Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

appear to confer protection from breakthrough infection.

This is the largest prospective study to investigate clinical outcomes related to breakthrough infection and was adequately sized to investigate specific immunosuppressive medications. Few severe outcomes occurred, and these were more common in the immunosuppressed participants with immune-mediated inflammatory diseases, particularly among those on B cell-depleting therapies. These patients remain susceptible to poor outcomes even after vaccination,[9] so strategies such as pre-exposure prophylaxis or additional vaccine doses should be strongly considered for this population.

Although there were some signals for breakthrough infection in specific patient groups (eg, seronegative status and some comorbidities), the findings of Boekel and colleagues are reassuring to patients who are immunosuppressed. After vaccination, overall rates and clinical severity of breakthrough infections among patients with immune-mediated inflammatory diseases was similar to among healthy controls. How subsequent variants, such as omicron (B.1.1.529) that might confer reduced vaccine effectiveness, will affect infection rates remains unknown. Patients with immune-mediated diseases who are immunosuppressed might have accelerated waning immunity, placing them at risk over time after vaccine receipt. Therefore, quantifying the effect of additional vaccine doses on breakthrough infection with contemporary circulating variants is needed. Finally, although the findings here offer some evidence that humoral responses confer clinical protection, the specific threshold that offers protection remains unclear. Those with absent humoral responses remain at risk for breakthrough infection, but we continue to caution clinicians to not overinterpret anti-spike antibody levels as a surrogate of protection at the individual level.

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Effectiveness of COVID-19 vaccination in immune-mediated inflammatory diseases

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The rapid development of safe and effective COVID-19 vaccines was a hallmark achievement in the pandemic. However, patients with immune-mediated inflammatory diseases were excluded from vaccine clinical trials and might be vulnerable to SARS-CoV-2 breakthrough infection due to immunosuppression and altered immunity.[1,2] Indeed, studies showed lower humoral responses after COVID-19 vaccination in these patients than in healthy controls.[3,4] Although most patients who are immunosuppressed had only a slightly reduced humoral response after COVID-19 vaccination, some medications, such as B cell-depleting therapies, are associated with severely reduced response.[3,4] There had been no previous systematic evaluation to quantify

the effectiveness of COVID-19 vaccination among patients with immune-mediated inflammatory diseases.

In *The Lancet Rheumatology*, Jessica Widdifield and colleagues[5] report on the effectiveness of COVID-19 vaccination among patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease from Ontario, Canada. Between March 1 and Nov 22, 2021, the authors identified 2127 (5·9%) test-positive cases among 36 145 individuals with rheumatoid arthritis who were tested for SARS-CoV-2, 476 (6·1%) test-positive cases among 7863 individuals with ankylosing spondylitis tested, 3089 (6·5%) test-positive cases among 47 199 individuals with psoriasis tested, and 1702 (5·4%) test-positive cases among 31 311 individuals with inflammatory bowel disease tested. Effectiveness of two doses of mRNA-based COVID-19 vaccines (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) against infection was more than 79% across all diseases.[5] Effectiveness against severe COVID-19 outcomes (defined as admission to hospital or death due to COVID-19) was even higher, ranging 92–97%.[5] These findings will immediately be helpful to clinicians and patients to gauge expectations of protection after vaccination. This might help combat vaccine hesitancy[6] by providing direct evidence that COVID-19 vaccines are highly effective in patients with immune-mediated inflammatory diseases.

Some methodological considerations of this investigation are noteworthy. First, the sample was population based from the entire province of Ontario, and used validated algorithms with high accuracy to identify individuals with the immune-mediated inflammatory diseases studied. The authors were able to link registries to identify dates of vaccine doses, SARS-CoV-2 testing, hospitalisations, and deaths. Second, they used a test-negative design to estimate vaccine effectiveness. This method has previously been reported to protect against bias by limiting the analysis to patients with similar access to and indications for testing, while assuring that the controls did not have COVID-19.[7] Rather than analysing all patients, the authors only examined those who presented for SARS-CoV-2 testing. This approach is a stronger study design than analysing the entire database and assuming that everyone without positive tests did not have COVID-19. Third, the authors examined a number of vaccine doses and the duration between vaccination and testing to look for waning effectiveness. They found moderate effectiveness after a single vaccine dose, but high effectiveness after two or three doses. Although there was some slight waning in effectiveness, vaccination remained highly effective even beyond 120 days after the second dose. Thus, the evidence generated here is rigorous to conclude that COVID-19 vaccines are effective in patients with these immune-mediated inflammatory diseases.

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Some limitations and future research directions are worth noting. First, the investigators only examined four immune-mediated inflammatory diseases because of limitations in accurately identifying conditions. How one might extrapolate these results to conditions not studied (eg, to systemic lupus erythematosus, or more diverse populations) is not clear. Notably, B-cell depletion, mycophenolate mofetil, and calcineurin inhibitors (each associated with impaired humoral response to vaccination[3,4]) are not typically used to treat most diseases studied by Widdifield and colleagues, with the exception of some patients with rheumatoid arthritis who might receive B cell-depleting therapy.[8] Thus, analysing patient populations for whom B-cell depletion is used more frequently, such as those with systemic vasculitis, might have yielded different results. Second, data on immunosuppressive medication use was unavailable and probably confounds results on an individual level. Patients on B cell-depleting therapies are likely to remain vulnerable even after vaccination.[8,9] Future studies should assess risk of breakthrough infection associated with specific immunosuppressive medications. Third, most patients included in the study received BNT162b2, so outcomes after receipt of this vaccine drove results. A sensitivity analysis suggested that mRNA-1273 might be even more effective. Future studies should examine differences in different types of vaccines for protection in patients with immune-mediated inflammatory diseases. Fourth, data for the study were collected before the omicron (B.1.1.529) variant wave of the pandemic, when vaccine effectiveness was reported to significantly decrease in the general population,[10] perhaps due to waning vaccine effect, behavioural changes, and evolution away from the ancestral SARS-CoV-2 strain for which vaccines were developed. Thus, repeating similar analyses for variants with longer time since vaccine receipt will be important because vaccine effectiveness

is ever-changing with new variants. These future studies might provide rationale for additional vaccine doses for patients who are immunosuppressed or use of novel vaccines against contemporary viral variants.

In summary, these important results confirm that the COVID-19 vaccines were highly effective against infection and severity among patients with immune-mediated inflammatory diseases. These findings should encourage continued uptake of COVID-19 vaccination and future research related to waning effects, the effectiveness of additional vaccine doses, and influence of specific immunosuppressive medications.

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Factors associated with poor antibody response to third-dose SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases

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Many immunosuppressed patients with rheumatic and musculoskeletal disease have a poor antibody response to two-dose SARS-COV-2 mRNA vaccination,[1,2] prompting widescale authorisation of a third vaccine dose for these patients. High antibody concentrations are required to overcome immune evasion by variants of concern in immunocompetent patients,[3] and although a third dose augments the immune response against SARS-CoV-2 in some immunosuppressed patients,[4,5] it is uncertain whether this response is sufficient for protection. Thus, identifying patients with rheumatic and musculoskeletal disease with poor response following a third dose is important in the selection of appropriate candidates for further medical interventions such as additional vaccine doses or prophylactic therapies. Herein, we describe the antibody response and factors associated with poor antibody response following a third vaccine dose in immunosuppressed patients with rheumatic and musculoskeletal disease.

Patients with rheumatic and musculoskeletal disease (aged ≥18 years) in the USA on immunosuppression without previous known COVID-19 who completed three-dose SARS-CoV-2 vaccination (two-dose mRNA series followed by single mRNA or adenoviral vector dose) were recruited via a social media campaign and provided informed consent electronically. This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540). Clinical characteristics were collected via participant report. Serial antibody responses were assessed using the semi-quantitative Roche Elecsys