syndrome, Vasculitis (small, medium and large vessel vasculitis and other forms of vasculitis except giant cell arteritis), Other rheumatological (giant-cell arteritis, polymyalgia rheumatica and others);*
[b]: *Multiple sclerosis and neuromyelitis optica spectrum disorder, Inflammatory neuropathies and myopathies (chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and inflammatory myositis), Myasthenia gravis;*
[c]: *Gastro-enterological: Crohn's disease, ulcerative colitis, auto-immune hepatitis, other inflammatory bowel disorders (auto-immune hepatitis, auto-immune sclerosing cholangitis);*
[d]: *Dermatological: atopic dermatitis, psoriasis, pemphigus, other dermatological (vitiligo, pemphigus, psoriasis and others)*
[e]: *Other immunosuppressants include abatacept, belimumab, calcineurin inhibitors, cladribine, corticosteroids, DHODH inhibitors, dimethylfumarate, dupilumab, eculizumab, glatiramer, hydroxychloroquine, IL-17A antagonists, IL-23 antagonists, immunoglobulin, interferon-bèta, JAK inhibitors, natalizumab, omalizumab, purine antagonists, tocilizumab, ustekinumab, vedolizumab, cyclophosphamide, anakinra, ixekizumab, sarilumab, sulfasalazine, leflunomide and azathioprine.*
[f]: *anti-CD20 therapy, sphingosine-1-phosphate receptor (S1P) modulators, and mycophenolate mofetil (MMF)*

Table S4. Sensitivity analyses

Table showing results for univariable and multivariable sensitivity analyses for potential clinical and humoral determinants. A) Includes IMID patients with and without seroconversion, healthy controls are excluded. B) Includes IMID patients with immunosuppressants and healthy controls, IMID patients without immunosuppressants are excluded. C) Includes IMID patients without immunosuppressants and healthy controls, IMID patients with immunosuppressants are excluded. D) Includes all participants. E) Includes participants without a history of a SARS-CoV-2 infection prior to vaccination (primary COVID-19), participants with primary COVID-19 are excluded. F) Includes participants without primary COVID-19 from the T2B-study only, all participants from the ARC study and participants from the T2B study with primary COVID-19 are excluded.

A) IMID patients with immunosuppressants compared to IMID patients without immunosuppressants only				
Univariable model *(N:4192, no. events: 201)*		**OR**	**95% CI**	**p-value**
	IMID patients without immunosuppressants*	1.00	-	
	IMID patients with immunosuppressants	0.87	(0.63 – 1.21)	0.42
Multivariable model *(N:4180, no. events: 199) #*				
	IMID patients without immunosuppressants*	1.00	-	
	IMID patients with immunosuppressants	0.85	(0.61 – 1.18)	0.34
B) IMID patients with immunosuppressants compared healthy controls only				
Univariable model *(N:4029, no. events: 183)*				
	Healthy controls*	1.00	-	
	IMID patients with immunosuppressants	1.13	(0.77 – 1.66)	0.53
Multivariable model *(N:39270, no. events: 177) #*				
	Healthy controls*	1.00	-	
	IMID patients with immunosuppressants	0.99	(0.65 – 1.50)	0.95
C) IMID patients without immunosuppressants compared to healthy controls				
Univariable model *(N:1807, no. events: 86)*				
	Healthy controls*	1.00	-	
	IMID patients without immunosuppressants	1.29	(0.83 – 2.01)	0.26
Multivariable model *(N:1705, no. events: 80)*				
	Healthy controls*	1.00	-	
	IMID patients without immunosuppressants	1.21	(0.75 – 1.97)	0.44
D) Clinical determinant analyses adjusted for time since vaccination [a]				
Multivariable model *(N:4906, no. events: 228) #*				
	Controls*	1.00	-	
	IMID patients with immunosuppressants	0.90	(0.67 – 1.21)	0.48

E) Clinical determinants analyses in participants without a SARS-CoV-2 infection prior to vaccination				
Univariable model *(N:4356, no. events: 220)*		**OR**	**95% CI**	**P-value**
	Controls*	1.00	-	
	IMID patients with immunosuppressants	0.95	(0.71 – 1.25)	0.70
Multivariable model *(N:4264, no. events: 214) ##*				
	Controls*	1.00	-	
	IMID patients with immunosuppressants	0.87	(0.65 – 1.16)	0.34
	Covariables; other potential risk factors			
	Age	**0.98**	**(0.97 – 0.99)**	**<0.0001**
	Sex			
	Male sex*	1.00	-	
	Female sex	0.95	(0.71 – 1.26)	0.71
	Obesity	1.12	(0.83 – 1.74)	0.34
	Cardiovascular disease	0.90	(0.55 – 1.46)	0.67
	Pulmonary disease	0.95	(0.57 – 1.57)	0.84
	Diabetes	**2.14**	**(1.26 – 3.64)**	**0.005**
	Vaccine type			
	AstraZeneca*	1.00	-	
	Pfizer/BioNTech	0.93	(0.63 – 1.39)	0.73
	Moderna	0.86	(0.52 – 1.40)	0.54
	Janssen	0.42	(0.12 – 1.41)	0.16
	Mix	0.27	(0.06 – 1.14)	0.08
F) Humoral determinants analyses in participants without a SARS-CoV-2 infection prior to vaccination (T2B! cohort)				
Multivariable model *(N:1861, no. events: 98) ###*				
	No seroconversion after full vaccination*	1.00	-	
	Seroconversion after full vaccination	0.59	(0.34 – 1.00)	0.05
Multivariable model *(N:1632, no. events: 80) ###*				
	4 – 53	0.97	(0.47 – 2.00)	0.93
	53 – 126	1.78	(0.96 – 3.29)	0.07
	126 – 250**	1.00	-	
	≥ 250	0.74	(0.35 – 1.57)	0.43

*: reference group
#: adjusted for age, sex, obesity, cardiovascular disease, pulmonary disease, diabetes, vaccine type, SARS-CoV-2 infection prior to vaccination and time since vaccination
##: only presented variables were included in the model.
###: adjusted for age, sex, obesity, cardiovascular disease, pulmonary disease, diabetes, vaccine type and SARS-CoV-2 infection prior to vaccination.
**Third quartile was chosen as reference group based on median antibody titers observed in controls with seroconversion (181 AU/mL, IQR: 84 – 299 AU/mL).
[a] Analyses were requested upon review of the manuscript.

Table S5 Characteristics of SARS-CoV-2 breakthrough cases treated with anti-CD20 therapy

Table showing case descriptions of IMID patients with a SARS-CoV-2 breakthrough infection who were treated with anti-CD20 therapy during SARS-CoV-2 vaccination and follow-up. Table showing the number of anti-CD20 infusions received from 01-01-2020 until the SARS-CoV-2 breakthrough infection. This time frame was chosen because of the long-term effects of anti-CD20 therapy on B cells. Table also showing the number of days between last anti-CD20 infusion and the SARS-CoV-2 breakthrough infection.

Patient	WHO COVID severity score	IMID diagnosis	Age	Sex	Immunosuppressants	Number of anti-CD20 infusions from 01-01-2020 until breakthrough infection	Number of days between last anti-CD20 infusion and breakthrough infection
1	Symptomatic independent	Granulomatosis with polyangiitis	47	Male	Anti-CD20, corticosteroids	6	52
2	Symptomatic independent	Granulomatosis with polyangiitis	75	Male	Anti-CD20	3	136
3	Symptomatic independent	Sjogren's syndrome	79	Female	Anti-CD20	1	316
4	Symptomatic independent	Rheumatoid arthritis	68	Female	Anti-CD20, methotrexate	4	133
5	Symptomatic independent	Pemphigus	45	Male	Anti-CD20, corticosteroids	2	84
6	Symptomatic independent	Sjogren's syndrome	44	Female	Anti-CD20	4	91
7	Symptomatic independent	Systemic lupus erythematosus	57	Male	Anti-CD20, corticosteroids, cyclophosphamide, methotrexate	4	107
8	Hospitalized with oxygen	Multiple sclerosis	50	Female	Anti-CD20	3	37
9	Symptomatic independent	Multiple sclerosis	50	Female	Anti-CD20	4	34
10	asymptomatic	Multiple sclerosis	47	Male	Anti-CD20	3	101
11	Symptomatic independent	Multiple sclerosis	41	Male	Anti-CD20	4	3
12	Symptomatic independent	Multiple sclerosis	31	Female	Anti-CD20	2	145
13	Symptomatic independent	Multiple sclerosis	54	Male	Anti-CD20	3	29
14	Symptomatic independent	Rheumatoid arthritis	60	Female	Anti-CD20	2	130
15	Hospitalized with oxygen	Rheumatoid arthritis	54	Male	Anti-CD20	2	75
16	Deceased	Rheumatoid arthritis	76	Male	Anti-CD20	1	60

IMID: immune-mediated inflammatory diseases

Table S6 Subgroup analyses based on immunosuppressive treatment regimens

Table showing results of univariable logistic regression analyses used to investigate associations between different types of immunosuppressants and the risk of SARS-CoV-2 breakthrough infections. These exploratory subgroup analyses were requested upon review of the manuscript.

Clinical determinant analysis				
Univariable model *(N:4162, no. events: 198)*				
No. participants		**OR**	**95% CI**	**P value**
N: 1806	Controls*	1.00	-	
N: 433	Anti-CD20, MMF or S1P modulators; mono- or combination therapy	1.17	(0.73 – 1.87)	0.50
N: 524	TNF-inhibitor, monotherapy	1.21	(0.79 – 1.86)	0.37
N: 442	Methotrexate, monotherapy	0.75	(0.44 – 1.29)	0.30
N: 957	Other immunosuppressants, monotherapy	0.92	(0.63 – 1.34)	0.66
Multivariable model *(N:4075, no. events: 193) #*				
N: 1719	Controls*	1.00	-	
N: 433	Anti-CD20, MMF or S1P modulators; mono- or combination therapy	1.05	(0.65 – 1.68)	0.85
N: 524	TNF-inhibitor, monotherapy	1.10	(0.71 – 1.71)	0.67
N: 442	Methotrexate, monotherapy	0.80	(0.46 – 1.38)	0.42
N: 957	Other immunosuppressants, monotherapy	0.85	(0.58 – 1.25)	0.41

*: reference group
#: adjusted for age, diabetes and SARS-CoV-2 prior to vaccination. These variables were selected based on results of overall analyses of clinical determinants.

Table S7. Disease severity of SARS-CoV-2 breakthrough infections

Table showing the distribution of the disease severity of SARS-CoV-2 breakthrough infections based on WHO criteria for IMID patients with immunosuppressants, IMID patients without immunosuppressants and healthy controls, in the combined cohort and the ARC and T2B! cohort seperately.

Combined cohort	**IMID patients with immunosuppressants (n= 148)**	**IMID patients without immunosuppressants (n=52)**	**Healthy controls (n=33)**
Ambulatory mild disease			
Asymptomatic (1)	27 (18)	8 (15)	9 (27)
Symptomatic; independent (2)	99 (67)	34 (65)	19 (58)
Symptomatic; assistance needed (3)	14 (9)	7 (13)	3 (9)
Hospitalized: moderate disease			
Hospitalized; no oxygen therapy (4)	2 (1)	1 (2)	0 (0)
Hospitalized; oxygen by mask or nasal prongs (5)	4 (3)	1 (2)	1 (3)
Hospitalized severe disease			
Hospitalized; oxygen by NIV or high flow (6)	0 (0)	0 (0)	
Intubation and mechanical ventilation (7) *pO2/FiO2 >= 150 or SpO2/FiO2 >= 200*	1 (1)	1 (2)	1 (3)
Mechanical ventilation (8) *pO2/FiO2 < 150 (SpO2/FiO2 < 200) or vasopressors*	0 (0)	0 (0)	0 (0)
Mechanical ventilation (9) *pO2/FiO2 < 150 and vasopressors, dialysis, or ECMO*	0 (0)	0 (0)	0 (0)
Dead			
Dead (10)	1 (1)	0 (0)	0 (0)
ARC cohort	**n = 55**	**n = 27**	**n = 26**
Ambulatory mild disease			
Asymptomatic (1)	20 (36)	8 (30)	9 (35)
Symptomatic; independent (2)	21 (38)	12 (44)	12 (46)
Symptomatic; assistance needed (3)	7 (38)	4 (15)	3 (12)
Hospitalized: moderate disease			
Hospitalized; no oxygen therapy (4)	2 (4)	1 (4)	
Hospitalized; oxygen by mask or nasal prongs (5)	3 (5)	1 (4)	1 (4)
Hospitalized severe disease			
Hospitalized; oxygen by NIV or high flow (6)	0 (0)	0 (0)	0 (0)
Intubation and mechanical ventilation (7) *pO2/FiO2 >= 150 or SpO2/FiO2 >= 200*	1 (2)	1 (4)	1 (4)
Mechanical ventilation (8) *pO2/FiO2 < 150 (SpO2/FiO2 < 200) or vasopressors*	0 (0)	0 (0)	0 (0)
Mechanical ventilation (9) *pO2/FiO2 < 150 and vasopressors, dialysis, or ECMO*	1 (2)	0 (0)	0 (0)
Dead			
Dead (10)			
T2B! cohort	**n = 93**	**n = 25**	**n = 7**
Ambulatory mild disease			
Asymptomatic (1)	7 (8)	0 (0)	0 (0)
Symptomatic; independent (2)	78 (84)	22 (88)	7 (100)
Symptomatic; assistance needed (3)	7 (8)	3 (12)	0 (0)
Hospitalized: moderate disease			
Hospitalized; no oxygen therapy (4)	0 (0)	0 (0)	0 (0)
Hospitalized; oxygen by mask or nasal prongs (5)	1 (1)	0 (0)	
Hospitalized severe disease			
Hospitalized; oxygen by NIV or high flow (6)	0 (0)	0 (0)	0 (0)
Intubation and mechanical ventilation (7) *pO2/FiO2 >= 150 or SpO2/FiO2 >= 200*	0 (0)	0 (0)	0 (0)
Mechanical ventilation (8) *pO2/FiO2 < 150 (SpO2/FiO2 < 200) or vasopressors*	0 (0)	0 (0)	0 (0)
Mechanical ventilation (9) *pO2/FiO2 < 150 and vasopressors, dialysis, or ECMO*	0 (0)	0 (0)	0 (0)
Dead			
Dead (10)	0 (0)	0 (0)	0 (0)

Table S8. Characteristics of hospitalized participants

Table showing case descriptions of IMID patients with immunosuppressants and controls with COVID-19 breakthrough infections that were hospitalized.

Patient	WHO COVID severity score	IMID diagnosis	Age	Sex	BMI	ISP	Comorbidities	SARS-CoV-2 vaccine type
1	**Hospitalized without oxygen**	Scleroderma	40	Male	25	-	-	Pfizer/BioNTech
2	**Hospitalized without oxygen**	RA	59	Male	32	MTX	Obesity	AZ
3	**Hospitalized without oxygen**	Bechterew	68	Female	25	TNF	-	Pfizer/BioNTech
4	**Hospitalized with oxygen**	MS	50	Female	23	Anti-CD20[1]	-	Moderna
5	**Hospitalized with oxygen**	RA	54	Male	26	Anti-CD20[2]	Cardiovascular disease	Pfizer/BioNTech
6	**Hospitalized with oxygen**	RA	55	Male	25	Other[3]	Diabetes	Pfizer/BioNTech
7	**Hospitalized with oxygen**	Healthy control	58	Male	28	-	-	
8	**Hospitalized with oxygen**	RA	70	Male	23	Other[4]	-	Pfizer/BioNTech
9	**Hospitalized with oxygen**	RA	74	Male	34	-	Obesity, cardiovascular disease, diabetes	Pfizer/BioNTech
10	**ICU admission**	Healthy control	65	Male	35	-	Obesity, cardiovascular disease, diabetes	AZ
11	**ICU admission**	Bechterew, raynaud	57	Female	33	-	Obesity, diabetes	AZ
12	**ICU admission**	RA, vasculitis, PMR	50	Female	32	MTX + other[5]	Obesity, diabetes	Moderna
13	**Deceased**	RA	76	Male	29	Anti-CD20[6]	-	Pfizer/BioNTech

[1]: Ocrelizumab
[2]: Anti-CD20
[3]: Other immunosuppressant
[4]: Other immunosuppressant
[5]: MTX + other immunosuppressant
[6]: Anti-CD20 + TNF- inhibitor + other immunosuppressant

RA: rheumatoid arthritis; MS: multiple sclerosis; HC: healthy control; a-CD20: anti-CD20 therapy; MTX: methotrexate; TNF: tumor necrosis factor-inhibitors; AZ: AstraZeneca

Table S9. Characteristics of participants who developed COVID-19 after receiving an additional vaccine dose

Table showing case descriptions of participants with COVID-19 breakthrough infections after receiving an additional vaccine dose. In September 2021, third vaccinations were offered to specific vulnerable populations, including patients treated with anti-CD20 therapy, S1P modulators and MMF combination therapies. Distribution of SARS-CoV-2 booster vaccinations among people of Dutch population started on the 18th of November, 2021. All people, including those who received a third vaccination, were eligible to receive a booster vaccination when the last SARS-CoV-2 vaccine dose was received at least three months prior. Third and booster vaccinations were given either with BNT162b2 (Pfizer/BioNtech) or CX-024414 (Moderna) vaccines.

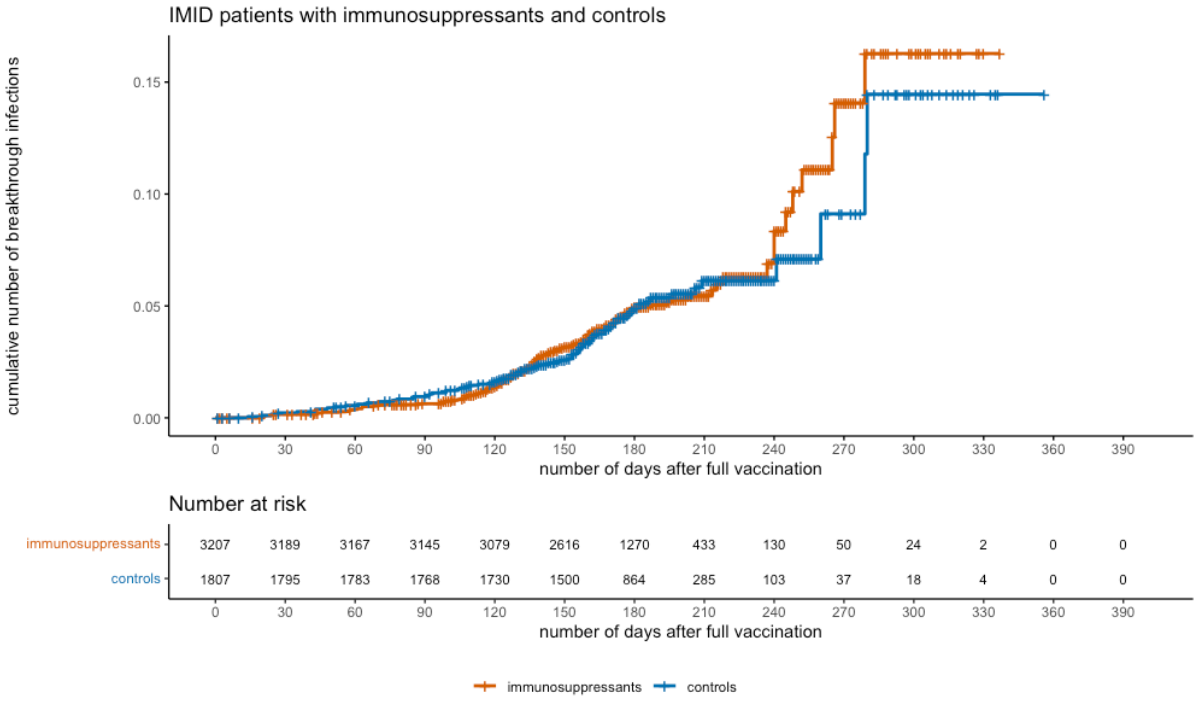
Patient	WHO COVID severity score	IMID diagnosis	Age	Sex	BMI	ISP	Comorbidities	SARS-CoV-2 vaccine type primary vaccinations	Seroconversion after primary vaccination
1	Symptomatic independent	Rheumatoid arthritis	58	Female	26	Abatacept, methotrexate	-	AstraZeneca	-
2	Hospitalized with oxygen	Rheumatoid arthritis	54	Male	26	Anti-CD20	Cardiovascular disease, obesity	Pfizer/BioNTech	-
3	Symptomatic independent	Vasculitis	47	Male	31	Anti-CD20, prednisone	Diabetes	Pfizer/BioNTech	No seroconversion
4	Symptomatic independent	Ulcerating colitis	63	Male	24	JAK inhibitor	Diabetes	AstraZeneca	No seroconversion
5	Asymptomatic	Crohn's disease	36	Female	25	TNF inhibitor	-	Moderna	Seroconversion
6	Symptomatic independent	Ulcerating colitis	54	Female	27	TNF inhibitor, purine antagonist	Chronic pulmonary disease	Moderna	Seroconversion
7	Symptomatic independent	Vasculitis	75	Male	19	Anti-CD20	Cardiovascular disease	Pfizer/BioNTech	No seroconversion
8	Asymptomatic	Myasthenia Gravis	44	Female	32	MMF, prednisone	Obesity	Moderna	Seroconversion
9	Symptomatic independent	Vasculitis	62	Female	25	Prednisone, purine antagonist	Cardiovascular disease, diabetes	AstraZeneca	No seroconversion
10	Symptomatic independent	Other rheumatological	79	Female	25	Anti-CD20	-	Pfizer/BioNTech	No seroconversion
11	Symptomatic independent	Rheumatoid arthritis	68	Female	29	Anti-CD20	-	Pfizer/BioNTech	No seroconversion
12	Symptomatic independent	Other dermatological	45	Male	25	Anti-CD20, prednisone	-	Pfizer/BioNTech	No seroconversion
13	Symptomatic independent	Other rheumatological	44	Female	24	Anti-CD20	-	Pfizer/BioNTech	No seroconversion
14	Symptomatic independent	Multiple sclerosis and neuromyelitis optica	46	Female	25	S1P modulator	-	Pfizer/BioNTech	No seroconversion
15	Symptomatic independent	Multiple sclerosis and neuromyelitis optica	50	Male	22	S1P modulator	-	Pfizer/BioNTech	No seroconversion
16	Symptomatic dependent	Multiple sclerosis and neuromyelitis optica	46	Female	22	S1P modulator	-	Moderna	No seroconversion
17	Symptomatic independent	Bechterew	36	Female	24	-	-	Moderna	-
18	Asymptomatic	Healthy control	45	Female	23	-	-	AstraZeneca	-

IMID: immune-mediated inflammatory disorder; MTX: methotrexate; TNF-inhibitor: tumor necrosis factor inhibitor; a-CD20: anti-CD20 therapy; MMF: mycophenolate mofetil; S1P: sphingosine-1-phosphate receptor modulators.

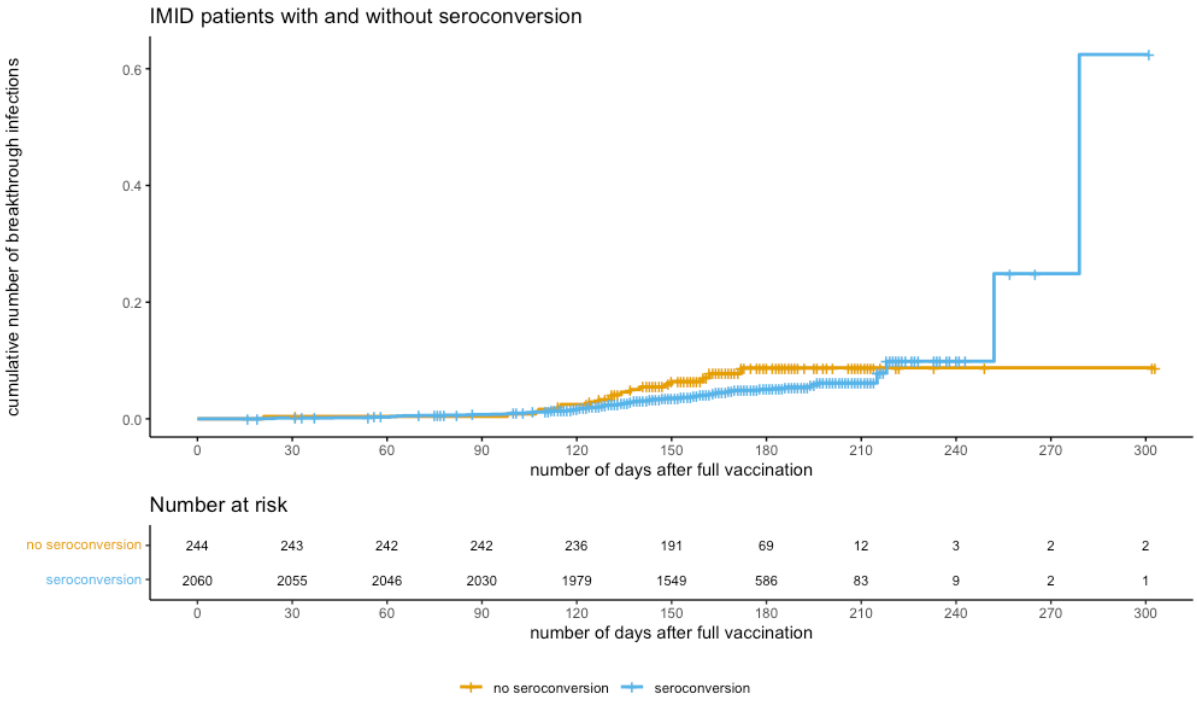
Figure S1. Cumulative incidence curve

Figure showing the of cumulative incidence curve in IMID patients with immunosuppressants and controls (A), and in participants of the T2B-study with and without seroconversion measured at 28 days after completing SARS-CoV-2 vaccination (B). Seroconversion was defined as an anti-RBD IgG response of 4.0 arbitrary units per mL (AU/mL) or higher.

A)



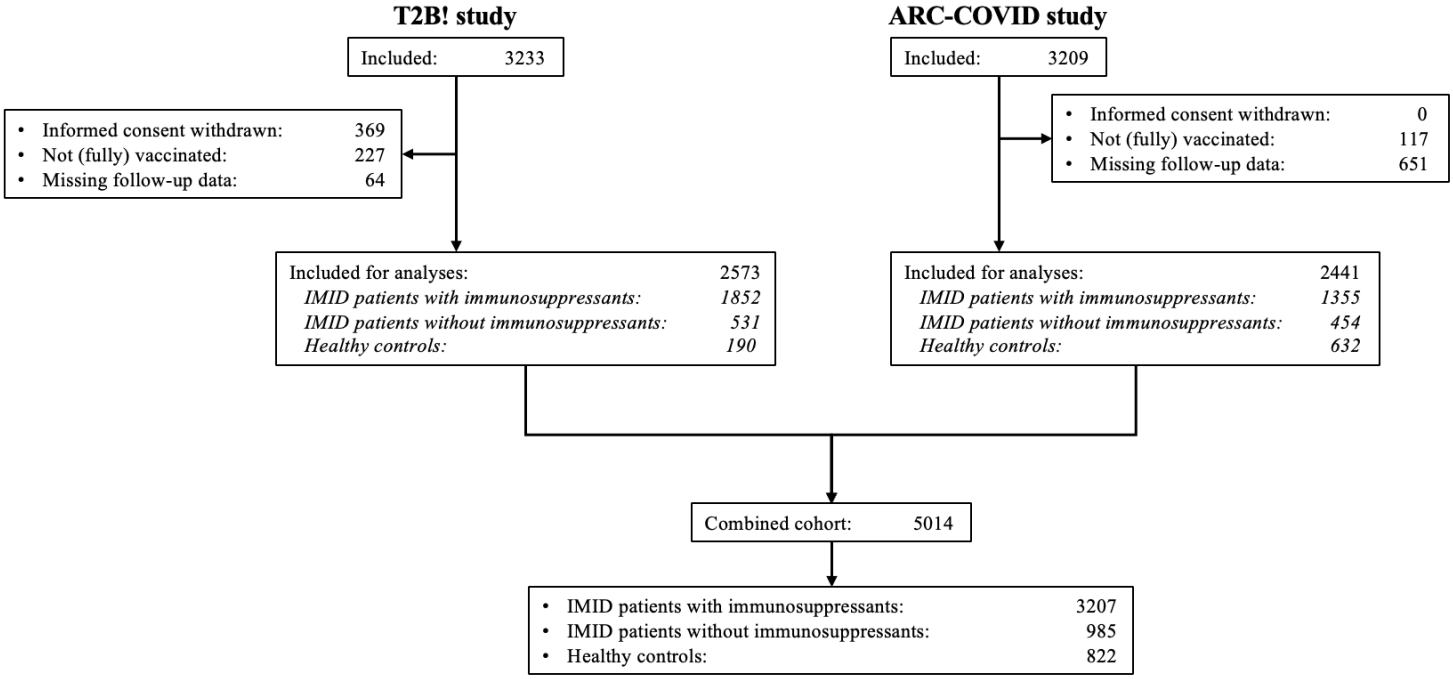
B)



IMID: immune-mediated inflammatory disorder

Figure S2. Flowchart of the two cohorts separately

Figure showing the flowcharts of both studies separately, panel A shows flowchart of the T2B! study, panel B the ARC-COVID study and panel C shows flowchart of both studies combined. The total number of included participants in the ARC-study is based on the number of participants that were not (yet) lost to follow-up on March 1, 2021. This number could differ from numbers that we have reported in previous publications, as participants from the ARC study could be invited for follow-up in the T2B study between March 1 and May 31, 2021.



IMID: immune-mediated inflammatory disorder

Figure S3. Relationship between antibody titers after vaccination and the incidence of SARS-CoV-2 breakthrough infections.

Figure showing the incidence with corresponding 95% confidence interval of SARS-CoV-2 breakthrough infections in percentiles of SARS-CoV-2 IgG antibody titers after vaccination. All quartiles included 515 participants.

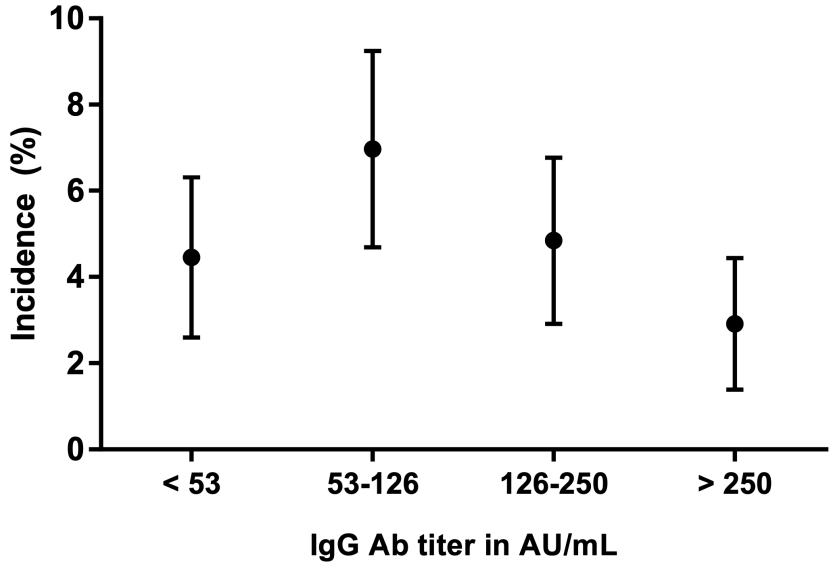
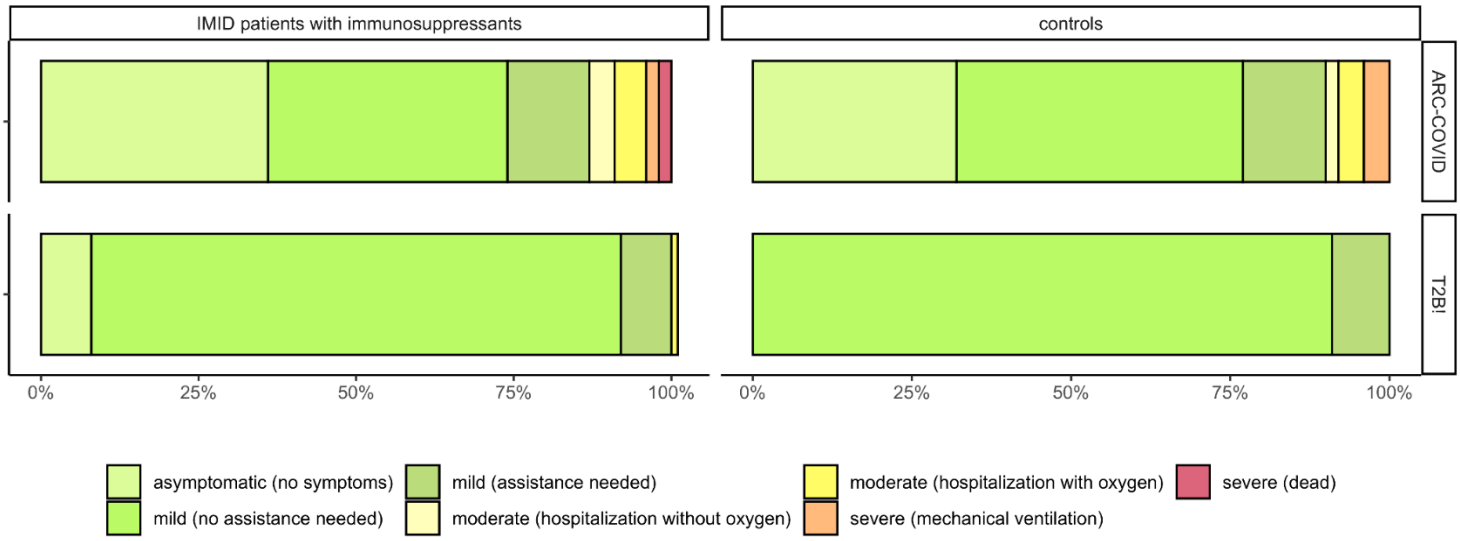


Figure S4 Disease severity of immune-mediated inflammatory disease (IMID) patients with immunosuppressants and controls for both cohorts separately

Figure showing disease severity of SARS-CoV-2 breakthrough infections categorized using the WHO COVID-19 Clinical Progression Scale. On the left participants from the ARC-COVID cohort were displayed, divided in IMID patients with immunosuppressants and controls (IMID patients without immunosuppressants and healthy controls). On the right side the same subdivision was made.



IMID: immune-mediated inflammatory disorder; ARC: ARC-COVID study; T2B: T2B! study