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Supplementary appendix

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Supplementary appendix

"SARS-CoV-2 breakthrough infections in patients with rheumatic immune-mediated inflammatory diseases during the omicron dominant period"

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Supplementary methods

Data collection

Vaccination naïve SARS-CoV-2 infections (Wildtype/Alpha variant)

Data were collected via digital questionnaires and serum sampling (1). 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. Information on demographic data were only collected at baseline and included age, sex, height, weight, smoking status, ethnicity, educational level, type of IMID and the presence of comorbidities. At baseline and during follow-up, participants reported their disease activity, medication use and COVID-19-related characteristics. Disease activity was evaluated only for patients with rheumatoid arthritis or spondyloarthritis using the multidimensional Health Assessment Questionnaire (HAQ) (Routine Assessment of Patient Index Data-3 (RAPID-3)/HAQ2) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), respectively. COVID-19-related characteristics included information on type and severity of COVID-19-related symptoms (cough, dyspnoea, fever, ageusia/agnosia, malaise, fatigue, headache, vomiting/diarrhoea), recent travelling history, (probable) contact with confirmed COVID-19 cases, social distancing measures, COVID-19 test results (PCR tests, loop-mediated isothermal amplification tests, rapid antigen tests, serological antibody test results acquired outside the study, hospitalisation and starting January 2021 (when the vaccination campaign started) COVID-19 vaccination status.

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. All serum samples used for this study were collected prior to COVID-19 vaccination. All these pre-vaccination serum samples were analyzed for the presence of SARS-CoV-2-specific antibodies with a receptor binding domain antibody (RBD-Ab) bridging ELISA (in house) with a 98.1% sensitivity and a 99.5% specificity (3). Participants with a positive test-result were classified as COVID-19 cases.

Breakthrough SARS-CoV-2 infections

Questionnaires to collect data on SARS-CoV-2 breakthrough infections were sent to participants at fixed timepoints: on April 26, Aug 24, Dec 10, 2021, and March 10, 2022 (2). Data collected included vaccination dates, vaccine type, information on COVID-19 symptoms, and admissions to hospital due

to COVID-19. Hospital discharge data were used to verify the COVID-19 disease severity score of participants who had been admitted to hospital. For analyses, only participants who were vaccinated against SARS-CoV-2 were included. Participants were excluded if their last follow-up date was before January 1, 2022.

Collaboration with Target-to-B! Consortium

Between February 2 and August 1, 2021, 499 patients with rheumatic IMIDs and 190 healthy controls were also included in another Dutch multi-center observational cohort study of the Target-to-B! (T2B!) Consortium (4). The primary aim of this study was to assess effects of various immunosuppressants on the development of humoral immunity after SARS-CoV-2 vaccination. Clinical data on SARS-CoV-2 breakthrough infections were collected via digital questionnaire that were sent to participants every 2 months after the first SARS-CoV-2 vaccination (2). As described previously (2), we collaborated with the T2B! study to compare the incidence and severity of Delta breakthrough infections between IMID patients and controls. In the present study, we only used data that were collected within the T2B! study from the 499 patients with rheumatic IMIDs and 190 healthy controls that have previously been included in our own study. For data collection on Omicron breakthrough infections, these participants received our questionnaire that was sent on March 10, 2022.

SARS-CoV-2 vaccination campaign in the Netherlands

In the Netherlands, the SARS-CoV-2 vaccination campaign started on Jan 6, 2021 using ChAdOx1 nCoV-19, BNT162b2, CX-024414 and Ad.26.COV2.S vaccines. For healthy individuals with a previous SARS-CoV-2 infection, a second vaccine dose was made optional. In September 2021, a third vaccination was offered to specific susceptible populations (i.e., patients treated with anti-CD20 therapy, S1P receptor modulators, and mycophenolate mofetil). Distribution of the first booster vaccinations (additional vaccine doses) among Dutch people of the general population started on November 18, 2021 using BNT162b2 and CX-024414 vaccines. After recognizing that protection provided by SARS-CoV-2 vaccines weakens slightly over time, additional booster vaccinations were advised for all individuals aged 60 years and over when the last SARS-CoV-2 vaccine dose or infection was at least 3 months ago (5). Additional booster vaccinations were made available for all individuals aged 12 years and over.

Outcomes and definitions

The primary objective of this substudy was to compare the severity of SARS-CoV-2 Omicron breakthrough infections between patients with rheumatic IMIDs and healthy controls. Other objectives were to compare the severity of Omicron breakthrough infections with vaccination-naïve Wildtype/Alpha and Delta breakthrough infections in IMID patients, and to assess the effects of anti-CD20 therapy on the severity of Omicron breakthrough infections. In addition, as we previously

explored associations between clinical determinants and the occurrence of Delta breakthrough infections (2), we aimed to explore this for Omicron breakthrough infections as well. Lastly, we compared symptomology of SARS-CoV-2 infections with different variants (Wildtype/Alpha variant, Delta variant and Omicron variant).

Vaccination-naïve SARS-CoV-2 infections were defined as PCR- or serological confirmed infections detected between February 1, 2020 and March 31, 2021 before the first SARS-CoV-2 vaccine dose was given. Breakthrough SARS-CoV-2 infections were defined as PCR- or antigen confirmed infections detected at least 14 days after SARS-CoV-2 vaccination. Individuals were considered as being vaccinated after having received two doses of BNT162b2 (Pfizer–BioNTech), CX-024414 (mRNA-1273; Moderna), or ChAdOx1 nCoV-19 (Oxford–AstraZeneca), or after one dose of Ad.26.COV2.S (Janssen, Johnsen & Johnsen). Individuals who had a SARS-CoV-2 infection in addition to a single SARS-CoV-2 vaccine dose of any type were also considered being vaccinated. Severe SARS-CoV-2 infections were defined as (unplanned) hospital admissions due to a SARS-CoV-2 infection. The disease severity of SARS-CoV-2 breakthrough infections was categorized using the WHO COVID-19 Clinical Progression Scale for descriptive proposes only.

Classification of SARS-CoV-2 infections

Vaccination-naïve infections were considered Wildtype or Alpha (B.1.1.7) variant infections, as data were collected before the emergence of the Delta variant in the Netherlands (6). Breakthrough infections were classified as Delta or Omicron SARS-CoV-2 infections based on publicly available data on the predominant circulating SARS-CoV-2 variant in the Netherlands (6). To limit misclassification, the following time-windows were used: July 1 until December 14, 2021 for the delta variant, and January 1 until April 15, 2022 for the omicron variant. Data on SARS-CoV-2 infections were self-reported and not verified.

WHO COVID-19 Clinical Progression Scale

A WHO score of 1 indicates asymptomatic infection, a score of 2 indicates mild disease without need for assistance, a score of 3 indicates mild disease with need for assistance (ie, could not care for themselves in daily life due to the severity of their symptoms) but no hospitalisation; we classified participants with a score of 1–3 as being ambulatory (7). A WHO score of 4 or higher indicated severe disease—ie, admission to hospital (hospitalisation) or death. A score of 4 indicates hospitalisation without oxygen supplementation; 5 indicates hospitalisation with oxygen supplementation via mask or nasal prongs; 6 indicates admission to an intensive care unit (ICU) and oxygen by non-invasive ventilation or high-flow ventilation; 7 indicates admission to an ICU with mechanical ventilation, with partial pressure of oxygen (pO_2) to fraction of inspired oxygen (FiO_2) ratio of ≥150 or peripheral blood oxygen saturation (SpO_2) to FIO_2 ratio of ≥200; 8 indicates mechanical ventilation with pO_2 to FIO_2 ratio of <150 or SpO_2 to FIO_2ratio of <200 or use of vasopressors; 9 indicates mechanical

ventilation with a SpO_2 to FIO_2 ratio of <150 and vasopressors, dialysis, or extracorporeal membrane oxygenation; and 10 indicates the patient has died. Participants had to score the severity of their symptoms (mild: annoying but not limiting daily activities; moderate: limiting daily activities; or severe: unable to execute daily activities). Participants received a COVID-19 disease severity score of 3 when they rated at least one of their symptoms as severe.

Statistical analyses

Patient characteristics are presented as mean (SD), median (IQR), or frequencies and proportions depending on the type and distribution of the data. Additionally, symptomology of SARS-CoV-2 infections and COVID-19 related hospitalization rates stratified for SARS-CoV-2 variant are presented in bar charts. Logistic regression analyses were used to compare hospitalization rates of Omicron breakthrough infections between patients with rheumatic IMID's and healthy controls. Confounding was investigated for age, sex, cardiovascular disease, diabetes, obesity and chronic pulmonary disease using a forward selection procedure. Fisher's exact test was used to compare hospitalization rates between patients receiving anti-CD20 therapy and patients receiving any other immunosuppressant.

Univariable and multivariable logistic regression analyses were used to compare hospitalization rates between Wildtype/Alpha vaccination-naïve infections, Delta breakthrough infections and Omicron breakthrough infections in patients with rheumatic IMIDs. A priori, multivariable analyses were adjusted for age, sex, cardiovascular disease, pulmonary disease, diabetes and obesity based on pre-existing literature that identified these variables as potential risk factors for severe COVID-19. All patients with rheumatic IMIDs with vaccination-naïve Wildtype/Alpha infections (1), Delta breakthrough infections (2) or Omicron breakthrough infections were included for analyses. Data presented on Delta breakthrough infections are somewhat different from our previous publication (2), as only a subgroup of patients were included for analyses in the present study: participants who were only included in our own study and participants of the T2B! study who have previously been included in our own study.

Lastly, multivariable logistic regression analyses were used to explore associations between clinical determinants (age, sex, obesity, rheumatic IMIDs, cardiovascular disease, pulmonary disease, diabetes, vaccine type, history of SARS-CoV-2 and third SARS-CoV-2 vaccine dose) and the occurrence of Omicron breakthrough infections. Effect modification with rheumatic IMIDs was investigated for variables that showed a statistically significant association (P value below 0.05) with the occurrence of Omicron breakthrough infections (age, history of SARS-CoV-2 and third vaccine dose). A threshold of P below 0.05 was used for interaction terms.

SPSS version 27.0 was used for analyses. P-values below 0.05 were considered statistically significant.

Extended version strengths and limitations

Strengths of this study include the prospective monitoring of SARS-CoV-2 infections since the start of the COVID-19 pandemic in a large cohort of patients with rheumatic IMIDs treated with various immunosuppressants and healthy controls. This allowed us to directly evaluate differences in the disease severity of the SARS-CoV-2 Omicron infections compared to previous SARS-CoV-2 variants, and whether IMID patients are affected differently by changes in characteristics of SARS-CoV-2 compared to the general population. Second, almost all participating patients and controls were screened for SARS-CoV-2 antibodies prior to SARS-CoV-2 vaccination (1), which allowed us to reliably estimate the incidence of vaccination naïve SARS-CoV-2 infections (Wildtype or Alpha variant) and assess whether these infections would protect against Omicron breakthrough infections. This is unique, as most studies rely on PCR-confirmed diagnoses for identification of COVID-19 cases, which results in underestimated incidence rates, especially for infections that occurred when PCR-tests were not yet widely available to the public (i.e., during the pre-vaccination period of the COVID-19 pandemic). Third, as our cohort consisted for an important part of people above 60 years of age (8), and older age has been shown to be a major risk factor for severe COVID-19 (9), our data are applicable to IMID patients for whom detection of additional risk factors is most relevant.

Our study also has some limitations. First, the limited number of observed COVID-19 cases that required hospitalization precluded accurate risk-estimations and detailed analyses. Especially our results on treatment specific effects should therefore be interpreted with caution. Second, because of the limited number of hospitalized COVID-19 cases, we used the occurrence rather than severity of SARS-CoV-2 Omicron breakthrough infections to explore effects of clinical determinants. This might introduce bias, as the likelihood of getting infected with SARS-CoV-2 depends on peoples' behaviour towards infection-prevention measures. Hence, our finding that rheumatic IMIDs and older age are associated with a lower risk of Omicron breakthrough infections likely reflect stricter adherence to infection-prevention measures rather than immunological superiority (10). Third, control participants were not a random sample of the general population, but often people with close ties to patients with rheumatic IMIDs (eg, friends or family). Fourth, only antigen or PCR-test confirmed COVID-19 diagnoses were used to detect Omicron breakthrough infections among participants. As people with symptomatic disease are more likely to get tested for COVID-19, the proportion of asymptomatic disease that we observed is probably an underestimation. This could mean that our finding that hybrid immunity and booster vaccinations are associated with protection against getting infected with SARS-CoV-2 Omicron represents protection against a symptomatic infection rather than any infection. Studies using serological confirmation of Omicron infections would be necessary to confirm this hypothesis. Fifth, most participants in our study had received a booster vaccination within three months before infection with the SARS-CoV-2 Omicron variant, which means that our results mainly reflect short-

term effectiveness of SARS-CoV-2 vaccinations in immunosuppressed IMID patients. Longer follow-up will therefore be necessary to evaluate the durability of protective immunity in these patients. Sixth, while we compared the disease severity of different SARS-CoV-2 variants within the same study cohort, the proportion of participants with hybrid immunity and the average number of SARS-CoV-2 vaccinations received differed. Observed differences in hospitalization rates therefore not solely reflect altered pathogenicity of the SARS-CoV-2 virus. Lastly, we did not perform additional analyses to explore whether different immunosuppressants affect associations of hybrid immunity and booster vaccination with protection against Omicron breakthrough infections. As numerous studies have shown varying effects of immunosuppressants on humoral and cellular immune responses, it will be relevant to evaluate treatment specific effects on the risk of SARS-CoV-2 breakthrough infections in future studies.

Table S1. Characteristics of patients with rheumatic IMID's and healthy controls.				
	Patients (n=1882)		Healthy controls (n=708)	
Patient characteristics				
Age, years – mean (SD)	59	(12)	59	(12)
Female sex – no. (%)	1231	(65)	480	(68)
Male sex – no. (%)	651	(35)	228	(32)
Body-mass index, kg/m^2 – mean (SD)	26	(5)	25	(4)
Coexisting conditions – no. (%)				
Cardiovascular disease	245	(13)	48	(7)
Chronic pulmonary disease	217	(12)	40	(6)
Diabetes	102	(5)	24	(3)
Obesity	320	(17)	71	(10)
Autoimmune disease type – no. (%)				
Rheumatoid arthritis	1022	(54)	-	
Psoriatic arthritis	301	(16)	-	
Ankylosing spondylitis	264	(14)	-	
Axial or peripheral spondylarthritis	36	(2)	-	
Juvenile idiopathic arthritis	31	(2)	-	
Systemic lupus erythematosus	99	(5)	-	
Vasculitis	40	(2)	-	
Polymyalgia rheumatica	94	(5)	-	
Sjogren's disease	102	(5)	-	
Systemic sclerosis	41	(2)	-	
Mixed connective tissue disease	11	(1)	-	
Other rheumatic diseases	132	(7)	-	
Immunosuppressants – no. (%)				
No immunosuppressive medication	364	(19)	-	
csDMARDs	1045	(56)	-	
Methotrexate	777	(41)	-	
Hydroxychloroquine	249	(13)	-	
Sulfasalazine	95	(5)	-	
Azathioprine	46	(2)	-	
Biologics	749	(40)	-	
TNF inhibitor	578	(31)	-	
Anti-CD20 therapy	48	(3)	-	
IL-6 inhibitor	31	(2)	-	
Abatacept	42	(2)	-	
Other immunosuppressants	284	(15)	6	(1)
Prednisone	263	(14)	4	(0.4)
SARS-CoV-2 vaccination – no. (%)				
Number of vaccine doses				
One	17	(1)	11	(2)
Two	232	(12)	117	(17)
Three	1406	(75)	529	(75)
More than three	227	(12)	51	(7)
Vaccine type primary vaccination*				
AstraZeneca	352	(19)	159	(23)
Pfizer/BioNTech	1214	(65)	391	(55)
Moderna	206	(11)	105	(15)
Janssen	35	(2)	31	(4)
Mix	33	(2)	4	(1)
History of SARS-CoV-2 infection – no. (%)				
Wildtype/Alpha variant	249	(13)	109	(15)
Delta variant	83	(4)	30	(4)

*Data are mean (SD), or n (%). One person can be diagnosed with more than one disease and receive more than one immunosuppressive drug. IMID = immune-mediated inflammatory disease. DMARD = disease modifying anti-rheumatic drug. TNF = tumor necrosis factor. *Vaccine type was unknown for 42 IMID patients and 18 healthy controls; valid percentages are presented.*

Table S2. Characteristics of patients with rheumatic IMID's and healthy controls with an Omicron breakthrough infection.				
	Patients with rheumatic IMID's (n=431)		Healthy controls (n=210)	
	Ambulatory care (n=426)	Hospitalized/deceased (n=5)	Ambulatory care (n=209)	Hospitalized/deceased (n=1)
Patient characteristics				
Age, years – mean (SD)	53 (13)	59 (15)	55 (12)	54 (N.A.)
Female sex – no. (%)	289 (68)	4 (80)	149 (71)	1 (100)
Male sex – no. (%)	135 (32)	1 (20)	60 (29)	0 (0)
Body-mass index, kg/m^2 – mean (SD)	26 (4)	25 (5)	25 (4)	25 (N.A.)
Coexisting conditions – no. (%)				
Cardiovascular disease	46 (11)	2 (40)	10 (5)	0 (0)
Chronic pulmonary disease	46 (11)	2 (40)	13 (6)	0 (0)
Diabetes	18 (4)	0 (0)	4 (2)	0 (0)
Obesity	56 (13)	1 (20)	22 (11)	0 (0)
Immunosuppressants – no. (%)				
No immunosuppressive medication	89 (21)	1 (20)	-	-
csDMARDs	218 (51)	1 (20)	-	-
Methotrexate	146 (34)	1 (20)	-	-
Hydroxychloroquine	63 (15)	0 (0)	-	-
Sulfasalazine	18 (4)	0 (0)	-	-
Azathioprine	14 (3)	0 (0)	-	-
Biologics	200 (47)	3 (60)	-	-
TNF inhibitor	155 (36)	0 (0)	-	-
Anti-CD20 therapy	9 (2)	3 (60)	-	-
IL-6 inhibitors	7 (2)	0 (0)	-	-
Abatacept	8 (2)	0 (0)	-	-
Other immunosuppressants	50 (12)	1 (20)	-	-
Prednisone	46 (11)	1 (20)	-	-
Primary SARS-CoV-2 vaccination – no. (%)				
Number of vaccine doses*				
One	4 (1)	0 (0)	6 (3)	0 (0)
Two	71 (17)	0 (0)	42 (20)	1 (100)
Three	329 (77)	4 (80)	157 (23)	0 (0)
More than three	22 (5)	1 (20)	4 (2)	0 (0)
Vaccine type primary vaccination[#]				
AstraZeneca	67 (16)	1 (20)	39 (19)	0 (0)
Pfizer/BioNTech	275 (65)	4 (80)	108 (52)	0 (0)
Moderna	55 (13)	0 (0)	40 (19)	0 (0)
Janssen	10 (2)	0 (0)	15 (7)	1 (100)
Mix	9 (2)	0 (0)	0 (0)	0 (0)
Last dose within 3 months of infection**	301 (71)	3 (60)	142 (68)	0 (0)
History of SARS-CoV-2 infection – no. (%)				
Wildtype/Alpha variant	49 (12)	0 (0)	22 (10)	0 (0)
Delta variant	7 (2)	0 (0)	6 (3)	0 (0)

*Data are mean (SD), or n (%). One person can be diagnosed with more than one disease and receive more than one immunosuppressive drug. IMID = immune-mediated inflammatory disease. DMARD = disease modifying anti-rheumatic drug. TNF = tumor necrosis factor. *Number of vaccine doses before Omicron infection. **The most recent vaccine dose could be primary vaccinations or booster vaccinations. #Vaccine type was unknown for 10 IMID patients and 7 healthy controls.*

Table S3. Characteristics of IMID patients of vaccine-naïve and delta variant cohort.				
	Vaccine-naïve cohort (n=3080)		Delta variant cohort (n=2206)	
Patient characteristics				
Age, years – mean (SD)	57	(14)	58	(13)
Female sex – no. (%)	1990	(65)	1464	(66)
Male sex – no. (%)	1089	(35)	742	(34)
Body-mass index, kg/m^2 – mean (SD)	26	(5)	26	(5)
Coexisting conditions – no. (%)				
Cardiovascular disease	392	(13)	278	(13)
Chronic pulmonary disease	376	(12)	250	(11)
Diabetes	183	(6)	127	(6)
Obesity	497	(16)	370	(17)
Autoimmune disease type – no. (%)				
Rheumatoid arthritis	1714	(56)	945	(43)
Psoriatic arthritis	505	(16)	304	(14)
Ankylosing spondylitis	459	(15)	273	(12)
Axial or peripheral spondylarthritis	76	(3)	46	(2)
Juvenile idiopathic arthritis	51	(2)	38	(2)
Systemic lupus erythematosus	175	(6)	108	(5)
Vasculitis	81	(3)	59	(3)
Polymyalgia rheumatica	125	(4)	98	(4)
Sjogren's disease	190	(6)	125	(6)
Systemic sclerosis	61	(2)	44	(2)
Mixed connective tissue disease	27	(1)	15	(0.7)
Other rheumatic diseases	131	(4)	97	(4)
Immunosuppressants – no. (%)				
No immunosuppressive medication	679	(22)	505	(23)
csDMARDs	1605	(52)		
Methotrexate	1183	(38)	851	(38)
Azathioprine	52	(2)	45	(2)
Biologics	1111	(36)		
TNF inhibitor	885	(29)	643	(29)
Anti-CD20 therapy	71	(2)	70	(3)
Other immunosuppressants	395	(13)	756	(34)
SARS-CoV-2 infection				
No detected infection	2733	(89)	2112	(96)
SARS-CoV-2 infection	347	(11)	104	(5)
Ambulatory care	324	(10)	94	(4)
Hospitalization	23	(0.7)	10	(0.5)
ICU admission	3	(0.1)	2	(0.1)
Deceased	1	(0.03)	1	(0.05)

Data are mean (SD), or n (%). One person can be diagnosed with more than one disease and receive more than one immunosuppressive drug. IMID = immune-mediated inflammatory disease. DMARD = disease modifying anti-rheumatic drug. TNF = tumor necrosis factor

Table S4. Case description of hospitalized SARS-CoV-2 Omicron breakthrough cases.

	WHO COVID severity score	IMID diagnosis	Age	Sex	BMI	ISP*	Comorbidities	SARS-CoV-2 vaccine type	Number of vaccine doses	Sero-conversion after vaccination**
1	**Hospitalized without oxygen**	Healthy control	55	Female	25	-	-	Janssen	2	Positive[1]: *30 AU/mL*
2	**Hospitalized without oxygen**	Polymyalgia rheumatica	46	Female	25	-	-	Pfizer/BioNTech	2	Not tested
4	**Hospitalized without oxygen**	Rheumatoid arthritis	42	Female	22	Anti-CD20	-	Pfizer/BioNTech	3	Negative[2]
5	**Hospitalized with oxygen**	Polymyalgia rheumatica	70	Male	23	Prednisone	Cardiovascular disease	AstraZeneca	3	Positive[2]: *12.05 AU/mL*
3	**Hospitalized with oxygen**	Rheumatoid arthritis	74	Female	34	Anti-CD20 Methotrexate	Cardiovascular and chronic pulmonary disease	Pfizer/BioNTech	4	Negative[2]
6	**Deceased**	Myositis	68	Female	22	Anti-CD20 MMF	Chronic pulmonary disease	Pfizer/BioNTech	3	Negative[2]

*Table showing case descriptions of participants with a SARS-CoV-2 Omicron breakthrough infection that required hospitalization. BMI = Body-mass index. ISP = immunosuppressant. Immunosuppressants used at the time of vaccination. ** The concentration of SARS-CoV-2 antibodies in serum samples was measured using an in-house anti-receptor binding domain (RBD) IgG ELISA. A cutoff of 4 AU/mL represents 99% specificity in pre-outbreak serum samples (ie, collected before December, 2019); seroconversion after vaccination was based on this cutoff. Participants' most recent test result before Omicron infection and after vaccination are presented. [1]Participant had received 2 vaccine doses before sampling. [2]Participants had received 3 vaccine doses before sampling.*

Table S5. Regression analyses for determinants of the incidence and severity of SARS-CoV-2 omicron breakthrough infections				
A) Disease severity analyses Risk of COVID-19 related hospitalization for Omicron breakthrough infections				
Univariable model *(N:641, no. events: 6)*				
	Healthy controls*	1.00	-	
	Patients with rheumatic IMIDs	2.45	(0.29 – 21.13)	0.41
Multivariable model *(N:641, no. events: 6)* [#]				
	Healthy controls*	1.00	-	
	Patients with rheumatic IMIDs	1.48	(0.16 – 13.28)	0.72
B) SARS-CoV-2 variant analyses Risk of COVID-19 related hospitalization in patients with rheumatic IMIDs only				
Univariable model (N: 778, no. events: 28)				
	Wildtype/Alpha variant infections* [1]	1.00	-	
	Omicron variant infections [2]	0.17	(0.062 – 0.44)	**< 0.0001**
Multivariable model (N: 778, no. events: 28) [##]				
	Wildtype/Alpha variant infections* [1]			
	Omicron variant infections [2]	0.16	(0.060 – 45)	**< 0.0001**
Univariable model (N: 535, no. events: 16)				
	Delta variant infections*[2]	1.00	-	
	Omicron variant infections[2]	0.11	(0.037 – 0.33)	**< 0.0001**
Multivariable model (N: 535, no. events: 16) [##]				
	Delta variant infections*[2]	1.00	-	
	Omicron variant infections[2]	0.08	(0.023 – 0.28)	**<0.0001**
C) Exploratory analyses Associations with the occurence of Omicron breakthrough infections				
Multivariable model *(N:2590, no. events: 624)*[3]				
	Healthy controls*	1.00	-	
	Patients with rheumatic IMIDs	0.69	(0.56 – 0.85)	**<0.0001**
	Age	0.96	(0.95 – 0.97)	**<0.0001**
	Sex			
	Male sex*	1.00	-	
	Female sex	1.02	(0.83 – 1.25)	0.87
	Obesity	0.78	(0.59 – 1.04)	0.085
	Cardiovascular disease	1.05	(0.76 – 1.45)	0.78
	Pulmonary disease	1.18	(0.86 – 1.62)	0.32
	Diabetes	0.82	(0.54 – 1.45)	0.62
	Vaccine type			
	AstraZeneca*	1.00	-	
	Pfizer/BioNTech	1.04	(0.81 – 1.34)	0.75
	Moderna	1.01	(0.71 – 1.42)	0.97
	Janssen	0.85	(0.46 – 1.56)	0.59
	Mix	1.21	(0.54 – 2.70)	0.64
	History of SARS-CoV-2			
	Wildtype/Alpha variant	0.53	(0.40 – 0.72)	**<0.0001**
	Delta variant	0.24	(0.13 – 0.43)	**<0.0001**
	Third vaccine dose[4]	0.66	(0.50 – 0.87)	**0.0030**

*Table showing results of logistic regression analyses. Data are odds ratios (OR) with corresponding 95% confidence intervals (CI's) and P values. IMID = immune-mediated inflammatory disease. A) Includes IMID patients and healthy controls with an Omicron breakthrough infection, the outcome variable is COVID-19 related hospitalization. B) Includes IMID patients with Wildtype/Alpha and/or Delta and/or Omicron breakthrough infections, the outcome variable is COVID-19 related hospitalization. C) Includes all IMID patients and healthy controls with follow-up data on Omicron breakthrough infections, the outcome variable is the occurrence of Omicron breakthrough infections. *Reference group. [#]Adjusted for cardiovascular disease and chronic pulmonary disease. [##]Adjusted for age, sex, cardiovascular disease, pulmonary disease, diabetes and obesity. [1] Infections before SARS-CoV-2 vaccination. [2] Breakthrough infections; infections occurring after SARS-CoV-2 vaccination. P value < 0.05 was considered statistically significant. [3]Data on vaccine type were missing for 42 IMID patients and 18 healthy controls. [4] Reference group is participants who received less than three vaccine doses.*

Table S6. P-values of interaction terms of variables associated with the occurrence of Omicron breakthrough infections and having a rheumatic IMID.	
	Having a rheumatic IMID
Age	0.81
History of SARS-CoV-2*	0.31
Wildtype/Alpha variant	0.27
Delta variant	0.32
Third vaccine dose	0.45

Data are P values of interaction terms. *Overall P value.

Figures

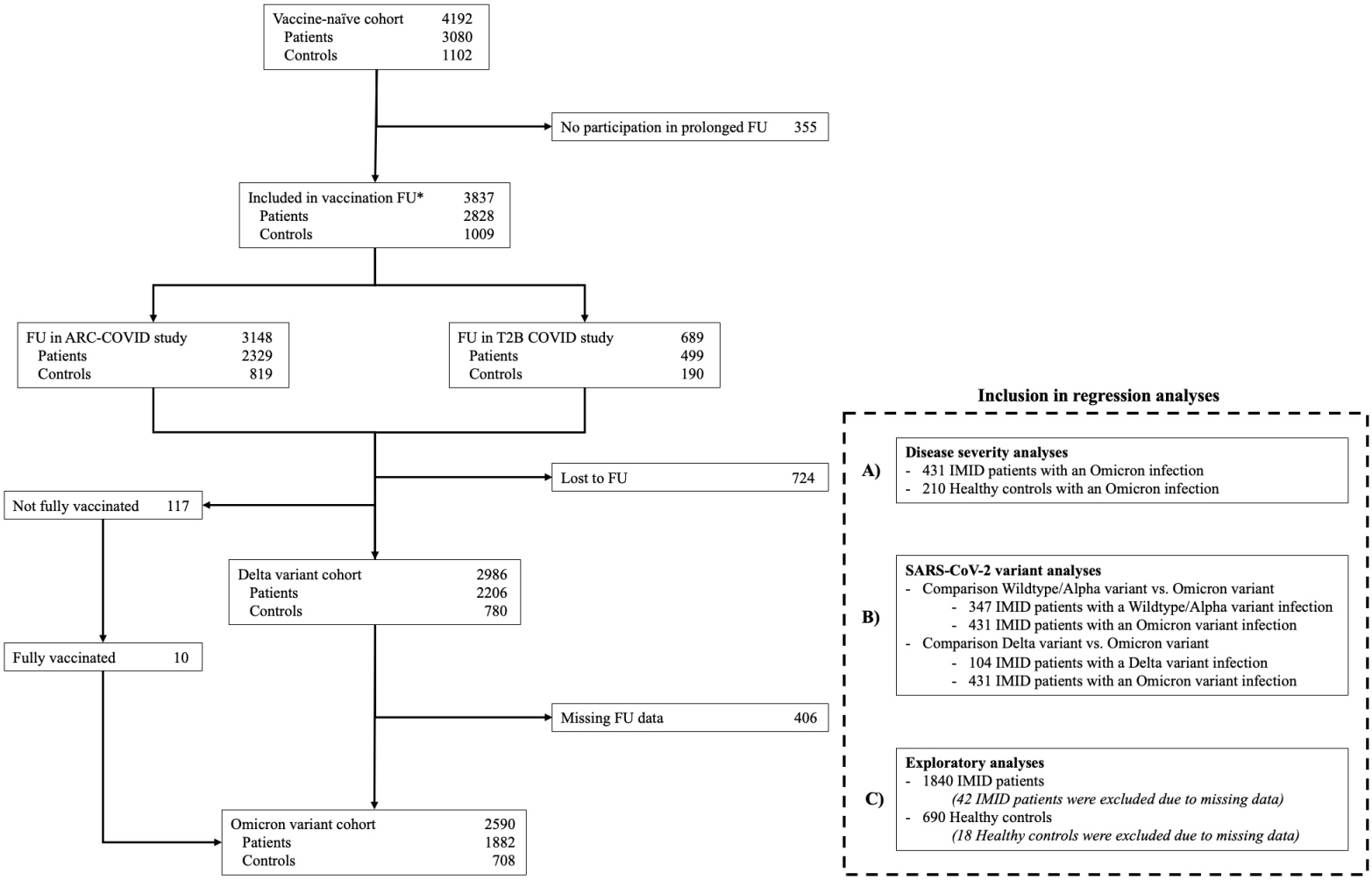

Figure S1. Flow-chart of study population.

*Dotted square shows information on participants that were included in regression analyses. *Participants from our study (ARC-COVID study) were invited to participants in a Dutch national vaccine trial of the Target-To-B! (T2B!) consortium when they fulfilled inclusion criteria for the study (T2B COVID study). Outcome variables for breakthrough infections were harmonized between both studies.*

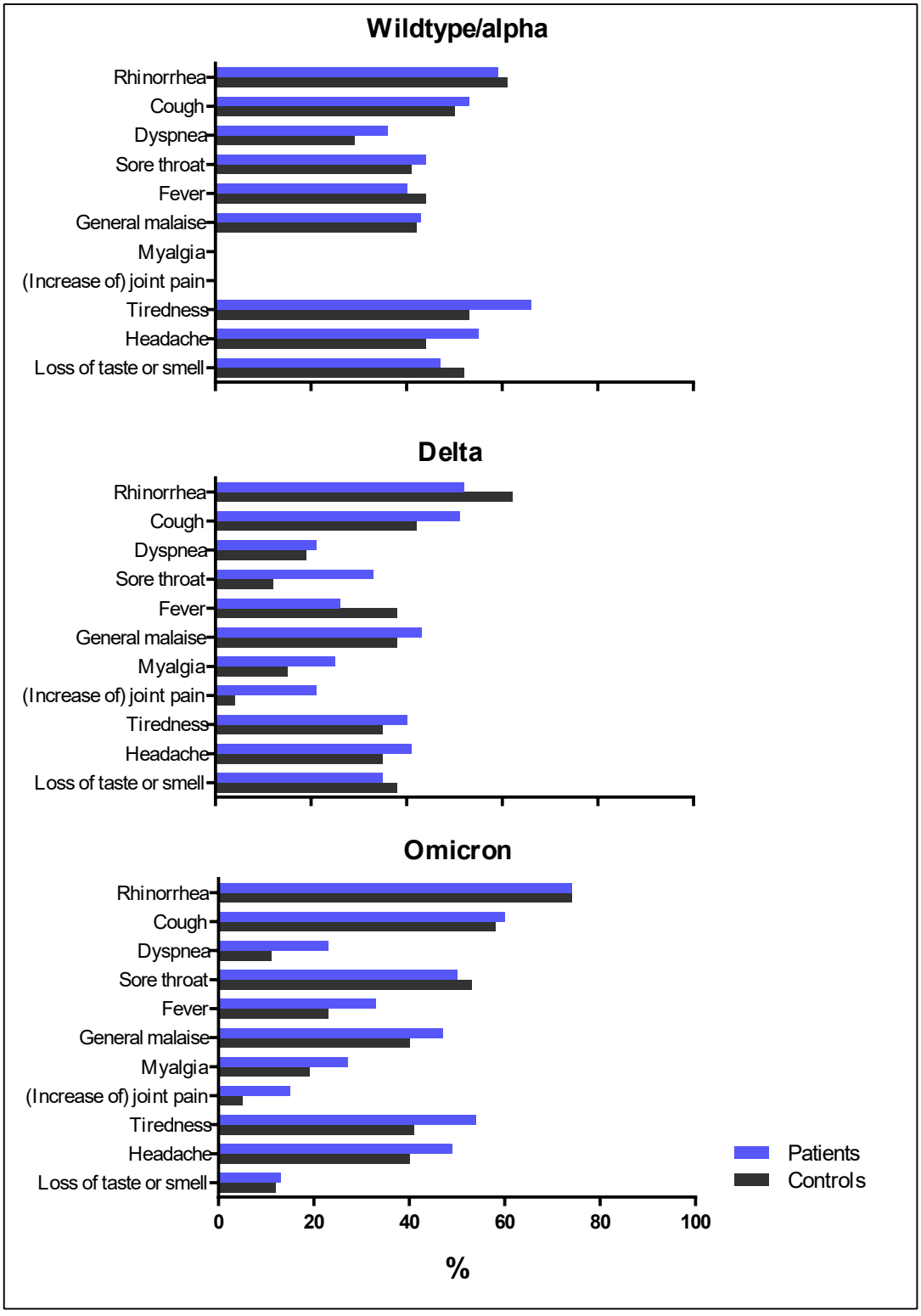

Figure S2. Symptomology of SARS-CoV-2 infections.

Figure showing the proportion of patients with rheumatic IMIDs (blue) and healthy controls (black) reporting COVID-19 related symptoms stratified for Wildtype/Alpha vaccination-naïve, Delta breakthrough and Omicron breakthrough infections. Myalgia and (increase of) joint pain were not yet included in the questionnaire during follow-up of vaccination-naïve SARS-CoV-2 infections.

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Survey to assess SARS-CoV-2 Omicron breakthrough infections

1. Have you experienced COVID-19 related symptoms since January 1, 2022? (E.g., cold-like symptoms, cough, sore throat, fever, headache, malaise, tiredness, loss of taste or smell etc.)
   Yes
   No

If "Yes" to question 1

1.1 Which of the following symptoms have you experienced?

- Runny nose
- Cough
- Shortness of breath
- Pain when breathing
- Sore throat
- Fever
- General malaise
- Nausea
- Diarrhea
- Stomach ache
- Muscle pain
- (Increase of) joint pain
- Irritability and/or confusion
- Tiredness
- Headache
- Loss of taste or smell
- Other

For each symptom indicated: number of days and severity of symptom (severity was assessed as multiple choice question: "mild, irritating but not limiting daily activities", "moderate, limiting daily activities", and "severe, unable to perform daily activities without help from others".

2. Have you been tested for COVID-19 since January 1, 2022? (e.g. nose/throat swab performed by yourself or healthcare worker)
   - No
   - Yes, once
   - Yes, multiple times

If answer to question 2 is not "no"

2.1 What kind of test(s) have been used?

- Rapid test (self-test, testing for access, antigen test)
- PCR test (throat AND nose swab performed by healthcare worker)
- Antibody test (blood draw)
- Other

2.2 Was/were one or more of the test result(s) positive? (Positive means that the test result indicates that you have COVID-19)

- Yes
- No

If answer to question 2.2 is "yes":

2.2.1 On which date have you been tested positive? (if you had multiple positive test results, enter the first date on which you tested positive)

3. Have you been hospitalized since January 1, 2022?
   - Yes
   - No

If answer to question 3 is "yes"

3.1 Have you been hospitalized because of the consequences of an infection with the coronavirus?
- Yes
- No

3.2 How many days have you been hospitalized?

3.3 Were you admitted to the intensive care unit?
- Yes
- No

If answer to question 3.3 is "yes"

3.3.1 How many days have you been on the intensive care unit?