Supplementary files:

Breakthrough infections with the SARS-CoV-2 omicron (B.1.1.529) variant in patients with immune-mediated inflammatory diseases

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Supplementary methods

Further details on methodology has been described before [1,2]

Recruiting centres
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 anti-CD20 (combination) therapies, cyclophosphamide, alemtuzumab and cladribine were defined as a last administration within 12 months prior to first vaccination or between the first and second vaccination. All other immunosuppressants were defined as active treatment as a last administration within 3 months prior to first vaccination or between the first and second vaccination. Combination therapies were grouped in the following order: any combination therapy involving anti-CD20 therapy, MMF, methotrexate TNF-inhibitors, and any other ISP. Start and stop dates of all immunosuppressants used since January 1st 2021 were retrieved from medical files, and for treatments with long-term effect (i.e. anti-CD-20 therapy or cyclophosphamide) since January 1st 2020. The following treatments were not regarded as systemic immunosuppressants in this study: any topical, inhaled, or rectal administered immunosuppressant, mesalazine, sulfasalazine, and budesonide.

Full in- and exclusion criteria
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. Participants who did not complete follow-up questionnaires on SARS-CoV-2 omicron breakthrough infections were excluded.

Vaccination campaign Netherlands
Vaccination for primary immunisation started in January 2021 in the Netherlands with one of the following vaccines: ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer/BioNtech), CX-024414 (Moderna), or Ad.26.COV2.S (Janssen). After recognizing that humoral responses were reduced after primary immunisation in several vulnerable groups, including some groups of IMID patients on specific immunosuppressants, additional

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vaccinations were implemented. Specifically, in September 2021, an additional ('third) vaccination with CX-024414 or BNT162b2 was offered to IMID patients on anti-CD20 (combination) therapy, sphingosine 1-phosphate receptor (S1P) modulators or mycophenolate mofetil (MMF) (combination) therapy based on our observation of strongly reduced seroconversion rates after vaccination in these medication groups.[2] For the analysis of this study, we considered the 'third' vaccination in this group as 'additional' vaccination and not part of the primary immunisation schedule. Additional ('booster') vaccinations with CX-024414 or BNT162b2 were advised for all individuals in the Netherlands starting from December 2021 onward. Individuals with a SARS-CoV-2 infection were advised to receive additional vaccinations at least three months after the last SARS-CoV-2 infection. Primary immunisations and "third" vaccinations were performed by the researchers as part of this study in some participants while in others, and all 'booster' vaccinations, vaccinations were performed by the relevant healthcare professionals.

Serum samples collected

Collection of serum samples was either by venipuncture or by fingerpick at home and serum was stored and analysed at the central laboratory of Sanquin in the Netherlands. All serological assays are in-house developed as described before.[3,4] The anti-RBD IgG enzyme-linked immunosorbent assay (ELISA) derived from the original alpha strain was used to measure SARS-CoV-2 antibodies, expressed in arbitrary units per litre (AU/mL).[3,4] A semi-quantitative total antibody RBD-Ab bridging ELISA was used to determine SARS-CoV-2 infections prior to first SARS-CoV-2 vaccination. Additionally, a semi-quantitative total antibody nucleocapsid (N)-Ab bridging ELISA was used to detect SARS-CoV-2 infections after SARS-CoV-2 vaccination.[3,4]

Data sharing

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

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Table S1. Characteristics of participants lost to follow-up

Table showing baseline characteristics of all participants included for analyses and participants that were lost to follow-up

	Participants included for analyses (n = 2172)		Participants lost to follow-up (n = 428)	
Group - no. (%)*				
IMID patients	2011	(93)	402	(93)
Healthy controls	161	(7)	26	(6)
Patient characteristics				
Age, years – mean (SD)	51	(13)	41	(14)
Female sex – no. (%)	791	(36)	195	(46)
IMID type, no. (%)*				
Rheumatic disease[a]	812	(37)	100	(23)
Neurological[b]	609	(28)	72	(17)
Gastro-enterological [c]	463	(21)	155	(36)
Dermatological[d]	288	(13)	101	(24)
Immunosuppressants – no. (%)*				
Other immunosuppressants	694	(32)	159	(37)
MTX	283	(13)	25	(6)
TNF-inhibitors	280	(13)	85	(20)
Anti-CD20	193	(9)	18	(4)
MMF	83	(4)	12	(3)
S1P modulator	60	(3)	5	(1)

[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: anti-CD20 therapy, sphingosine-1-phosphate receptor (S1P) modulators, and mycophenolate mofetil (MMF)

**:Percentages calculated as percentage of the total number in a category*

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

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Table S2. Characteristics separate IMID patients on immunosuppressants and IMID not on immunosuppressants and healthy controls

Table showing baseline characteristics of participants divided in to patients with immune-mediated inflammatory disorders on immunosuppressants, patients with immune-mediated inflammatory disorders not on immunosuppressants and healthy controls

	Patients with immune-mediated inflammatory disorders on immunsuppressants (n = 1593)		**Patients with immune-mediated inflammatory disorders not on immunsuppressants (n = 418)**		**Healthy controls (n = 161)**	
	With SARS-CoV-2 omicron breakthrough infection (n= 472)	**Without SARS-CoV-2 omicron breakthrough infection (n= 1121)**	**With SARS-CoV-2 omicron breakthrough infection (n= 126)**	**Without SARS-CoV-2 omicron breakthrough infection (n= 292)**	**With SARS-CoV-2 omicron breakthrough infection (n= 55)**	**Without SARS-CoV-2 omicron breakthrough infection (n= 106)**
Patient characteristics						
Age, years – mean (SD)	46 (13)	53 (13)	48 (13)	54 (12)	48 (12)	50 (10)
Female sex – no. (%)	317 (67)	657 (60)	84 (67)	192 (66)	44 (80)	69 (65)
IMID, no. (%)						
Rheumatic disease[a]	157 (33)	425 (38)	23 (18)	46 (16)	-	-
Neurological[b]	140 (30)	307 (27)	42 (33)	120 (41)	-	-
Gastro-enterological [c]	127 (27)	246 (22)	22 (18)	68 (23)	-	-
Dermatological[d]	48 (10)	143 (13)	39 (31)	58 (20)		
Prior SARS-CoV-2 infection– no. (%)						
Any infection prior omicron wave	61 (13)	156 (14)	21 (17)	42 (14)	14 (26)	43 (41)
Two infections prior to omicron wave	4 (0.4)	1 (0.2)	3 (1)	0 (0)	0 (0)	1 (1.8)
Additional vaccination prior SARS-CoV-2 omicron - no. (%)						
Any additional vaccination	386 (82)	1015 (91)	92 (73)	259 (89)	42 (76)	97 (92)
Two additional vaccinations	62 (13)	170 (15)	0 (0)	4 (1.4)	0 (0)	0 (0)
Available humoral response data after primary vaccination	**n = 430**	**n = 1027**	**n = 108**	**n = 255**	**n = 49**	**n = 94**
Seroconversion – no. (%)	353 (82)	897 (87)	105 (97)	251 (98)	48 (98)	94 (100)

[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: anti-CD20 therapy, sphingosine-1-phosphate receptor (S1P) modulators, and mycophenolate mofetil (MMF)

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

Table S3. Characteristics for IMID patients on strongly antibody-impairing immunosuppressants

Table showing baseline characteristics of patients with immune-mediated inflammatory disorders on strongly antibody-impairing immunosuppressants; i.e. anti-CD-20 (combination), MMF (combination) therapy and S1P-modulators

	Patients on anti-CD-20 (combination) therapy (n = 193)		**Patients on MMF (combination) therapy (n = 83)**		**Patients on S1P-modulators (n = 60)**	
	With SARS-CoV-2 omicron breakthrough infection (n= 64)	**Without SARS-CoV-2 omicron breakthrough infection (n= 129)**	**With SARS-CoV-2 omicron breakthrough infection (n= 27)**	**Without SARS-CoV-2 omicron breakthrough infection (n= 56)**	**With SARS-CoV-2 omicron breakthrough infection (n= 31)**	**Without SARS-CoV-2 omicron breakthrough infection (n= 29)**
Patient characteristics						
Age, years – mean (SD)	47 (13)	54 (13)	43 (13)	52 (14)	44 (10)	47 (8)
Female sex – no. (%)	39 (61)	79 (61)	23 (85)	34 (61)	22 (71)	17 (59)
IMID, no. (%)						
Rheumatic disease[a]	18 (28)	50 (39)	17 (63)	27 (48)	-	-
Neurological[b]	44 (67)	74 (57)	5 (19)	19 (34)	31 (100)	29 (100)
Gastro-enterological [c]	-	-	4 (15)	3 (5)	-	-
Dermatological[d]	2 (3)	4 (3)	1 (4)	6 (11)	-	-
Prior SARS-CoV-2 infection– no. (%)						
Any infection prior omicron wave	7 (11)	27 (21)	4 (14)	13 (23)	4 (13)	9 (31)
Two infections prior to omicron wave	0 (0)	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Additional vaccination prior SARS-CoV-2 omicron - no. (%)						
Any additional vaccination	59 (92)	126 (98)	22 (82)	53 (95)	30 (97)	28 (97)
Two additional vaccinations	21 (33)	64 (50)	3 (11)	23 (41)	13 (42)	17 (59)
Available humoral response data after primary vaccination – no. (%)	**n = 58**	**n = 123**	**n = 27**	**n = 54**	**n = 27**	**n = 25**
Seroconversion	20 (34)	47 (38)	22 (81)	39 (72)	9 (33)	13 (52)

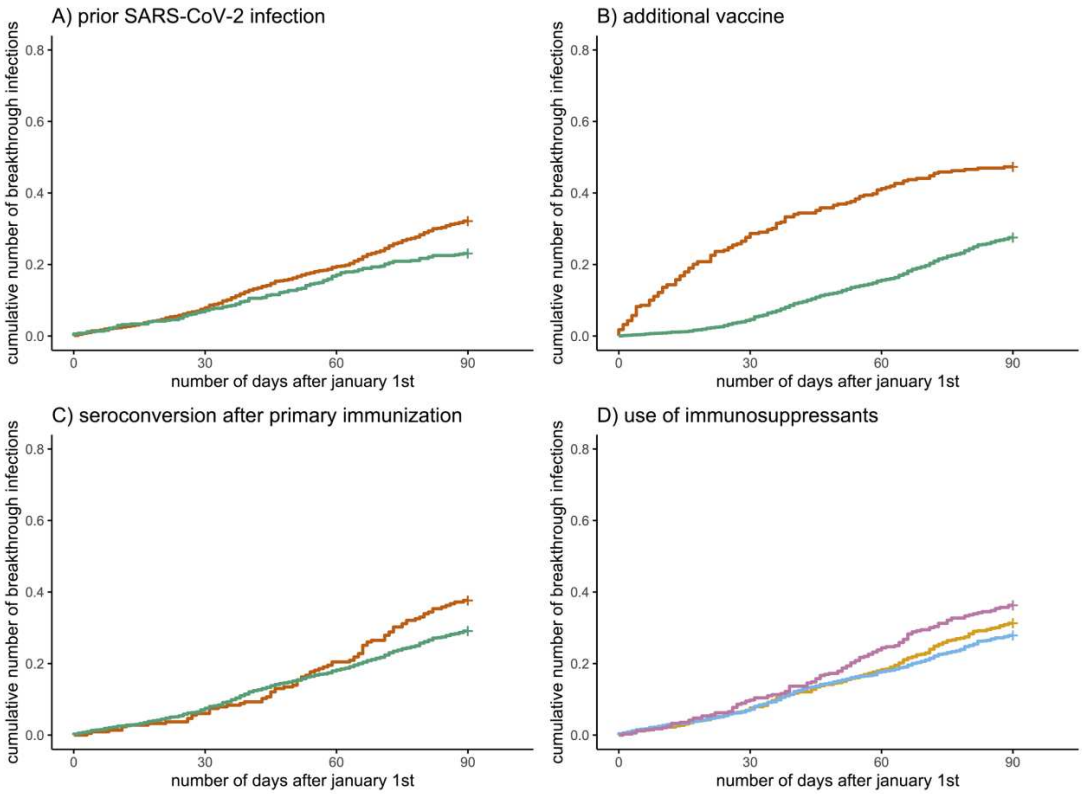
[a]: Including rheumatoid arthritis, spondylarthritis, systemic lupus erythematosus and Sjogren's syndrome, Vasculitis (small, medium and large vessel vasculitis and other forms of vasculitis except giant cell arteritis), Other rheumatological (giant-cell arteritis, polymyalgia rheumatica and others); [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: anti-CD20 therapy, sphingosine-1-phosphate receptor (S1P) modulators, and mycophenolate mofetil (MMF)

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

Figure S1. Cumulative event curves for the different clinical groups and determinants

Figure showing cumulative event curves for the different determinants included in the analysis. Panel A shows participants with (in green) and without prior SARS-CoV-2 infections. Panel B shows participants with (in green) and without any additional vaccine. Panel C shows participants with (in green) and without seroconversion after primary immunisation. Panel D shows cumulative event curves for participants without immunosuppressants (in yellow), patients treated with strongly antibody-impeding immunosuppressant (in purple) and patients treated with other immunosuppressants (in blue).



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