ORIGINAL RESEARCH

Characteristics and outcomes of SARS-CoV-2 breakthrough infections among double-vaccinated and triple-vaccinated patients with inflammatory rheumatic diseases

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ABSTRACT

Objective To analyse the clinical profile of SARS-CoV-2 breakthrough infections in at least double-vaccinated patients with inflammatory rheumatic diseases (IRDs).

Methods Data from the physician-reported German COVID-19-IRD registry collected between February 2021 and July 2022 were analysed. SARS-CoV-2 cases were stratified according to patients' vaccination status as being not vaccinated, double-vaccinated or triple-vaccinated prior to SARS-CoV-2 infection and descriptively compared. Independent associations between demographic and disease features and outcome of breakthrough infections were estimated by multivariable logistic regression.

Results In total, 2314 cases were included in the analysis (unvaccinated n=923, double-vaccinated n=551, triple-vaccinated n=803, quadruple-vaccinated n=37). SARS-CoV-2 infections occurred after a median of 151 (range 14–347) days in patients being double-vaccinated, and after 88 (range 14–270) days in those with a third vaccination. Hospitalisation was required in 15% of unvaccinated, 8% of double-vaccinated and 3% of triple-vaccinated/quadruple-vaccinated patients (p<0.001). Mortality was 2% in unvaccinated, 1.8% in the double-vaccinated and 0.6% in triple-vaccinated patients. Compared with unvaccinated patients, double-vaccinated (OR 0.43, 95% CI 0.29 to 0.62) and triple-vaccinated (OR 0.13, 95% CI 0.08 to 0.21) patients showed a significant lower risk of COVID-19-related hospitalisation. Using multivariable analysis, the third vaccination was significantly associated with a lower risk for COVID-19-related death (OR 0.26; 95% CI 0.01 to 0.73).

Conclusions Our cross-sectional data of COVID-19 infections in patients with IRD showed a significant reduction of hospitalisation due to infection in double-vaccinated or triple-vaccinated patients compared with those without vaccination and even a significant reduction of COVID-19-related deaths in triple-vaccinated patients. These data strongly support the beneficial effect of COVID-19 vaccination in patients with IRD.

Trial registration number EuDRACT 2020-001958-21.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients with inflammatory rheumatic disease (IRD), the use of SARS-CoV-2 vaccines is well tolerated and not associated with a significant increase of disease activity.

⇒ Recent data indicate the necessity of a third dose of SARS-CoV-2 vaccination to decrease the risk of severe SARS-CoV-2, especially in vulnerable patients.

WHAT THIS STUDY ADDS

⇒ In this group of patients with IRD, double-vaccinated and triple-vaccinated patients showed a significant lower rate of COVID-19-related hospitalisation.

⇒ Triple-vaccinated patients had a significant reduction of COVID-19-related deaths.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results support the recommendation to administer a third dose of COVID-19 vaccine in patients with IRD.

⇒ In vulnerable double-vaccinated patients with IRD, the use of monoclonal antibodies or antiviral drugs might be considered to reduce the risk of COVID-19-related death.

INTRODUCTION

Recent data show that individuals who have had a booster (triple) vaccination appear to be better protected against SARS-CoV-2—especially against the Omicron variant—than those who received double vaccination only.[1] In addition, the safety profiles of SARS-CoV-2 vaccines have been shown to be comparable in patients with inflammatory rheumatic diseases (IRDs) and individuals not suffering from IRD.[2]

The majority of patients with IRD develop a sufficient immune response after two-dose SARS-CoV-2 messenger RNA (mRNA) vaccination, although lower median antibody titres were observed in patients treated with mycophenolate and rituximab.[3] Cytokine inhibitors (eg, tumour necrosis factor inhibitors, TNFi), by contrast, do not seem to hamper sufficient SARS-CoV-2 antibody responses after vaccination.[3 4]

In summer 2021, several countries started to administer booster vaccine doses, primarily to elderly and vulnerable individuals, including immunocompromised individuals and healthcare workers.[5] In a small cohort of patients with IRD, the third ('booster') vaccination was followed by a substantial increase of antibody titres against SARS-CoV-2 spike protein in 80% of the patients who did not develop sufficient or even any titres on their initial vaccine series.[6] However, infection with SARS-CoV-2 has been observed in individuals after full vaccination, including patients with IRD.[7 8] In a case report, two patients with IRD with inflammatory joint diseases under treatment with TNFi were described who contracted SARS-CoV-2 infection after three doses of mRNA SARS-CoV-2 vaccination with a mild course and without the need for hospitalisation.[7] In 197 partially or double-vaccinated (DV) patients with IRD, breakthrough infections were reported.[8] More than half of the DV individuals who required hospitalisation received B-cell depleting treatment for their IRD before infection.[8] This study did not include data on breakthrough infection after a third dose of vaccination.[8]

So far, little is known about the frequency and the course of SARS-CoV-2 'breakthrough' infections in patients with IRD, who have been vaccinated twice or three times.

To investigate the frequency and course of SARS-CoV-2 breakthrough infections among patients with IRD, who had been vaccinated at least two times, data from the German COVID-19-IRD registry were analysed.

METHODS

Data from February 2021 to July 2022 were included in our analysis. Patients with double vaccination (primary course of vaccination) against COVID-19, at least 14 days prior to documented SARS-CoV-2 infection, were identified. Only cases of first SARS-CoV-2 infections were considered, no cases of reinfections. Beyond the type of IRD, immunomodulation as well as comorbidities, dates and type of vaccinations, and specifically the outcome of the SARS-CoV-2 infection were compared with unvaccinated (UV) patients with IRD who had contracted SARS-CoV-2. COVID-19-related complications, such as concomitant infections, thromboembolic events, myocarditis, heart failure and new onset of arrhythmia, were also recorded.

Data source

The German COVID-19 registry for patients with IRD was launched in March 2020 by the German Society for Rheumatology together with the Justus-Liebig-University Giessen. Rheumatologists from all over Germany voluntarily entered data on patients with IRD with SARS-CoV-2 infection into a web-based registry with implemented plausibility checks (www.covid19-Rheuma.de; for more details, see reference 9). Patients with a known IRD and positive testing for SARS-CoV-2 were included by their treating rheumatologists after registration. Patients had to have positive PCR-swabs for SARS-CoV-2 for inclusion in our registry. In contrast to other registries, presumptive diagnosis of COVID-19 based on suggestive symptoms, X-ray or CT findings or on other 'unknown' findings was not sufficient to enter the patients into the database. The definition of 'absence of immunomodulation' excludes all treatments with DMARDs and/or glucocorticoids. The definition of 'absence of relevant comorbidities' excludes comorbidities such as cardiovascular diseases (eg, heart failure, myocardial infarction, coronary artery disease), arrhythmia, arterial hypertension, bronchial asthma, chronic obstructive pulmonary disease, interstitial lung disease, chronic renal failure, liver cirrhosis, osteoporosis, pregnancy, diabetes mellitus, pulmonary hypertension, cancer/history of cancer, other relevant physician-reported comorbidities (individual input).

At the end of December 2020, vaccine-related questions were added to the registry, including whether patients had received a COVID-19 vaccine, and if so, which vaccine was given, how many doses and the dates of all received COVID-19 vaccinations.

Statistical analysis

Patients' characteristics were first analysed descriptively for each group (UV, DV, triple-vaccinated (TV) and quadruple-vaccinated (QV)). Due to the limited case number of QV breakthrough infections (n=37), further investigations focused on UV, DV and TV cases. Median was calculated for age, body mass index and time elapsed between second/third vaccine dose and SARS-CoV-2 infection. Categorical variables are reported as numbers and percentages. Groups were compared using nonparametric (χ^2, Fisher's exact test, Kruskal-Wallis' test) tests, depending on the measurement level of the variables and cell sizes in crosstabs. P values were calculated.

Univariate logistic regression was used to assess the individual association between COVID-19-related hospitalisation or COVID-19-related death (dependent variables) and patients' vaccination status. Age, gender, use of TNFi, the absence of immunomodulation and the absence of relevant comorbidities were included in the regression models as potential

Table 1 Patient characteristics

	Unvaccinated (reference)		Double-vaccinated		Triple-vaccinated		
	n	%	n	%	n	%	P value
	923		551		803		
Age (years, median, range)	55 (18–93)		55 (20–93)		56 (16–93)		0.630*
Female	603	65.3	356	64.6	576	71.7	**0.005†**
Body mass index (median, range)	26.5 (16–53)		26.7 (17–55)		25.8 (16–53)		**0.004***
1. Vaccine							
Moderna			29	5.3	56	7.0	
Pfizer/BioNTech			426	77.3	573	71.4	
AstraZeneca			56	10.2	139	17.3	
Janssen/Johnson&Johnson			17	3.1	4	0.5	
Nuvaxovid			1	0.2	5	0.6	
Unknown			22	4.0	26	3.2	
2. Vaccine							
Moderna			40	7.3	66	8.2	
Pfizer/BioNTech			459	83.3	644	80.2	
AstraZeneca			36	6.5	60	7.5	
Janssen/Johnson&Johnson			1	0.2	0	0	
Nuvaxovid			1	0.2	7	0.9	
Unknown			14	2.5	26	3.2	
3. Vaccine							
Moderna					201	25.0	
Pfizer/BioNTech					573	71.4	
AstraZeneca					‡	0.4	
Janssen/Johnson&Johnson					†	0.2	
Nuvaxovid					0	0	
Unknown					24	3.0	
Time between SARS-CoV-2 infection and last vaccination (days, median, range)			151 (14–347)		88 (14–270)		
IRD (multiple selection possible)							
Rheumatoid arthritis	393	42.6	240	43.6	331	41.2	0.681†
Spondyloarthritis	278	30.2	161	29.4	252	31.4	0.719†
Connective tissue diseases	132	14.3	74	13.4	116	14.2	0.856†
Other vasculitides	60	6.5	28	5.1	45	5.6	0.499†
ANCA-associated vasculitis	25	2.7	19	3.4	20	2.5	0.561†
Other type of IRD	93	10.1	51	9.3	74	9.2	0.798†
Immunomodulation (multiple selection possible)							
Glucocorticoids	247	26.8	134	24.3	194	24.2	0.392†
Prednisolone ≤5 mg/day	169		83		121		
Prednisolone 6–9 mg/day	10		5		7		
Prednisolone ≥10 mg/day	33		18		26		
Methotrexate, leflunomide, sulfasalazine	461	49.9	258	46.8	366	45.6	0.176†
Azathioprine	22	2.4	16	2.9	28	3.5	0.395†
Tumour necrosis inhibitors (adalimumab, certolizumab, infliximab, golimumab, etanercept)	192	20.8	125	22.7	197	24.5	0.180†
Other cytokine inhibitors (IL-6/IL-1/IL12/23/IL17 inhibition)	81	8.8	68	23.8	79	9.8	0.086†

Continued

Table 1 Continued

	Unvaccinated (reference)		Double-vaccinated		Triple-vaccinated		
	n	%	n	%	n	%	P value
Janus kinase inhibitors (baricitinib, tofacitinib, upadacitinib, filgotinib)	70	7.6	51	9.3	71	8.8	0.468†
Immunsuppressives (cyclosporine, mycophenolate, cyclophosphamide)	28	3.0	14	2.5	20	2.5	0.766†
Abatacept	10	1.1	8	1.5	10	1.2	0.824†
Rituximab	28	3.0	24	4.4	35	4.4	0.270†
Belimumab	8	0.9	7	1.3	7	0.9	0.704†
Immunoglobulins	‡	0.3	1	0.2	7	0.9	0.191‡
Apremilast	4	0.4	2	0.4	‡	0.4	1.000‡
Other immunmodulators (eg, colchicine)	51	5.5	18	3.3	29	3.6	0.057†
No immunmodulation	100	10.8	44	8.0	57	7.1	**0.018†**
Disease activity							
No/low	780	84.5	478	86.8	710	88.4	0.059†
Moderate/high	129	14.0	65	11.8	78	9.7	**0.024†**
Comorbidities (multiple selections possible)							
Arterial hypertension	287	31.1	172	31.2	229	28.5	0.428†
Other relevant comorbidities	168	18.2	110	20.0	130	16.2	0.197†
Heart failure/arrhythmia	93	10.1	67	12.2	68	8.5	0.084†
Diabetes mellitus	83	9.0	50	9.1	47	5.9	0.028†
Osteoporosis	52	5.6	35	6.4	74	9.2	**0.011†**
Chronic renal failure	47	5.1	29	5.3	48	6.0	0.704†
Cancer/history of cancer	26	2.8	19	3.4	22	2.7	0.719†
Chronic obstructive lung diseases	22	2.4	12	2.2	24	3.0	0.597†
Interstitial lung diseases	23	2.5	12	2.2	18	2.2	0.909†
Bronchial asthma	39	4.2	27	4.9	42	5.2	0.607†
Pregnancy	9	1.0	4	0.7	†	0.2	0.159‡
Pulmonal hypertension	7	0.8	2	0.4	†	0.2	0.340‡
Liver cirrhosis	4	0.4	1	0.2	‡	0.4	0.821‡
Absence of relevant comorbidities	350	37.9	250	45.4	371	46.2	**0.001†**
COVID-19-associated complications							
Hospitalisation	142	15.4	44	8.0	22	2.7	**<0.001†**
Invasive ventilation	25	2.7	11	2.0	1	0.1	**<0.001‡**
Relevant complications (eg, concomitant infection, thromboembolic events)	57	6.2	23	4.2	6	0.7	**<0.001†**
COVID-19-related death	18	2.0	10	1.8	5	0.6	0.050†

*Kruskal-Wallis test.
†χ^2 test (Pearson).
‡Fisher's exact test.
IRD, inflammatory rheumatic disease.

confounders. Results were reported as ORs including their respective 95% CIs. P values were reported to describe the statistical significance of the respective independent variable's influence on the COVID-19 hospitalisation and COVID-19-related death. P values <0.05 were considered significant.

Factors potentially associated with the COVID-19 outcome considered in the model were age, gender, use of TNF inhibitors, no immunomodulatory treatment and regarding the significant differences additionally absence of relevant comorbidities (see tables 1 and 2). Comedication rather than immunomodulatory/immunosuppressive drugs was not recorded in the registry, and therefore, could not be included in the model.

UV patients were defined as the reference group. Calculations were carried out using SPSS Statistics (IBM SPSS Statistics, V.26.0).

Table 2 Patient characteristics (hospitalised)

	Unvaccinated (reference)		Double-vaccinated		Triple-vaccinated		
	n	%	n	%	n	%	P value
	142		44		22		
Age (years, median, range)	65 (19–93)		65 (28–86)		67 (41–87)		0.685*
Female	89	62.7	23	52.3	18	81.8	0.065†
Body mass index (median, range)	27.9 (18–46)		27.6 (19–43)		26.45 (18–42)		0.560*
1. Vaccine							
Moderna			1	2.3	2	9.1	
Pfizer/BioNTech			34	77.3	16	72.7	
AstraZeneca			3	6.8	2	9.1	
Janssen/Johnson&Johnson			0	0	0	0	
Nuvaxovid			0	0	0	0	
Unknown			6	13.6	2	9.1	
2. Vaccine							
Moderna			3	6.8	2	9.1	
Pfizer/BioNTech			35	79.5	16	72.7	
AstraZeneca			4	9.1	0	0	
Janssen/Johnson&Johnson			0	0	0	0	
Nuvaxovid			0	0	1	4.5	
Unknown			2	4.5	3	13.6	
3. Vaccine							
Moderna					‡	13.6	
Pfizer/BioNTech					14	63.6	
AstraZeneca					0	0	
Janssen/Johnson&Johnson					0	0	
Nuvaxovid					0	0	
Unknown					5	22.7	
Time between SARS-CoV-2 infection and last vaccination (days, median, range)			149.5 (17–307)		78.5 (22–120)		
IRD (multiple selection possible)							
Rheumatoid arthritis	79	55.6	18	40.9	12	54.5	0.227†
Spondyloarthritis	22	15.5	6	13.6	1	4.5	0.490‡
Connective tissue diseases	15	10.6	10	22.7	4	18.2	0.091‡
Other vasculitides	9	6.3	3	6.8	1	4.5	1.000‡
ANCA-associated vasculitis	14	9.9	7	15.9	4	18.2	0.326‡
Other type of IRD	13	9.2	2	4.5	2	9.1	0.667‡
Immunomodulation (multiple selection possible)							
Glucocorticoids	72	50.7	23	52.3	15	68.2	0.310†
Prednisolone ≤5 mg/day	53	37.3	14	31.8	11	50.0	
Prednisolone 6–9 mg/day	1	0.7	1	2.2	0	0	
Prednisolone ≥10 mg/day	12	8.5	5	11	1	4.5	
Methotrexate, leflunomide, sulfasalazine	84	59.1	24	54.5	10	45.5	0.457†
Azathioprine	6	4.2	1	2.3	0	0	1.000‡
Tumour necrosis inhibitors (adalimumab, certolizumab, infliximab, golimumab)	16	11.3	4	9.1	3	13.6	0.833‡
Other cytokine inhibitors (IL-6/IL-1/IL12/23/IL17 inhibition)	5	3.5	3	6.8	2	9.1	0.124‡
Janus kinase inhibitors (baricitinib, tofacitinib, upadacitinib, filgotinib)	14	9.9	5	11.4	1	4.5	0.404‡

Continued

Table 2 Continued

	Unvaccinated (reference)		Double-vaccinated		Triple-vaccinated		
	n	%	n	%	n	%	P value
Immunsuppressives (cyclosporine, mycophenolate, cyclophosphamide)	4	2.8	5	11.4	2	9.1	**0.046‡**
Abatacept	3	2.1	2	4.5	2	9.1	0.109‡
Rituximab	16	11.3	15	34.1	7	31.8	**0.001†**
Belimumab	1	0.7	0	0	0	0	
Immunoglobulins	1	0.7	0	0	1	1.0	
Other immunmodulators	5	3.5	1	2.3	0	0	
No immunmodulation	9	6.3	2	4.3	0	0	
Disease activity							
No/low	111	78.2	30	68.2	20	90.9	0.106†
Moderate/high	21	14.8	14	31.8	2	9.1	**0.026‡**
Comorbidities (multiple selections possible)							
Arterial hypertension	74	52.1	26	59.1	12	54.5	0.718†
Other relevant comorbidities	47	33.1	17	38.6	6	27.3	0.634†
Heart failure/arrhythmia	34	23.9	17	38.6	6	27.3	0.162†
Diabetes mellitus	31	21.8	4	9.1	2	9.1	**0.015‡**
Osteoporosis	14	9.9	6	13.6	5	22.7	0.210†
Chronic renal failure	27	19.0	7	15.9	6	27.3	0.540†
Cancer/history of cancer	8	5.6	4	9.1	1	4.5	0.398‡
Chronic obstructive lung diseases	5	3.5	4	9.1	0	0	0.379‡
Interstitial lung diseases	9	6.3	6	13.6	3	13.6	0.149‡
Bronchial asthma	10	7.0	1	2.3	3	13.6	0.192‡
Pregnancy	2	1.4	0	0	0	0	
Pulmonal hypertension	1	0.7	1	2.3	1	4.5	
Liver cirrhosis	2	1.4	0	0	0	0	
Absence of relevant comorbidities	21	14.8	7	15.9	2	9.1	0.785‡
COVID-19-associated complications							
Invasive ventilation	25	17.6	11	25.0	1	4.5	0.112‡
Relevant complications (eg, concomitant infection, thromboembolic events)	50	35.2	19	43.2	4	18.2	0.128‡
COVID-19-related death	18	12.7	10	22.7	5	22.7	0.182†

*Kruskal-Wallis test.
†χ^2 test (Pearson).
‡Fisher's exact test.
IRD, inflammatory rheumatic disease.

Results

Patient characteristics

Since the beginning of the registry, until July 2022, 5296 cases of SARS-CoV-2 infection were reported. In the observation period (February 2021 until July 2022), 2688 cases were reported. After excluding cases with missing information regarding vaccination status, SARS-CoV-2 reinfection, only single vaccination as well as last vaccination less than 14 days prior to documented SARS-CoV-2 infection, 2314 cases remained for the analysis (UV n=923, DV n=551, TV n=803, QV n=37). Most of the patients were female (UV: 65.3%, DV: 64.6%, TV: 71.7%, QV: 65.9%). The median age was over years 55 (UV, DV) and 56 (TV, table 1, data of QV are included in online supplemental table 1). More than half of the patients had an inflammatory joint disease, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and enteropathic arthritis, followed by connective tissue diseases, vasculitides and other types of IRD. In more than 80% of all cases, no or only low disease activity was reported at the time of SARS-CoV-2 infection (table 1). Immunomodulatory treatment and comorbidities at the onset of SARS-CoV-2 infection are listed in table 1.

Among UV, DV and TV patients, there were neither significant differences regarding the type of IRD nor age (table 1). In addition, no significant differences
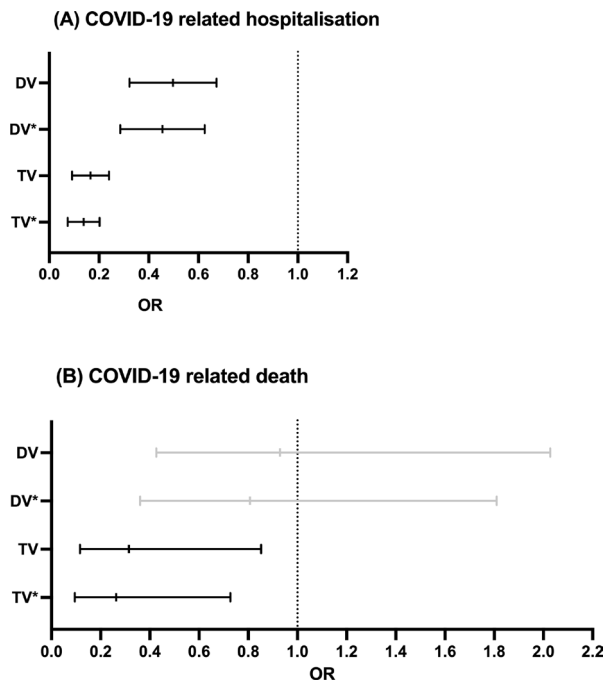
(A) COVID-19 related hospitalisation

(B) COVID-19 related death

Figure 1 COVID-19-related hospitalisation. (B) COVID-19-related death. Results of the univariate and multivariable logistic regression reported as ORs and 95% CIs for the main outcome parameter of this analysis. Unvaccinated patients were defined as reference category. Associations with COVID-19-related hospitalisation are shown in (A) and with COVID-19-related death in (B). (Grey) indicates non-significant data. *Indicates multivariable analyses adjusted for age, gender, use of TNF inhibitor, no immunomodulation and absence of any relevant comorbidities. DV, double vaccinated; TNF, tumour necrosis factor; TV, triple vaccinated.

could be detected regarding immunomodulation (table 1). The proportion of cases without any relevant comorbidity differed significantly (UV: 37.9%, DV: 45.4%, TV: 46.2%, p=0.001).

VACCINES
Most patients received Pfizer/BioNTech vaccine for their first, second and third vaccination (table 1). Novavax's protein-based vaccine was used in n=6 patients for the second vaccination and in n=8 patients for the third vaccination. All vaccines available in Germany were reported (table 1).

Course of SARS-CoV-2 infection
COVID-19-related hospitalisations were lowest in TV with 2.7% (n=22/803), more common in DV with 8.0% (n=44/551) and highest in UV patients with 15.4% (n=142/923, χ^2(p)<0.001). COVID-19-related complications were significantly more frequently reported in UV with 6.2% (n=57/923), followed by 4.2% in DV (n=23/551) and 0.7% in TV (n=6/803, p<0.001). While n=18/923 (2.0%) UV patients died, a lower frequency of deaths was reported in DV (n=10/551, 1.8%) and TV (n=5/803, 0.6%) patients (χ^2(p)=0.05).

Patients requiring hospitalisation were in median older compared with non-hospitalised patients, without notable differences regarding vaccination (UV: 65 (19–93) years, DV: 65 (28–86) years, TV: 67 (41–97) years). In DV and TV patients, the use of immunosuppressive medication and rituximab was significantly more often reported than in UV (table 2). Compared with other comorbidities, diabetes mellitus was significant less often reported in DV and TV patients (table 2).

Association of COVID-19 vaccination with COVID-19-related hospitalisation and death
In the univariate logistic regression, DV (OR 0.48, 95% CI 0.33 to 0.68) and TV (OR 0.16, 95% CI 0.10 to 0.25) were significantly associated with a lower risk of hospitalisation (table 3, figure 1A). Multivariable logistic regression, including age, gender, use of TNFi, no immunomodulation and the absence of relevant comorbidities, confirmed a significantly lower risk for hospitalisation in DV (OR 0.43, 95% CI 0.29 to 0.62) and TV (OR 0.13, 95% CI 0.08 to 0.21) patients (table 3, figure 1A).

Regarding COVID-19-related death, in the univariate logistic regression, only TV (OR 0.32, 95% CI 0.12 to 0.85) was significantly associated with a lower risk (table 4, figure 1B). Multivariable logistic regression, including age, gender, use of TNFi, no immunomodulation and the absence of any relevant comorbidities, still revealed a significant lower risk of COVID-19-related death in TV (OR 0.26, 95% CI 0.09 to 0.71) patients (table 4, figure 1B).

Discussion
To our knowledge, these are the first data comparing the outcome of breakthrough infections in DV and TV patients with IRD to UV patients with IRD with

Table 3 Logistic regression regarding COVID-19-related hospitalisation

	Double-vaccinated		Triple-vaccinated		Unvaccinated
	OR (95% CI)	P value	OR (95% CI)	P value	(reference)
Hospitalisation (univariate)	0.477 (0.334 to 0.682)	<0.001	0.155 (0.098 to 0.245)	<0.001	Ref.
Hospitalisation (multivariable analysis*)	0.426 (0.292 to 0.621)	<0.001	0.128 (0.080 to 0.207)	<0.001	Ref.

*Adjusted for age, gender, use of TNF inhibitor, no immunomodulation and absence of any relevant comorbidities.
TNF, tumour necrosis factor.

Table 4 Logistic regression regarding COVID-19-related death

	Double-vaccinated		Triple-vaccinated		Unvaccinated (reference)
	OR (95% CI)	P value	OR (95% CI)	P value	
COVID-19-related death (univariate)	0.929 (0.426 to 2.028)	0.854	**0.315 (0.116 to 0.852)**	**0.023**	Ref.
COVID-19-related death (multivariable analysis)	0.807 (0.360 to 1.810)	0.602	**0.263 (0.095 to 0.727)**	**0.010**	Ref.

*Adjusted for age, gender, use of TNF inhibitor, no immunomodulation, and absence of any relevant comorbidities
TNF, tumour necrosis factor.

SARS-CoV-2 infections in a large group of patients with IRD.

Use of immunosuppressives (including rituximab) was significantly more frequently reported in DV and TV patients requiring hospitalisation due to breakthrough infection compared with UV inpatients. This is in accordance with previous studies showing an increased risk of severe COVID-19 regarding the use of rituximab and other immunosuppressives.[10–13] Breakthrough infections in DV and TV patients could be due to impaired immune response on vaccination resulting in lower titres of neutralising antibodies against SARS-CoV-2. This occurs especially on B-cell depleting therapy with rituximab. In solid-organ transplant recipients, administration of the third dose of mRNA COVID-19 vaccines resulted in a pronounced increase of antibody titres.[14] Likewise, the third dose resulted in seroconversion of 44% of individuals who had remained seronegative on the first two vaccinations.[14] Since antibody titres were not part of the data set collected in our registry, no association between breakthrough infections and antibody titres

could be retrieved. However, until now, no threshold has been identified for the minimum neutralising antibody titre required for protective immunity. Therefore, studies examining infection rates and antibody titres postvaccination in healthy and in immunosuppressed populations would be necessary.[15]

In our study, no relevant differences regarding the rate of different types of vaccines could be observed in DV and TV patients. Nevertheless, differences in immune response regarding different type of vaccines could already be observed, which might have in influence on the course of breakthrough infections.[16] COVID-19 vaccination involves numerous immune responses such as activation of lymphocytes and producing of neutralising antibodies. However, other pathways such as kinetics involved in cytokines and their receptors, and stimulation of non-T cell responses remain poorly understood. Potential differences depending on the type of vaccines might have an impact on immune response and thus on the outcome of breakthrough infection.[17]

Our findings support the relevance of triple vaccination for patients with IRD, since in this cohort of patients, triple vaccination was associated with lower rate of hospitalisation and fatal outcome compared with UV. Double vaccination was not significantly associated with lower rate, as in our study only TV patients (n=56) showed a significantly reduced rate of COVID-19-related deaths. Data of the general population were not recorded. But our data are in line with recent published data regarding outcome of breakthrough infection in patients with cancer.[18]

The strengths of this study are (1) a considerable large number of breakthrough infections in IRDs, (2) the homogenicity of the data that are retrieved from one healthcare system, so all patients received the same standard of medical care and (3) the collection of data by the treating rheumatologists rather than the patients or their relatives. In addition to missing antibody titres, further limitations are (1) a reporting bias which could lead to more severe cases of breakthrough infections, (2) the cross-sectional data collection. It needs to be mentioned that most cases were reported from private practices who performed/organised the vaccinations in conjunction with the general physicians. (3) Despite the large sample size, the results of our study should not be interpreted as
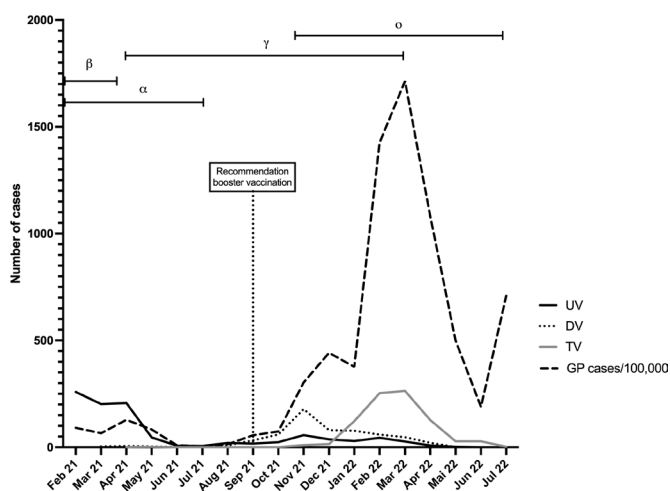

Figure 2 Time course of registry data and number of SARS-CoV-2 infections in the general population in Germany. Number of cases reported in the registry regarding the status of vaccination: unvaccinated (UV), double-vaccinated (DV), triple-vaccinated (TV) and cases of SARS-CoV-2 infection in the general German population (GP) per 100 000 individuals as reported from the Robert-Koch institute. The period of dominance of each virus mutation (α, β, γ, ο) in Germany is shown at the top.

incidence rates. We restricted our analysis to confirmed cases of SARS-CoV-2 infection. (4) Although we were able to adjust for several potential confounders in our models, there may still be residual unmeasured confounding. (5) We did not have data available on disease duration or prior medication use, apart from what was reported at the time of SARS-CoV-2 infection. (6) Finally, due to the given caring situations and the German healthcare system, information of type of virus mutation was not available for most of the patients in this dataset. However, using a specific period regarding date of SARS-CoV-2 infection, this might minimise the effect of infection with different type of virus mutation.

With the beginning of the COVID-19 vaccination campaign which began on 26 December 2020 in Germany, prioritisation rules of specific population groups who should be vaccinated first were established to enable a fair distribution regarding the risk profile of individuals. Depending on the prioritisation rules, patients with IRD younger than 70 years old belonged to group 4 of prioritisations. This group received first vaccine not earlier than spring/summer 2021. As the median age in all three groups was around 55 years, it should be considered that at the beginning of the observation period most patients were UV, and the number of UV patients decreased over time (figure 2). The time between last vaccination and infection might decrease due to the time of recommendation of booster vaccination, which was in September 2021 in Germany. The time course of the pandemic and the number of cases reported in the registry were included in figure 2 to show possible influences of the pandemic on the number of cases depending on the vaccination status in the registry.

Taken together, our findings support the general recommendation to administer a third dose of SARS-CoV-2 vaccines in patients with IRD.

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