COVID-19 vaccine hesitancy in inflammatory arthritis patients: serial surveys from a large longitudinal national Australian cohort

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Abstract

Objectives: To determine COVID-19 vaccine hesitancy rates in inflammatory arthritis patients and identify factors associated with changing vaccine hesitancy over time.

Methods: Prospective cohort study of inflammatory arthritis patients from community and public hospital outpatient rheumatology clinics enrolled in the Australian Rheumatology Association Database (ARAD). Two surveys were conducted, one immediately prior to (pre-pandemic) and then approximately one year after the start of the pandemic (follow-up). COVID-19 vaccine hesitancy was measured at follow-up and general vaccine hesitancy was inferred pre-pandemic; these were used to identify factors associated with fixed and changing vaccine beliefs, including sources of information and broader beliefs about medication.

Results: Of the 594 participants who completed both surveys, 74 (12%) were COVID-19 vaccine hesitant. This was associated with pre-pandemic beliefs about medications being harmful ($p<0.001$) and overused ($p=0.002$), with stronger beliefs resulting in vaccine hesitancy persistent over two time points ($p=0.008$, $p=0.005$). For those not vaccine hesitant pre-pandemic, the development of COVID-19 vaccine hesitancy was associated with a lower likelihood of seeking out vaccine information from healthcare professionals ($p<0.001$). COVID-19 vaccine hesitancy was not associated with new influenza vaccine hesitancy ($p=0.138$).

Conclusion: In this study of vaccine beliefs before and during the COVID-19 pandemic, factors associated with COVID-19 vaccine hesitancy in inflammatory arthritis patients varied, depending on vaccine attitudes immediately prior to the start of the pandemic. Fixed beliefs reflected broader views about medications, while fluid beliefs were highly influenced by whether they sought out information from healthcare professionals, including rheumatologists.

Keywords: rheumatic disease, vaccine hesitancy, COVID-19, patient education

Key messages

- COVID-19 vaccine hesitant patients reported less advice from healthcare professionals and more from peers/online.
- COVID-19 vaccine hesitant patients had varied beliefs, depending on their vaccine acceptance prior to COVID-19.
- COVID-19 vaccine hesitancy was not associated with new influenza vaccine hesitancy.

Introduction

The widespread uptake of effective vaccines has been the cornerstone of the COVID-19 pandemic response, reducing symptomatic and severe disease despite variants(1). Particularly critical is vaccine uptake among rheumatology patients, not only to reduce their individual risk, but also to limit the extent of future public health measures designed to protect patients like them(2,3). Despite this imperative to vaccinate rheumatology patients against COVID-19, substantial COVID-19 vaccine hesitancy still exists(4,5), and little is currently understood about how and why vaccine attitudes have changed throughout the pandemic.

For rheumatology patients, vaccine hesitancy is particularly complicated. Those with inflammatory arthritis and other rheumatic diseases balance their substantially greater risk of COVID-19-related harm, from both their disease and its commonly prescribed therapies(6), with concerns about reduced vaccine efficacy or the potential for vaccine-induced disease flares(7,8). Vaccine hesitancy in these patients defies simple explanations: although they are more familiar with novel and preventative medicine, in 2021 their vaccine hesitancy was as high as the general population(9), driven by a lack of information(10). To address this, it is critical to understand drivers of their vaccine hesitancy at an individual level.

Similar to what has been observed in the general population, we hypothesised that there is significant heterogeneity in drivers of COVID-19 vaccine hesitancy among inflammatory arthritis patients. However, unlike in unselected populations with high demographic diversity, we hypothesised that COVID-19 vaccine hesitancy does not strongly correlate with demographic features(11). The aim of this study was to examine both demographic and non-demographic drivers of vaccine hesitancy in inflammatory arthritis patients. In particular, we investigated whether vaccine hesitancy relates to fixed beliefs about medication benefits and harms. Given that a lack of appropriate information is reported as a major driver of vaccine hesitancy, we also investigated whether information sources can drive change in vaccine hesitancy.

Methods

Study Population

The Australian Rheumatology Association Database (ARAD) is an Australian national database that has been collecting longitudinal data from patients with inflammatory arthritis for over 15 years and it is described in detail elsewhere (12). All ARAD participants have a diagnosis of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or juvenile idiopathic arthritis made by their treating rheumatologist. All participants provide permission

to be contacted by ARAD investigators to complete surveys by email or mail (according to preference) every 6-12 months, including health assessment questionnaires, and all participants give written informed consent for participation in the registry and any resultant publications.

For this analysis, two surveys were performed, each open for response over a 6-week period. In January 2020, prior to the start of the pandemic or local transmission of COVID-19 in Australia, ARAD participants who had completed an ARAD survey in the preceding 12 months were invited to respond to a survey on a broad range of questions relating to medical therapy, non-COVID-19 vaccines, and their rheumatic disease (see Supplementary Data S1, available at *Rheumatology* online).

A follow-up survey was sent to all active ARAD cohort patients in May 2021, regardless of recent survey participation. In anticipation of imminent availability, the survey also included questions relating to the COVID-19 vaccines. This survey was released 65 days after the first COVID-19 vaccine dose was administered in Australia and 37 days after the Australian Government issued its first advice limiting the use of the Vaxzevria (AstraZeneca) vaccine after concerns about thrombosis with thrombocytopaenia syndrome(3).

ARAD has ethics approval from Monash University and other sites, including the Central Adelaide Local Health Network Human Research Ethics Committee that provided ethical approval for this specific substudy.

Survey Questions - Beliefs About Medicines

The Beliefs about Medicines Questionnaire (BMQ)(13) is a validated tool for assessing specific and general beliefs about medications. The general component comprises two sets of four questions relating to general beliefs about medication harms and overuse, reported as aggregate scores on a 5-point scale, with higher scores indicating greater concern. These questions were included in both the pre-pandemic and follow-up surveys.

COVID-19 Vaccine Hesitancy

We defined COVID-19 hesitant individuals from these questions as anyone who, having not yet received at least one COVID-19 vaccine dose, answered “No” or “Unsure” to the question “Do you believe you should have the COVID vaccine?”. We compared vaccine hesitant and non-hesitant individuals from the ARAD follow-up survey results, to determine whether there were major demographic or disease predictors of COVID-19 vaccine hesitancy. At the time of the follow-up survey, the state of Victoria had experienced a significantly greater burden of COVID-19 infections and public health interventions where other states had not, and therefore we compared patients from Victoria to those from the rest of Australia, to explore what role such a lived experience may have played.

Change in Vaccine Hesitancy

Although both the pre-pandemic and follow up surveys included questions about vaccine beliefs and experiences including general vaccine hesitancy, only the follow up questionnaire asked specifically about COVID-19 vaccination hesitancy (see Supplementary Data S1). Given general vaccine hesitancy may differ from COVID-19 vaccine hesitancy, we used LASSO regression (see Supplementary Data S2, available at *Rheumatology* online) (14) to predict pre-pandemic (January 2020) vaccine hesitancy from these general questions about vaccines (see 'vaccine views' questions in Supplementary Data S1). We split the dataset into training (75%) and test (25%) sets. On the training set, using bootstrap cross-validation with 25 resamples, we tuned the lambda parameter to determine the degree of regularisation. The final model was then trained on the full training set. Model accuracy was assessed on the holdout test set. Finally, this model was used to predict pre-pandemic COVID-19 vaccine hesitancy, with predictions above the Youden's J-point classified as vaccine hesitant(15). This pre-pandemic COVID-19 vaccine hesitancy was then compared to the follow-up survey to identify four groups: persistently hesitant, newly hesitant, newly non-hesitant and persistently non-hesitant.

Statistical Analysis

Continuous variables were summarised and presented as means with standard deviations, categorical or binary variables are presented as counts and percentages. Between groups, null hypothesis statistical testing was performed using Pearson's chi-square test for categorical or binary measures and the Wilcoxon rank-sum test for continuous variables.

Results

Patient characteristics

A total of 1,498 ARAD participants were invited to the first survey, of which 994 responded (response rate 66%). Separately, 999 ARAD participants were invited to the follow-up survey, of which 842 responded (response rate 84%). Because inclusion criteria for the two surveys differed, some participants completed one survey or the other, with 594 participants completing both, allowing for investigation of changing beliefs over time in this cohort (Table 1). Inferred vaccine hesitancy did not differ at baseline between the 594 participants who completed the follow-up survey (16% hesitant) and the 400 participants who did not (15% hesitant). The most common rheumatic disease was rheumatoid arthritis (53%) and there were no JIA patients in this cohort. The average age was 62 years, with a predominantly female cohort in an approximately 2:1 ratio.

Table 1: Disease and Demographic Characteristics

Categorical values are presented as count and percentage; continuous values are presented as mean and standard deviation.

Characteristic	**N = 594**
COVID-19 Vaccine Hesitant	74 (12%)
Rheumatic Disease	
RA	317 (53%)
AS	150 (25%)
PsA	127 (21%)

Age (years)	62 (11)
Female	382 (64%)
Ethnicity	
Caucasian	566 (95%)
Aboriginal / Torres Strait Islanders	3 (0.5%)
Asian	10 (1.7%)
Other	15 (2.5%)
Language Spoken at Home	
English	584 (98%)
Other	10 (1.7%)
Education	
Did not complete High School	70 (12%)
Completed High School	129 (22%)
Post High School	395 (66%)

COVID-19 Vaccine Hesitancy

Other than younger age (mean difference -4 years), COVID-19 vaccine hesitant participants did not differ in demographic features or current health status in univariate analyses (Table 2). Fewer COVID-19 vaccine hesitant participants experienced an episode of infection between surveys, although this was not statistically significant (p=0.08). There were no differences in vaccine hesitancy between the state of Victoria and the rest of Australia (p=0.77), despite Victoria being the only state to have experienced a large COVID-19 outbreak and prolonged restrictions at that time.

Those who were hesitant were more likely to view medications as being harmful (p<0.001) and overused (p=0.002) pre-pandemic, based on their scores on the BMQ questionnaire (Table 2). Those living alone were also numerically less likely to be hesitant, although this did not reach statistical significance (15% vs 25%, p=0.06).

Table 2: Comparison of demographic features and health status between vaccine hesitant and non-hesitant.

Continuous values are presented as mean and standard deviation; categorical values are presented as count and percentage. BMQ = Beliefs about Medicines Questionnaire, IRSAD = Index of Relative Socio-economic Advantage and Disadvantage

Characteristic	**Not hesitant, N = 520**	**Hesitant, N = 74**	**p-value**
Age (years)	63 (11)	59 (13)	0.02
Female	330 (63%)	52 (70%)	0.25
Ethnicity			0.21
Caucasian	498 (96%)	68 (92%)	
Aboriginal / Torres Strait Islanders	2 (0.4%)	1 (1.4%)	
Asian	8 (1.5%)	2 (2.7%)	
Other	12 (2.3%)	3 (4.1%)	

Language Spoken at Home			0.12
English	513 (99%)	71 (96%)	
Other	7 (1.3%)	3 (4.1%)	
Region			0.77
Victoria	110 (21%)	14 (19%)	
Rest of Australia	410 (79%)	60 (81%)	
Living Alone	130 (25%)	11 (15%)	0.06
Education			0.50
Did not complete High School	62 (12%)	8 (11%)	
Completed High School	109 (21%)	20 (27%)	
Post High School	349 (67%)	46 (62%)	
IRSAD percentile(16)	60 (29)	54 (30)	0.14
Change of employment status due to COVID-19	25 (4.8%)	4 (5.5%)	0.77
Disease Rating Scale (0 - 100)	32 (24)	30 (25)	0.54
SF36 Physical Component(17)	39 (12)	39 (13)	0.69
SF36 Mental Component(17)	49 (11)	49 (10)	0.62
At least one infection since last survey	157 (30%)	15 (20%)	0.08
Inflammatory arthritis			0.46
Rheumatoid arthritis	277 (53%)	40 (54%)	
Ankylosing Spondylitis	135 (26%)	15 (20%)	
Psoriatic arthritis	108 (21%)	19 (26%)	
BMQ Harms	2.23 (0.60)	2.56 (0.77)	<0.001
BMQ Overuse	2.55 (0.73)	2.88 (0.86)	0.002

Change in Vaccine Hesitancy

At the chosen cut-point, the LASSO regression model had an overall accuracy of 90% (sensitivity 78%, specificity 88%). The model was well calibrated, with a Brier score of 0.078. By applying this model to the initial survey, 97 patients were predicted to be vaccine hesitant pre-pandemic. Of these patients, 66 (68%) were no longer hesitant at follow-up.

Beliefs that medications are harmful and overused were greatest among those who were vaccine hesitant pre-pandemic (Figure 1), with beliefs stronger in those who remained persistently hesitant at follow-up (harmful: p=0.008, overused: p=0.005). Among those who were not vaccine hesitant pre-pandemic, there was no difference in beliefs about medication

harms (p=0.88) or overuse (p=0.75) between those who became vaccine hesitant at follow-up and those who did not.

Only persistently hesitant patients were less likely to seek vaccine information from healthcare professionals pre-pandemic (Table 3). On follow-up, there was a decrease in obtaining vaccine information from health professionals across all groups, however this was most marked in those who were hesitant at follow-up, regardless of pre-pandemic vaccine hesitancy. The highest rate of seeking vaccine information from healthcare professionals at follow-up was seen in those who transitioned from vaccine hesitant to non-hesitant. Although these trends were seen for both rheumatologists and general practitioners, in general there was a greater drop in seeking information from rheumatologists (Figure 2). In contrast, all groups sought more advice from both peers and online sources at follow-up.

Influenza Vaccine Hesitancy

Overall rates of influenza vaccine hesitancy remained low, decreasing from 12.8% pre-pandemic survey to 9.4% at follow-up. Among those who were not hesitant pre-pandemic, only 1.5% became hesitant at follow-up. There was no relationship between change in COVID-19 vaccine hesitancy and new influenza vaccine hesitancy (p=0.138).

Table 3: Sources of vaccine information across four groups of dynamic COVID-19 vaccine hesitancy. Healthcare professionals = nurse, general practitioner, rheumatologist or pharmacist. Peers = relatives, friends or other patients. Online= social media, chat forums, message boards or non-educational websites

Characteristic	Persistently Non-hesitant, N = 454	Newly non-hesitant, N = 66	Newly hesitant, N = 43	Persistently hesitant, N = 31	p-value
Healthcare Professionals (pre-pandemic)	441 (97%)	63 (95%)	42 (98%)	26 (84%)	0.011
General practitioner (pre-pandemic)	414 (91%)	55 (83%)	36 (84%)	24 (77%)	0.016
Rheumatologist (pre-pandemic)	344 (76%)	50 (76%)	36 (84%)	18 (58%)	0.10
Healthcare Professionals (followup)	391 (86%)	59 (89%)	25 (58%)	14 (45%)	<0.001
General practitioner (followup)	349 (77%)	46 (70%)	24 (56%)	9 (29%)	<0.001
Rheumatologist (followup)	223 (49%)	39 (59%)	15 (35%)	8 (26%)	0.005

Peers (pre-pandemic)	171 (38%)	27 (41%)	18 (42%)	17 (55%)	0.3
Peers (followup)	249 (55%)	42 (64%)	27 (63%)	17 (55%)	0.5
Online (pre-pandemic)	147 (32%)	29 (44%)	14 (33%)	12 (39%)	0.3
Online (followup)	170 (37%)	30 (45%)	22 (51%	17 (55%)	0.067

Figure 1: Box and whisker plots showing the results of the BMQ general questions relating to medication harms and overuse.
Individual scores are on a 5-point scale (1-5). From top to bottom, the three horizontal lines of the boxes are the 75%, 50% and 25% quantiles and the lines extend to the largest values, up to a maximum of 1.5 times the interquartile range. Points beyond this are considered outliers and represented as solitary dots.
PN=persistently non-hesitant, NN=newly non-hesitant, NH=newly-hesitant, PH=persistently hesitant.

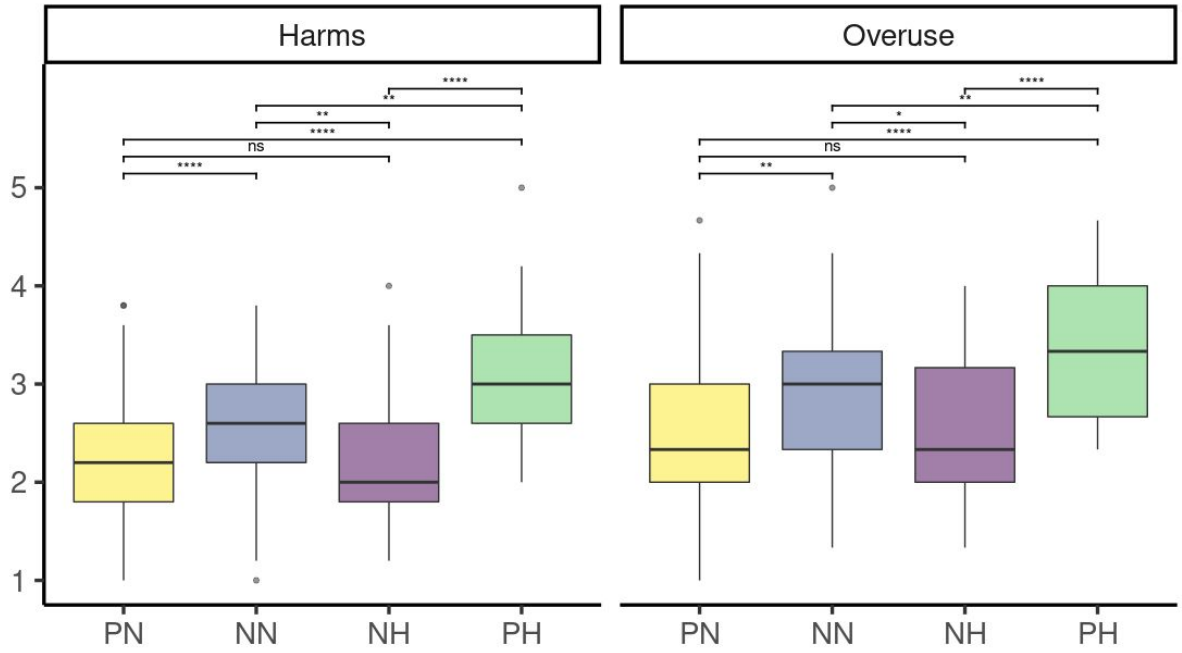
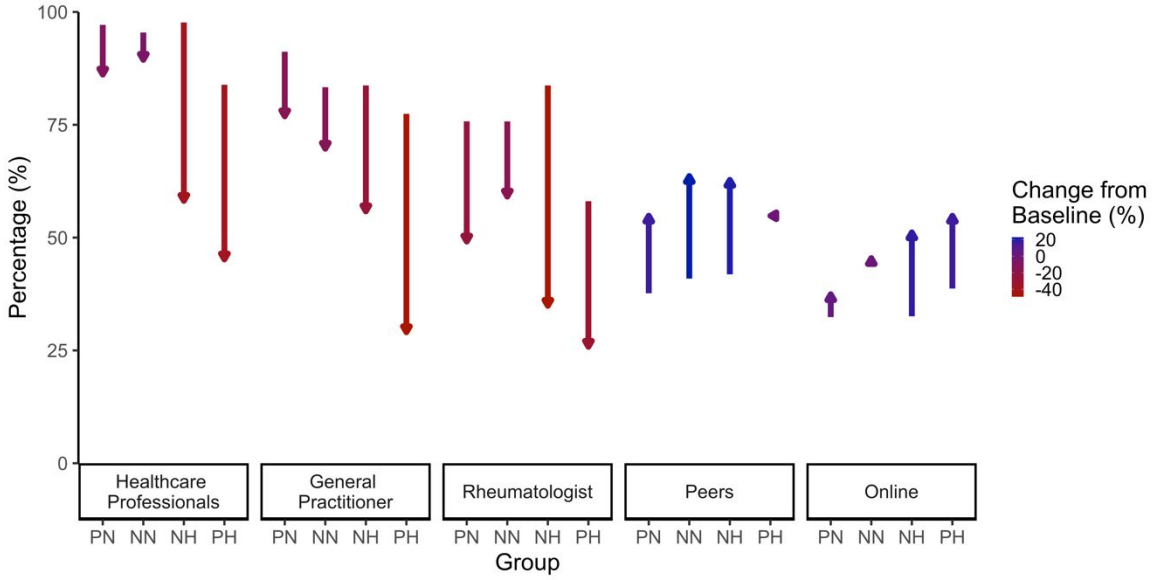


Figure 2: Change in sources of vaccine information between the pre-pandemic and follow-up surveys.
The chart shows the percentage of patients in each group that received vaccine information from each source. The start of each arrow is the percentage pre-pandemic and the tip is the percentage at follow-up. The colour of the arrow reflects the magnitude and direction of that change, with increased source utilisation in blue and decreased utilisation in red).
PN=persistently non-hesitant, NN=newly non-hesitant,NH=newly-hesitant, PH=persistently hesitant



Discussion

This study identified heterogeneous correlates of COVID-19 vaccine hesitancy among a cohort of inflammatory arthritis patients. COVID-19 vaccine hesitancy was associated with taking less advice from healthcare professionals and more advice from peers and online sources, highlighting the important role health care providers play in vaccine-related patient education during the COVID-19 pandemic.

While other studies have only been able to observe attitudes during the pandemic without reference to pre-pandemic attitudes or beliefs, this study found that these pre-pandemic beliefs about vaccines and medicines were more negative for those who were persistently hesitant compared to those who became newly hesitant during the pandemic. Those newly hesitant, in contrast, during COVID-19 had similar beliefs about medicines as those who were non-hesitant, suggesting new drivers for vaccine hesitancy in this group have emerged during the pandemic. Rather than seeking to combat this new vaccine hesitancy in the same way as pre-existing vaccine hesitancy, a different approach is required which considers this apparent difference in mechanism.

Importantly, unlike what has been found in other cohorts, the major correlates of vaccine hesitancy were not related to participant sociodemographic characteristics(18,19). Additionally, despite significant differences in COVID-19 incidence and government response between states(20), we did not observe different rates of COVID-19 vaccine hesitancy between Victoria and the rest of Australia. There was also no association between COVID-19 vaccine hesitancy and new influenza vaccine hesitancy.

Consistent with our hypothesis, patients with persistent vaccine hesitancy reported more negative beliefs about medication harms and overuse pre-pandemic. This may reflect broader beliefs about medical interventions that impact individual utility calculation in a way that is harder to modify with new information(21). In contrast, those whose hesitancy was fluid over time reported fewer negative beliefs about medication harms and overuse, with information sources being the key drivers of hesitancy.

In Australia, COVID-19 vaccine hesitancy has changed over time, rising from 26.4% in October 2020 to 35.5% in May 2021, before falling to 6.4% in November 2021(22). Rather than greater knowledge and education about vaccines, rises to May 2021 may reflect complacency in the face of low community transmission, and falls after this may partly reflect vaccine-dependent activity restrictions(23). Understanding the factors that drive this fluidity in vaccine hesitancy will help current and future efforts to increase vaccine uptake.

In our cohort, there was a strong correlation between different sources of information and changes in vaccine hesitancy. Those who became vaccine hesitant self-reported seeking information from healthcare professionals less, with the greatest decline seen for rheumatologists (35% down from 84% at baseline). In contrast to general medication beliefs, sources of information were the best predictors of changing hesitancy, rather than persistent hesitancy. While this does not address those who remain persistently vaccine hesitant, it

does underscore the important role that healthcare professionals in general, and rheumatologists in particular, play in increasing COVID-19 vaccine uptake.

Even prior to the COVID-19 pandemic, the heterogeneous factors predisposing to hesitancy had been extensively studied(21,24,25). While some propose vaccine hesitancy is best managed by identifying the 'Four Cs' (complacency, convenience, a lack of confidence, and utility calculation(21)) and directly addressing individual reasons for it, others have suggested core morality may affect both vaccine hesitancy and individual responses to interventions targeting hesitancy(25). What unifies these models of vaccine hesitancy, however, is a recognition that driving factors are heterogeneous and need to be addressed on an individual basis.

This focus on individual drivers means healthcare professionals must seek to understand patients' motivators within these frameworks. Although this study does not establish a causal link between increased healthcare provider involvement in vaccine education and reduced vaccine hesitancy, it underscores the need for greater education from healthcare professionals to maximise the effectiveness of these (26). We have seen, both in this study and in broader Australian national data, that vaccine hesitancy is fluid and amenable to change. Nevertheless, the different factors seemingly driving hesitancy among those with new hesitancy, versus those with pre-existing vaccine hesitancy, would suggest that varied approaches are required to reach all patient groups. While health promotion campaigns have the benefit of providing broad education across all population groups, those with persistent vaccine hesitancy may also require more targeted individual counselling which should, on the basis of these data, include asking about previous vaccine beliefs.

Notably, changes in COVID-19 vaccine hesitancy did not predict changes in influenza vaccine hesitancy. This poses important questions about the specific drivers of hesitancy, and particularly questions what distinguishes beliefs between these two vaccines. On a more practical level, we did not find any evidence to suggest that the development of COVID-19 vaccine hesitancy will drive similar hesitancy about the influenza vaccine, which may help to quell concerns that many patients may now shun the annual influenza vaccine.

A major strength of this study is capturing vaccine hesitancy pre-pandemic, prior to the COVID-19 pandemic. This allowed us to follow vaccine hesitancy longitudinally and identify factors associated with fixed and fluid vaccine hesitancy. This strength is also a limitation, because pre-pandemic COVID-19 vaccine hesitancy is not measured, but inferred from general vaccine beliefs. While these beliefs were closely related to COVID-19 vaccine hesitancy in the follow-up survey, we could not test this pre-pandemic. There is also the potential for sampling bias, with survey responses being entirely voluntary. Participants in these surveys may be more engaged, and thus these might not be generalisable. We do not know whether vaccine beliefs were correlated with propensity to respond to these surveys and how this might have changed our results. We also considered whether worsened disease activity or perceived overall health could lead to less COVID-19 vaccine hesitancy due to contact with treating clinicians, as well as more opportunities to seek advice from those clinicians, but notably the patient-reported disease rating scale and SF-36 physical and mental components were similar between hesitant and non-hesitant participants.

Conclusion

The rapid, population-wide drive for COVID-19 vaccination has focused the attention of the medical community on the issue of vaccine hesitancy, particularly in those patients most vulnerable to poor COVID-19 outcomes. Protecting these patients forms a substantial part of the rationale for broader public health measures. While this is an area of significant and active research, specific insights into COVID-19 vaccine hesitancy are only just emerging. Within this context, it is important that we identify factors that might influence COVID-19 vaccine hesitancy in inflammatory arthritis patients, to improve ongoing vaccine uptake. Within our cohort of inflammatory arthritis patients, a group vulnerable largely because of their prescribed medications, we found that, while persistent vaccine hesitancy strongly correlates with wider views on medication overuse and harm, more fluid beliefs correlate strongly with different sources of information. Importantly for the rheumatologist seeing vaccine-hesitant patients in the clinic, it is vaccine information from health professionals that is correlated with fluid vaccine hesitancy. As rheumatologists, we must acknowledge the central role we play and make effective, individualised communication with vaccine hesitant patients a priority in practice.

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Data availability statement:
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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