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Original article

Cluster analysis reveals three main patterns of beliefs and intention with respect to SARS-CoV-2 vaccination in patients with autoimmune and inflammatory diseases

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Abstract

Introduction. Given the COVID-19 pandemic, it is crucial to understand the underlying behavioural determinants of SARS-CoV-2 vaccine hesitancy in patients with autoimmune or inflammatory rheumatic diseases (AIIRDs). We aimed to analyse patterns of beliefs and intention regarding SARS-CoV-2 vaccination in AIIRD patients, as a mean of identifying pragmatic actions that could be taken to increase vaccine coverage in this population.

Methods. Data relating to 1258 AIIRD patients were analysed using univariate and multivariate logistic regression models, to identify variables associated independently with willingness to get vaccinated against SARS-CoV-2. Subsets of patients showing similar beliefs and intention about SARS-CoV-2 vaccination were characterized using cluster analysis.

Results. Hierarchical cluster analysis identified three distinct clusters of AIIRD patients. Three predominant patient attitudes to SARS-COV-2 vaccination were identified: voluntary, hesitant and suspicious. While vaccine willingness differed significantly across the three clusters ($P < 0.0001$), there was no significant difference regarding fear of getting COVID-19 ($P = 0.11$), the presence of comorbidities ($P = 0.23$), the use of glucocorticoids ($P = 0.21$), or immunocompromised status ($P = 0.63$). However, patients from cluster #2 (hesitant) and #3 (suspicious) were significantly more concerned about vaccination, the use of a new vaccine technology, lack of long-term data in relation to COVID-19 vaccination, and potential financial links with pharmaceutical companies ($P < 0.0001$ in all) than patients from cluster #1 (voluntary).

Discussion. Importantly, the differences between clusters in terms of patient beliefs and intention was not related to the fear of getting COVID-19 or to any state of frailty, but was related to specific concerns about vaccination. This study may serve as a basis for improved communication and thus help increase COVID-19 vaccine coverage among AIIRD patients.

Key words: COVID-19, autoimmune diseases, inflammatory rheumatic diseases, vaccination, behaviour, cluster analysis

CLINICAL SCIENCE

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Introduction

The SARS-CoV-2 vaccines will improve the current world health crisis related to the pandemic, by preventing future infections and complications, reducing the number of patients with severe forms of COVID-19 [1]. Rheumatologists and other specialists need to work together with general practitioners to increase SARS-CoV-2 vaccine coverage in patients with autoimmune or inflammatory rheumatic diseases (AIIRDs) [2, 3], who could be at increased risk of severe forms of COVID-19 [4, 5]. Our

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Rheumatology key messages

- SARS-CoV-2 vaccine willingness is limited in patients with autoimmune or inflammatory rheumatic diseases (AIIRDs).
- We identified significant differences in beliefs between patients willing and those unwilling to get vaccinated against SARS-CoV-2.
- This study may improve communication between medical specialists/healthcare agencies and AIIRD patients, and thus increase SARS-CoV-2 vaccine coverage.

recently published international VAXICOV study reported on expectations and potential concerns related to SARS-CoV-2 vaccination in AIIRD patients [2]. One of the main findings of VAXICOV was the limited willingness of AIIRD patients to get SARS-CoV-2 vaccination . From a public health perspective, it is therefore crucial to understand the underlying determinants of vaccine hesitancy [6] in the context of the SARS-CoV-2 pandemic in this sector. The objective of the current study was to analyse the different types of attitudes to SARS-CoV-2 vaccination among AIIRD patients, as well as the determinants of those attitudes (i.e. the underlying beliefs), using a data-driven approach, the purpose being to identify pragmatic means by which a rheumatologist might positively impact those behaviours.

Methods

Study design and dissemination

The VAXICOV study consisted of an online questionnaire of 57 questions that addressed epidemiological, sociodemographic and therapeutic elements associated with expectations and potential concerns regarding SARS-CoV-2 vaccination. The online survey took place from 12 December 2020 to 21 December 2020. The questionnaire was translated from English into French and Spanish by native speakers. The detailed methods used in the VAXICOV study and the main findings have been already described [2].

Study participants and main study outcomes

The study included patients with a self-reported diagnosis of AIIRDs. The main study outcomes included: demographical characteristics (age, prior chronic medical conditions, marital status, children, profession, income); experiences related to COVID-19; history of vaccination against seasonal influenza and pneumococcus; intention to get vaccinated if a COVID-19 vaccine were available; vaccine hesitancy; and fears and expectations about COVID-19 vaccination. Participants rated their feelings about SARS-CoV-2 vaccination using 0–10 scales (0: not at all in agreement; 10: fully agree). An immunocompromised status was defined as participants taking at least one immunosuppressant or glucocorticoid at a dose of >10 mg per day of prednisone-equivalent. The study was approved by the ethics review board of Strasbourg (#CE-2020–199), and informed consent was obtained from patients (via a dedicated question at the beginning of the online questionnaire).

Statistical analysis

Continuous data are presented as medians and their 25th–75th percentile interquartile range (IQR), and categorical data as counts and percentages. Comparisons between independent groups were made using the Mann–Whitney test for continuous outcomes and the Chi^2 test (or Fisher's exact test when appropriate) for quantitative data.

Univariate and multivariate logistic regression models using a backward stepwise approach were built to identify variables associated independently with willingness to get vaccinated against SARS-CoV-2 (selected as the dependent variable). All Likert statements with a *P*-value of <0.10 in univariate analysis were included as independent variables in the multivariate logistic regression models. Subsets of patients showing similar specific perception about SARS-CoV-2 vaccination (based on the patients' responses to the five significant statements from the VAXICOV study, see Results) were characterized using cluster analysis. Hierarchical cluster analysis via Ward's method was used as the principal clustering technique, the optimal number of clusters was determined using the gap/elbow method and pre-specified in a k-means cluster analysis, and the agreement between the two clustering methods was calculated using Cohen's kappa. Principal component analysis was performed using data from the statements that remained significant in the stepwise multivariable model, using a colour code to represent the main clustering group for each patient. All tests were bilateral, and *P*-values of <0.05 were considered statistically significant. Statistical analyses were performed with the software JMP13 (SAS institute, Cary, NC, USA).

Results

Patients characteristics

The study included 1258 patients with AIIRDs [1138 (90.5 %) women and 120 (9.5 %) men; median age 50 (IQR: 40–61) years] from 56 countries. The most common inflammatory or autoimmune conditions (Table 1)

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were SLE ($n = 492$, 39.1%), SpA ($n = 174$, 13.8%), RA ($n = 157$, 12.5%) and PMR/ GCA ($n = 144$, 11.5%).

Main characteristics of the three clusters

From the 14 statements assessed in VAXICOV, the multivariate logistic regression models identified five statements independently associated with willingness to get vaccinated against SARS-CoV-2 (#3, #6, #10, #13 and #14, Table 2). Based on the patient's answers to these five significant statements, hierarchical cluster analysis identified three distinct clusters within the study population (labelled clusters #1, #2 and #3, Fig. 1A and B), regrouping 180, 688 and 390 patients, respectively. The detailed characteristics of the three clusters are shown in Table 3. The concordance with k-means clustering was high (Cohen's kappa: 0.76).

Table 1 Patient characteristics

Parameters	
Number of patients	1258
Age (years), median [IQR 25–75]	50 [40–61]
Female, *n* (%)	1138 (90.5%)
Male, *n* (%)	120 (9.5%)
Country, *n* (%)	
UK	345 (27.4%)
France	313 (24.9%)
Chile	123 (9.7%)
USA	114 (9.1%)
Spain	57 (4.5%)
Mexico	53 (4.2%)
Argentina	45 (3.6%)
Venezuela	43 (3.4%)
Other[a]	165 (13.1%)
Rheumatic diagnosis, *n* (%)	
SLE	492 (39.1%)
SpA	174 (13.8%)
RA	157 (12.5%)
PMR/GCA	144 (11.5%)
Primary APS	64 (5.1%)
Inflammatory myositis	62 (4.9%)
Relapsing polychondritis	45 (3.6%)
Other[b]	120 (9.6%)
Associated comorbidities, *n* (%)	
Diabetes	68 (5.4%)
Hypertension	263 (20.9%)
Myocardial infarction, stroke, transient stroke	58 (4.6%)
Respiratory disease (asthma, chronic bronchitis, emphysema, etc.)	168 (13.4%)
Renal failure	43 (3.4%)
Obesity (BMI > 30)	227 (18.0%)
At least one associated comorbidity, *n* (%)	582 (46.3%)
Smoker, *n* (%)	1250
Current	126 (10.1%)
Past	407 (32.6%)
Never	717 (57.4%)
Use of oral glucocorticoids, *n* (%)	547 (56.1%)
Immunocompromised[c], *n* (%)	766 (60.9%)

[a]Other countries: Algeria ($n = 1$), Australia ($n = 10$), Austria ($n = 1$), Belgium ($n = 3$), Bolivia ($n = 2$), Brazil ($n = 1$), Canada ($n = 18$), Colombia ($n = 12$), Costa Rica ($n = 3$), Cuba ($n = 2$), Denmark ($n = 1$), Ecuador ($n = 4$), El Salvador ($n = 3$), Estonia ($n = 2$), Finland ($n = 1$), Germany ($n = 8$), Gibraltar ($n = 1$), Greece ($n = 1$), Guatemala ($n = 2$), Honduras ($n = 1$), Iceland ($n = 7$), India ($n = 7$), Ireland ($n = 7$), Israel ($n = 2$), Italy ($n = 1$), Jordan ($n = 1$), Lebanon ($n = 1$), Lithuania ($n = 2$), Luxembourg ($n = 1$), New Zealand ($n = 4$), Nicaragua ($n = 2$), Norway ($n = 2$), Panama ($n = 2$), Paraguay ($n = 2$), Peru ($n = 27$), Philippines ($n = 1$), Poland ($n = 1$), Portugal ($n = 1$), Puerto Rico ($n = 3$), Slovakia ($n = 2$), Sweden ($n = 3$), Switzerland ($n = 2$), The Netherlands ($n = 3$), Uruguay ($n = 6$). [b]Other rheumatic diagnosis: Behçet ($n = 11$), mixed CTD ($n = 10$), other type of vasculitis ($n = 8$), overlap ($n = 23$), undifferentiated CTD ($n = 8$), unknown ($n = 7$), sarcoidosis $n = 2$, SS ($n = 18$), SSc ($n = 16$), other autoimmune or inflammatory diseases ($n = 17$). [c]At least one immunosuppressant (except HCQ/chloroquine and apremilast) or glucocorticoids at a dose >10 mg per day of prednisone-equivalent.

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TABLE 2 Association between the likelihood of refusing SARS-CoV-2 vaccination and VAXICOV statements

Statements	Proportions[a] among those willing to get vaccinated	Proportions[a] among those unwilling to get vaccinated	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*-values	OR (95% CI)	*P*-values
#1: I am one of those people who never get sick/ill; therefore. vaccines are not useful in my case.	4.2%	19.8%	1.44 (1.35, 1.53)	<0.0001	–	–
#2: A COVID-19 vaccine may have DECREASED EFFICACY in my personal situation.	23.9%	30.3%	1.15 (1.09, 1.21)	<0.0001	–	–
#3: There is a lack of hindsight regarding new anti-COVID-19 vaccines.	35.5%	89.5%	1.81 (1.65, 2.02)	<0.0001	1.37 (1.23, 1.54)	<0.0001
#4: There is a lack of hindsight regarding vaccines in general.	21.0%	59.3%	1.37 (1.29, 1.45)	<0.0001	–	–
#5: I will be careful if the anti-COVID-19 vaccine uses a technology that has never been used before (e.g. RNA vaccine).	35.9%	77.3%	1.50 (1.39, 1.62)	<0.0001	–	–
#6: Maybe a COVID-19 vaccine can induce a flare of my auto-immune/inflammatory disease.	39.6%	80.8%	1.60 (1.47, 1.75)	<0.0001	1.17 (1.05, 1.30)	<0.0001
#7: I am afraid of the pain of the injection, or of developing a local reaction after the vaccination.	12.3%	32.6%	1.20 (1.15, 1.26)	<0.0001	–	–
#8: I am concerned about vaccination, in general.	17.3%	50.6%	1.32 (1.25, 1.39)	<0.0001	–	–
#9: I am concerned about the general management of this health crisis by governments.	62.9%	82.6%	1.26 (1.17, 1.36)	<0.0001	–	–
#10: I am afraid of potential side-effects induced by the COVID-19 vaccine.	39.3%	95.3%	2.11 (1.86, 2.43)	<0.0001	1.43 (1.24, 1.68)	<0.0001
#11: A COVID-19 vaccine could induce a disease, such as a chronic disease, an infection or a cancer.	12.0%	66.3%	1.59 (1.49, 1.70)	<0.0001	–	–
#12: A COVID-19 vaccine could give me COVID-19.	7.2%	43.6%	1.46 (1.38, 1.55)	<0.0001	–	–
#13: I think a COVID-19 vaccine is not needed in my case.	3.7%	32.0%	1.76 (1.64, 1.90)	<0.0001	1.43 (1.32, 1.56)	<0.0001
#14: I think COVID-19 vaccination is mostly recommended because of the financial links between governments and pharmaceutical companies.	6.4%	54.6%	1.63 (1.54, 1.74)	<0.0001	1.21 (1.12, 1.31)	<0.0001

Odds ratio (OR) and 95% CI for the likelihood of refusing SARS-CoV-2 vaccination *vs* that of getting vaccinated (as the reference category), in association with each statement. [a]Proportion of patients with a value ≥ 7 (on the 0–10 Likert scale) for each statement, according to willing/unwilling status.

Vaccine willingness across the three clusters

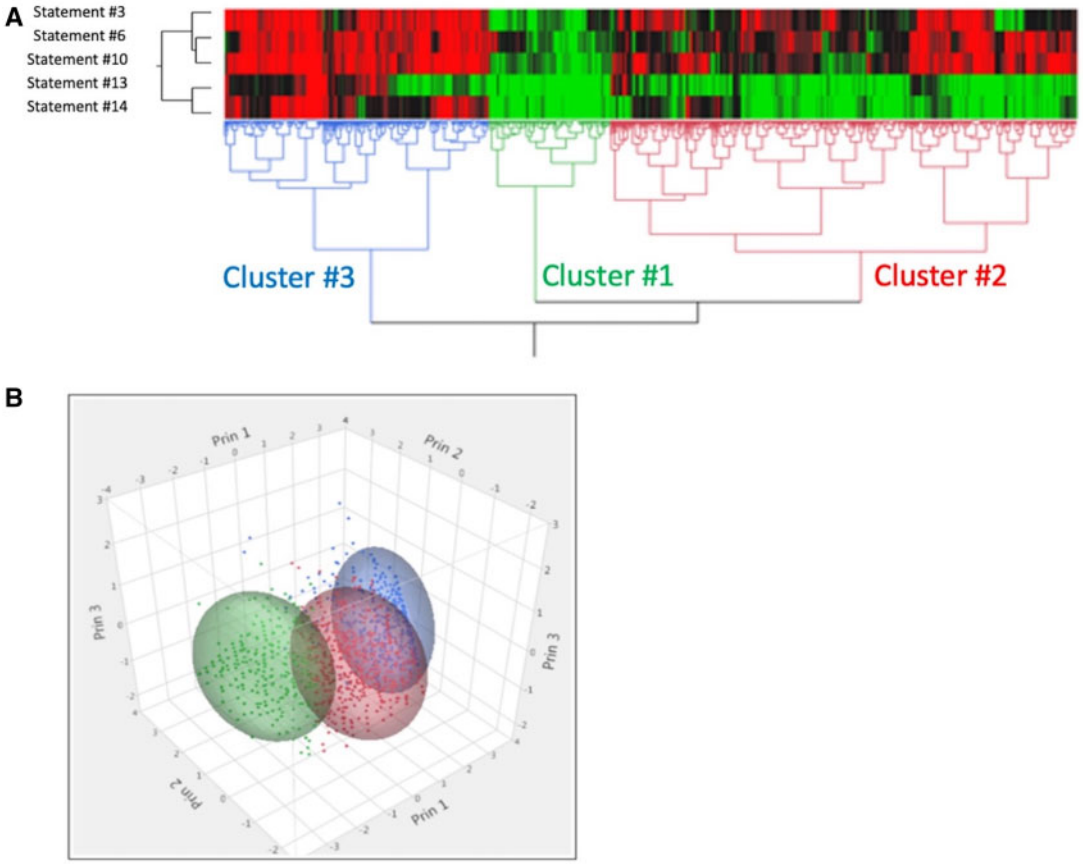
Vaccine willingness was significantly different across the three clusters (Table 3): patients from cluster #1 were the most willing to get vaccinated (willing in 97.2%, unsure in 1.7% and would decline vaccination in 1.1%). Patients from cluster #2 were more hesitant (willing in 64.8%, unsure in 30.1%, would decline for 5.1%), while patients from cluster #3 were mostly opposed to getting vaccinated (willing in 15.6%, unsure in 49.7%, would decline for 34.6%). These patterns were similar even when their doctor advised them to get vaccinated (Table 3). Importantly, the most trusted healthcare professional across the three clusters was the medical specialist (as stated by 70.0% of patients in cluster #1, 70.9% in cluster #2, and 68.0% in cluster #3). However, 14.1% of patients from cluster #3 did not trust any healthcare professional (*vs* 0.6% and 4.9% in clusters #1 and #2, respectively, $P < 0.0001$).

Main predictors of cluster membership

While vaccine willingness and hesitancy were significantly different across the three clusters ($P < 0.0001$, Table 3), there was no difference regarding the fear of

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Fig. 1 Cluster analysis



(A) Hierarchical Ascending Clustering showing the three clusters. Dendrogram showing the three clusters based on the patients' answers [colour-coded from green (lowest value) to red (highest value)] to the five significant statements (statements #3, #6, #10, #13, #14) from the VAXICOV study. **(B)** Principal component analysis showing the three clusters. Principal component analysis (3D plot) based on individual patients' answers to the five significant statements from the VAXICOV study, according to the three first principal components (labeled Prin 1, 2 and 3), and colour-coded to represent the three clusters (cluster #1: green; cluster #2: red; and cluster #3: blue).

getting COVID-19 (median score on the 0–10 Likert scale: 8 [6–10] for cluster #1, 8 [7–10] for cluster #2, and 8 [6–10] for cluster #3, $P = 0.11$) or the fear of getting a severe form of COVID-19 (Cluster #1: 9 [7–10], cluster #2: 9 [8–10], and cluster #3: 9 [6–10], $P = 0.11$) (Table 4). Strikingly, patients from cluster #3 were significantly more concerned about vaccination in general ($P < 0.0001$), thought it was less important to get vaccinated ($P < 0.0001$), were significantly more concerned about the use of a new vaccine technology (e.g. RNA vaccine) ($P < 0.0001$), and were significantly more concerned about the lack of long-term data for COVID vaccination ($P < 0.0001$) as well as about potential financial links between governments and pharmaceutical companies ($P < 0.0001$) than in the other two clusters (Table 4). Patients in clusters #2 and #3 were significantly more concerned that the vaccine would induce a flare of their disease than those in cluster #1 ($P < 0.0001$). Detailed behavioural results across the three clusters are shown in Table 4. The proportion of men was significantly higher in cluster #1 than in the two other clusters (18.9% in cluster #1 *vs* 8.7% in cluster #2 and 6.7% in cluster #3, $P < 0.0001$). Patients in cluster #3 were significantly younger [median age: 46.5 (37–56) years] than those in cluster #1 [56.5 (41–67) years] and cluster #2 [51 (41–63) years], $P < 0.0001$ (Table 3). Also, countries of origin ($P < 0.0001$) and rheumatic diseases ($P < 0.0001$) were statistically different between the three clusters. Importantly, there was no significant difference as to the presence of comorbidities ($P = 0.23$), the use of glucocorticoids ($P = 0.21$) or the immunocompromised status ($P = 0.63$) (Table 3).

Discussion

Our results, based on a cluster analysis of a large international sample of patients with autoimmune and

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Table 3 Comparison of patient characteristics and vaccine willingness in the clusters

Subject groups	Cluster #1 Voluntary	Cluster #2 Hesitant	Cluster #3 Suspicious	*P*-value
Number of patients, *n* (%)	180	688	390	–
Age (years), median [IQR 25–75]	56.5 [41–67]	51 [41–63]	46.5 [37–56]	**<0.0001**
Female, *n* (%)	146 (81.1%)	628 (91.3%)	364 (93.3%)	**<0.0001**
Male, *n* (%)	34 (18.9%)	60 (8.7%)	26 (6.7%)	
Country, *n* (%)				**<0.0001**
UK	71 (39.4%)	215 (31.3%)	41 (10.5%)	
France	26 (14.4%)	155 (22.5%)	132 (33.9%)	
Chile	9 (5.0%)	55 (8.0%)	59 (15.1%)	
USA	28 (15.6%)	63 (9.2%)	23 (5.9%)	
Spain	1 (0.6%)	35 (5.1%)	21 (5.4%)	
Mexico	5 (2.8%)	25 (3.6%)	23 (5.9%)	
Argentina	7 (3.9%)	19 (2.8%)	19 (4.9%)	
Venezuela	0	20 (2.9%)	23 (5.9%)	
Other[a]	33 (18.3%)	101 (14.6%)	49 (12.6%)	
Rheumatic diagnosis, *n* (%)				**<0.0001**
SLE	60 (33.3%)	271 (39.4%)	161 (41.3%)	
SpA	14 (7.8%)	94 (13.7%)	66 (16.9%)	
RA	19 (10.6%)	78 (11.3%)	60 (15.4%)	
PMR/GCA	40 (22.2%)	91 (13.2%)	13 (3.3%)	
Primary APS	4 (2.2%)	41 (6.0%)	7 (1.8%)	
Inflammatory myositis	13 (7.2%)	30 (13.2%)	19 (4.9%)	
Relapsing polychondritis	6 (3.3%)	27 (3.9%)	12 (3.1%)	
Other[b]	24 (13.3%)	56 (8.1%)	52 (13.3%)	
Associated comorbidities, *n* (%)				
Diabetes	7 (3.9%)	41 (6.0%)	20 (5.1%)	0.53
Hypertension	38 (21.1%)	140 (20.4%)	85 (21.8%)	0.85
Myocardial infarction, stroke, transient stroke	6 (3.3%)	38 (5.5%)	14 (3.6%)	0.24
Respiratory disease (asthma, chronic bronchitis, emphysema, etc.)	25 (13.9%)	87 (12.7%)	56 (14.4%)	0.71
Renal failure				
Obesity (BMI $>$ 30)	9 (5.0%)	17 (2.5%)	17 (4.4%)	0.12
At least one associated comorbidity, *n* (%)	33 (18.3%)	111 (16.1%)	83 (21.3%)	0.11
	83 (46.1%)	305 (44.3%)	194 (49.7%)	0.23
Smoker, *n* (%)				**0.0009**
Current	13 (7.3%)	54 (7.9%)	59 (15.2%)	
Past	60 (33.7%)	217 (31.7%)	130 (33.5%)	
Never	105 (59.0%)	413 (60.4%)	199 (51.3%)	
Use of oral glucocorticoids, *n* (%)	90 (50%)	299 (43.5%)	158 (40.5%)	0.21
Immunocompromised[c], *n* (%)	114 (63.3%)	421 (61.2%)	231 (59.2%)	0.63
Willing to get vaccinated: yes/uncertain/no, %	97.2/1.7/1.1	64.8/30.1/5.1	15.6/49.7/34.6	**<0.0001**
Willing to get vaccinated after medical advice: (yes/uncertain/no), %	98.9/0.6/0.6	72.8/24.3/2.9	28.7/48.2/23.1	**<0.0001**
Vaccine hesitancy, *n* (%)	15 (8.3%)	166 (24.1%)	176 (45.1%)	**<0.0001**

[a]Other countries: Algeria ($n=1$), Australia ($n=10$), Austria ($n=1$), Belgium ($n=3$), Bolivia ($n=2$), Brazil ($n=1$), Canada ($n=18$), Colombia ($n=12$), Costa Rica ($n=3$), Cuba ($n=2$), Denmark ($n=1$), Ecuador ($n=4$), El Salvador ($n=3$), Estonia ($n=2$), Finland ($n=1$), Germany ($n=8$), Gibraltar ($n=1$), Greece ($n=1$), Guatemala ($n=2$), Honduras ($n=1$), Iceland ($n=7$), India ($n=7$), Ireland ($n=7$), Israel ($n=2$), Italy ($n=1$), Jordan ($n=1$), Lebanon ($n=1$), Lithuania ($n=2$), Luxembourg ($n=1$), New Zealand ($n=4$), Nicaragua ($n=2$), Norway ($n=2$), Panama ($n=2$), Paraguay ($n=2$), Peru ($n=27$), Philippines ($n=1$), Poland ($n=1$), Portugal ($n=1$), Puerto Rico ($n=3$), Slovakia ($n=2$), Sweden ($n=3$), Switzerland ($n=2$), The Netherlands ($n=3$), Uruguay ($n=6$). [b]Other rheumatic diagnosis: Behçet ($n=11$), mixed CTD ($n=10$), other type of vasculitis ($n=8$), overlap ($n=23$), undifferentiated CTD ($n=8$), unknown ($n=7$), sarcoidosis $n=2$, SS ($n=18$), SSc ($n=16$), other autoimmune or inflammatory diseases ($n=17$). [c]At least one immunosuppressant (except HCQ/chloroquine and apremilast) or glucocorticoids at a dose $>$10 mg per day of prednisone-equivalent. *P*-values in bold remain statistically significant after Bonferroni correction for multiple testing.

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TABLE 4 Comparison of beliefs and intentions regarding vaccination against SARS-CoV-2 in the patients in the clusters

Statements	Subject groups			*P*-value
	Cluster #1 Voluntary	Cluster #2 Hesitant	Cluster #3 Suspicious	
#1: I am one of those people who never get sick/ill; therefore. vaccines are not useful in my case.	0 [0–0]	0 [0–2]	3 [0–5]	**<0.0001**
#2: A COVID-19 vaccine may have DECREASED EFFICACY in my personal situation.	1 [0–5]	5 [1–7]	5 [5–8]	**<0.0001**
#3: There is a lack of hindsight regarding new anti-COVID-19 vaccines.	1.5 [0–3]	6 [5–9]	10 [8–10]	**<0.0001**
#4: There is a lack of hindsight regarding vaccines in general.	0 [0–2]	5 [1–6]	8 [5–10]	**<0.0001**
#5: I will be careful if the anti-COVID-19 vaccine uses a technology that has never been used before (e.g. RNA vaccine).	2 [0–5]	6 [4–8]	9 [7–10]	**<0.0001**
#6: Maybe a COVID-19 vaccine can induce a flare of my auto-immune/inflammatory disease.	3 [1–5]	7 [5–9]	9 [8–10]	**<0.0001**
#7: I am afraid of the pain of the injection, or of developing a local reaction after the vaccination.	0	1 [0–5]	4 [1–8]	**<0.0001**
#8: I am concerned about vaccination, in general.	0 [0–1]	3 [0–6]	7 [5–10]	**<0.0001**
#9: I am concerned about the general management of this health crisis by governments.	6 [3–10]	8 [5–10]	10 [8–10]	**<0.0001**
#10: I am afraid of potential side-effects induced by the COVID-19 vaccine.	1 [0–2]	7 [5–9]	10 [9–10]	**<0.0001**
#11: A COVID-19 vaccine could induce a disease, such as a chronic disease, an infection or a cancer.	0 [0–1]	5 [1–6]	8 [6–10]	**<0.0001**
#12: A COVID-19 vaccine could give me COVID-19.	0	1 [0–5]	6 [3–9]	**<0.0001**
#13: I think a COVID-19 vaccine is not needed in my case.	0	0 [0–1]	5 [2–7]	**<0.0001**
#14: I think COVID-19 vaccination is mostly recommended because of the financial links between governments and pharmaceutical companies.	0	0 [0–3]	8 [5–10]	**<0.0001**
How important is it to get people vaccinated?	10	10 [9–10]	9 [7–10]	**<0.0001**
How important is it to get YOU (personally) vaccinated?	10	10 [9–10]	8 [6–10]	**<0.0001**
How suspicious are you about vaccination in general?	0 [0–1]	3 [1–9]	7 [3–9]	**<0.0001**
How afraid are you of getting infected by COVID-19?	8 [6–10]	8 [7–10]	8 [6–10]	0.11
How afraid are you of getting a SEVERE COVID-19 infection?	9 [7–10]	9 [8–10]	9 [6–10]	0.11

Median [IQR]. *P*-values in bold remain significant after Bonferroni correction. Answers were assessed on a 0–10 Likert scale.

inflammatory diseases, enabled the identification of three distinct clusters of behaviour with respect to SARS-COV-2 vaccination. Identifying those patients behaviours can help tailor the approach to be adopted by healthcare professionals and governments (at the individual and collective level) to improve SARS-CoV-2 vaccination coverage. Based on patient willingness to get vaccinated and the responses to the statements presented in Tables 2 and 4, cluster #1 members can be considered *voluntary,* cluster #2 members as

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hesitant, and cluster #3 members as *suspicious* with respect to SARS-CoV-2 vaccination.

Contrary to what might have been expected, willingness to get vaccinated was not statistically related to level of frailty, as evidenced by the lack of association between willingness to be vaccinated and level of immunosuppression or presence of associated comorbidities. Importantly, fear of getting COVID-19 was high among all three groups. While this does not mean it is an irrelevant factor to whether or not someone would ultimately get vaccinated, the fear of getting COVID-19 or of getting a severe form of SARS-CoV-2 infection was not statistically different across the three clusters, which suggests that there seems to be no benefit in using this element as an anchor to convince AIIRD patients to get vaccinated.

In addition, this study highlighted important differences that may exist between countries regarding vaccine willingness (Table 3). Such differences have previously been shown in a worldwide study showing disparities in acceptance of COVID vaccination ranging from 90% in China to <55% in Russia [7]. Also, another important finding was the difference in age across the three clusters (Table 3). In the VAXICOV study, willingness to get vaccinated increased significantly with age [2]. Similarly, in a previous study [8], COVID-19 vaccine hesitancy and refusal were both significantly negatively associated with U shape. Interestingly, this was not explained by a difference in the fear of getting COVID-19 or severe COVID-19.

What differed the most between the three clusters were concern about *vaccination in general* or about *COVID-19 vaccines*, lack of long-term data for the use of *new vaccine technologie*s (such as RNA vaccines), and *possible financial links* with the pharmaceutical companies. Patients for whom giving the medical reasons for vaccination would be most effective were those from clusters #2 (*hesitant*) and #3 (*suspicious*) (Table 3). Accordingly, based on the significant patient concerns identified in this study, the physician's approach with a reluctant patient with an AIIRD should be to discuss the general principles behind vaccination, including its immunological basis, the main efficacy and safety data from the large phase 3 trials [9–12], and information on the general drug approval and licensing process . This is an important point, because it was found to be the medical specialist who was most trusted by the patients in all clusters.

Another issue for hesitant or suspicious patients was the potential induction of a flare by the SARS-CoV-2 vaccine. This point seems to be worthy of discussion with patients : it would be important to emphasize that the benefit–risk analysis at this stage appears to favour vaccination. International registries will probably provide clarification of the data for our patients in the near future.

This cluster analysis, based on a large international sample of AIIRD patients, enabled the identification of three main patterns of patient intention in relation to SARS-COV-2 vaccination: hesitant, voluntary and suspicious. Importantly, the differences between those intentions were not found to be related to the level of fear of getting COVID-19 or to the level of any state of frailty, such as immunodepression, but instead to concerns about available scientific data on vaccination, lack of long-term data, and potential financial links with the pharmaceutical industry. Interestingly, these specific concerns about vaccination are also major factors related to non-adherence to chronic treatment in patients with inflammatory rheumatic diseases. This study may serve as a basis for improved communication between physicians / healthcare agencies and AIIRD patients, thus increasing COVID-19 vaccine coverage in this sector at both the individual and population levels.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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