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## Factors associated to COVID-19 vaccine acceptance in Mexican patients with rheumatic diseases: A cross-sectional and multicenter study

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### ABSTRACT

COVID-19 vaccination is recommended in patients with rheumatic diseases (RDs) to prevent hospitalized COVID-19 and worse outcomes. However, patients' willingness to receive a SARS-CoV-2 vaccine and the associated factors vary across populations, vaccines, and time. The objective was to identify factors associated with COVID-19 vaccine acceptance (VA) in Mexican outpatients with RDs. This multicenter study was performed between March 1 and September 30, 2021, and four national centers contributed with patients. Participants filled out a questionnaire, which included 32 items related to patients' perception of the patient-doctor relationship, the COVID-19 vaccine component, the pandemic severity, the RD-related disability, comorbid conditions control, immunosuppressive treatment impact on the immune system, and moral/civil position of COVID-19 vaccine. Sociodemographic, disease-related, and treatment-related variables and previous influenza record vaccination were also obtained. Multiple logistic regression analyses identified factors associated with VA, which was defined based on a questionnaire validated in our population. There were 1439 patients whose data were analyzed, and the most frequent diagnoses were Rheumatoid Arthritis in 577 patients (40.1%) and Systemic Lupus Erythematosus in 427 (29.7%). Patients were primarily middle-aged women (1235 [85.8%]), with (mean±SD) 12.1 (±4.4) years of formal education. Years of education, corticosteroid use, patient perceptions about the vaccine and the pandemic severity, patient civil/moral position regarding COVID-19 vaccine, and previous influenza vaccination were associated with VA. In Mexican patients with RDs, COVID-19 VA is associated with individual social-demographic and disease-related factors, patient's perceptions, and previous record vaccination. This information is crucial for tailoring effective vaccine messaging in Mexican patients with RDs.

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## Introduction

During the preceding months, it has become evident that either no or mild differences in COVID-19 severity had been identified in patients affected by rheumatic diseases (RDs) although particular subgroups of patients might be susceptible to poor outcomes<sup>1</sup>. Recent evidence suggests that immunocompromised patients may have prolonged viral infection and viral evolution that might result in SARS-CoV-2 variants.<sup>1</sup> Meanwhile, COVID-19 vaccination offers the possibility of protecting patients with RDs for hospitalized COVID-19 and worse outcomes,<sup>1,2</sup> without a significant negative impact on the trajectory of the underlying disease.<sup>3,4</sup>

Previous descriptions of RDs patients' willingness to receive a SARS-CoV-2 vaccine had shown substantial variation across populations,<sup>5–13</sup> ranging from 29.2% in participants from Istanbul (Turkey)<sup>8</sup> to 82% in Italian patients.<sup>11</sup> Reasons for vaccine hesitancy (VH), the term used to define refusal or reluctance in accepting vaccination despite the availability of vaccination

services,<sup>14</sup> are multifaceted and vary across vaccines, time, and regions. Meanwhile, the most widespread sources of VH pertain to fear of vaccine side effects, perceived low risk of vaccine-preventable diseases, and mistrust in healthcare providers.<sup>14</sup> A recent international survey among 2860 vaccinated adult patients with RMDs,<sup>4</sup> primarily white middle-aged females with RA, reported that adverse events affected up to 48% of the participants; the most frequently identified were fatigue, headache, and widespread muscle/joint pain. Similar results were confirmed in 2025 Mexican patients with autoimmune and inflammatory rheumatic diseases (AIIRD) who received six different SARS-CoV-2 vaccines.<sup>15</sup> People with RDs may have additional concerns on how their underlying disease and their immunomodulatory therapies affect the benefit and safety of receiving COVID-19 vaccination.<sup>4,16</sup> More recently, specific individual characteristics, such as experience being vulnerable, had shown to weigh on individual vaccination decisions in young, healthy Italian adults.<sup>17</sup> These findings align with the empathy-altruism hypothesis, which argues that

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empathetic concern produces altruistic motivations and triggers decisions to vaccinate to help those unable to do so.<sup>18</sup> Such a hypothesis might have a particular impact in patients with RDs, where both extrinsic and intrinsic sources of vulnerability have been described.<sup>19</sup>

In less than a year, the scientific community has succeeded in the monumental task of developing safe and effective vaccine platforms against SARS-CoV-2. The most recent COVID-19 Vaccine Clinical Guidance for Patients with Rheumatic and Musculoskeletal Diseases recommend COVID-19 vaccination (primary series and booster) in patients with RMDs and AIIRD, consistent with an age restriction (currently) valid in the EUA.<sup>2</sup> In particular, for AIIRD patients unvaccinated, either of the mRNA vaccines is recommended over other vaccine platforms, while the rapidly evolving evidence is recognized and frequent updates of the guidance are anticipated.<sup>2</sup> We are now facing the equally important question of how to convince a hesitant public to vaccinate and to continue to engage in behaviors that safeguard those unable to vaccinate until herd immunity is achieved, which appears a distant target with novel SARS-CoV-2 variants identification.<sup>17</sup> In such context, understanding the reasons for patients and physicians regarding VH is critical for informing the design of effective vaccine messaging in the community of patients with RDs. When it comes to VH, what matters most varies across time and communities, highlighting the relevance of addressing the topic from a cultural perspective. However, published evidence regarding the COVID-19 VH phenomenon in patients with RDs lacks the perspective of the Latin-American region, highly represented with low- and middle-income countries; interestingly, a higher willingness to take a COVID-19 vaccine was recently found in low-middle-income countries, compared with the United States and Russia, in the general population.<sup>20</sup>

We recently presented the rationale and the methods for the translation and cultural adaptation and validation process of a questionnaire allowing for assessing the COVID-19 VH phenomenon in Spanish-speaking patients with RDs; the questionnaire was valid, reliable, and feasible in a real outpatient setting.<sup>21</sup> The objective of the current study was to identify factors associated with COVID-19 vaccine acceptance (VA), which belongs to the continuum of the VH phenomenon, in outpatients with a wide variety of RDs from four national centers in Mexico's metropolitan areas.

## Patients and methods

### Setting and study population

Four public tertiary care level and academic centers for RDs, located in metropolitan areas in Mexico, contributed with participants: The Instituto Nacional de Ciencias Médicas y Nutrición Salvador-Zubirán (INCMYN-SZ) (Mexico City), the Hospital General de México Dr. Eduardo Liceaga (HGM-EL) (Mexico City), the Hospital General Dr. Salvador Zubirán (HG-SZ) (Chihuahua, Chihuahua) and the Hospital Universitario José Eleuterio González (HU-JEG) (Monterrey, Nuevo León). Before the pandemic, between 1,500 and 13,000 patients were attending each outpatient clinic and suffered from various RDs (Supplementary Table S1). During the

study period, consecutive outpatients with a definite rheumatologic diagnosis according to the attendant rheumatologist criteria were invited to participate. Exclusion criteria included patients on palliative care.

### Study design and patients' assessments

This cross-sectional and multicenter study was performed between March 1 and September 30, 2021 (ClinicalTrials.gov Identifier: NCT04775563). Potential participants were identified at the outpatient clinic while waiting for a scheduled consultation. Upon patient's agreement to participate, two questionnaires were administered to patients, who were instructed to fill them: The COVID-19 VH questionnaire (C19VHQ)<sup>21</sup> and a locally developed questionnaire directed to assess factors associated with vaccine uptake (C19FAVUQ). Patients could be assisted in filling questionnaires depending on patient institution allocation and patient education level.

In addition, standardized formats were used at patient study entry, by primary physicians, to assess each patient's current level of disease activity (remission, mild, moderate, and high disease activity level), disease activity control (Yes/No), and (direction of) treatment recommendations.<sup>21</sup> Relevant socio-demographic variables (sex, years of age and formal education, occupation, living with a partner, and access to Social Security benefits), disease-related variables (specific rheumatic diagnosis, years of disease duration, and comorbid conditions),<sup>22</sup> treatment-related variables (corticosteroid use [further categorized as  $\leq$  or  $>$  to 10 mg/day of prednisone or equivalent], use of conventional disease-modifying antirheumatic drugs [cDMARDs], and use of biologic DMARDs [bDMARDs] and use of other immunosuppressive treatment), and previous influenza record vaccination were obtained in standardized formats, after a careful chart review and patient interview.

### Questionnaires' construction and description

#### The C19VHQ

It is a seven-item questionnaire, in which construction and psychometric properties have been previously described.<sup>21</sup> It has been proven to be valid and reliable for assessing the COVID-19 VH phenomenon in Mexican patients with RDs. Each item is scored on a Likert scale, from 1 to 5, with higher scores translating into more VH. The "Do not know" option response is excluded from scoring. A global score is obtained as the mean of individual item scores, and to provide a score, at least six out of the seven items should be scored, which led that (mean) score range from .86 to 7.00<sup>21</sup>.

#### The C19FAVUQ

The questionnaire was integrated with 32 items distributed in 7 components (Supplementary Table S2). Items were selected based on literature review,<sup>14,23-25</sup> clinical experience of rheumatologists involved in patient care and derived from patients' participation in a focus group.

Briefly, the focus group was conducted by a social worker (Ph.D. in Sciences) and was approximately 60 min long. It was integrated with nine patients that all together were assigned four different rheumatic diagnoses (six women, age range was

34–63 years). The topic of the assessment was exploratory on particular aspects proposed by the investigators about the factors associated with vaccine uptake, with a particular focus on COVID-19 vaccine uptake.

### Description of sample

Each center contributed with at least data from 300 patients (but HU-JEG that included 288 patients), and quotes were considered to represent the distribution of the RDs for each outpatient clinic.

The final sample, which data were analyzed and the patient distribution allowed us to have a  $\geq 95\%$  power for a two-tailed test to achieve the objective described.

### Strategies for quality control

Before the study initiation, its design and objectives were shared with all the physicians involved in outpatients' care, and agreement on terminology and concepts was achieved. Also, 100 patients with RDs from the different centers participated in C19FAVUQ pilot testing.

In all the cases, questionnaires and scales were applied by trained personnel not involved in patient care, on the same day that patients visited their primary rheumatologists, and in a particular location within the outpatient clinic that was suitable for clinical research, to facilitate confidentiality and to reduce bias associated with questionnaire administration.

### Statistical analysis

Descriptive statistics were performed to describe the variables of the patients included, with frequencies and percentages for categorical variables and the mean and standard deviation (SD) for continuous variables (normal distribution of data was assumed, considering  $n \geq 1000$ ).

VH and vaccine acceptance (VA) were defined if the C19VHQ global score was  $\geq$  and  $<$  to 1.86, respectively (this cutoff was based on the 75-percentile data). Also, Likert-scale responses for each of the seven items of the C19VHQ were further grouped, and 1 and 2 Likert-scale responses were reassigned to item derived-VA.

Characteristics of patients with VA (based on the C19VHQ global score) were compared with those of their counterparts, using the  $\chi^2$  test for the categorical variables and Student's *t*-test for continuous variables.

Multiple logistic regression analysis was performed to identify factors associated with VA (dependent variable). We initially conceived a global model where variables' inclusion was based on their statistical significance in the univariate analysis ( $p \leq .10$ ) and/or their clinical relevance. A test-based backward selection was used to define the final model. Correlations between variables were examined to avoid overfitting the models, but none was relevant ( $\rho \leq .65$ ). Cox and Snell's pseudo- $R^2$  tests are reported as a measure of model fit goodness. The results are expressed as adjusted Odds Ratios (exponentiated regression coefficients,  $\exp[\beta]$ ) and their 95% confidence interval (95% CI).

Missing data (MD) were below 3%, and no imputation was performed.

All statistical tests were two-sided and evaluated at the .05 significance level. All analyses were performed using STATA (version 16.0, Stata Corp LLC, College Station, TX, USA) and SPSS (version 21.0, IBM Corp., Armonk, NY, USA).

### Ethics

The Internal Review Board from each center approved the study: Comité de Ética e Investigación del INCMYN-SZ (reference number: IRE-3467), Comité de Ética e Investigación del HGM-EL (DI/21/404-D/03/21), Comité de ética en Investigación FMyCB (CI-033-21), and Comité de Ética en Investigación de la Facultad de Medicina y Hospital Universitario Dr. José Eleuterio González (RE21–00005). Written informed consent was obtained from all the participants.

### Results

#### Population characteristics

There were 1480 patients included during the study period, although, in 1439 patients (97.2%), their information was consistently obtained, and their data were considered for analyses. The majority of patients were referred from the two centers located in Mexico City (891 [61.9%]), and the most frequent diagnoses were rheumatoid arthritis (RA) in 577 patients (40.1%) and systemic lupus erythematosus (SLE) in 427 (29.7%). There were some differences in the rheumatic diagnoses' distribution between the four centers (Table 1). In the global population, 109 patients (7.6%) had two or more different rheumatic diagnoses.

The most relevant patients' characteristics are presented in Table 2. Patients were primarily middle-aged women (1235 [85.8%]), living with a partner (812 [56.4%]) and working (650 [45.2%]). They had (mean [ $\pm$ SD]) 12.1 ( $\pm 4.4$ ) years of formal education and 10.4 ( $\pm 9.4$ ) years of disease duration. A substantial proportion of the patients (532 [37%]) had comorbid conditions. Also, their primary rheumatologist assessed the majority of them with adequate control of the underlying RD (926 [65.7%]). Regarding treatment, most of the patients received cDMARDs (1094 [76%]), while few received corticosteroids (517 [35.9%]) and immunosuppressive drugs (335 [23.3%]), and a minority bDMARDs (70 [4.9%]). Finally, and in accordance with disease activity status at study entry, there were no treatment changes recommended in the majority of patients (868 [61.6%]).

#### Attitudes regarding COVID-19 vaccine

Table 3 summarizes the most relevant results from the C19FAVUQ. Overall, patients totally agreed/agreed with positive components of the patient–doctor relationship (PDR) (1286 [89.4%] to 1337 [92.9%]), and their additional responses translated into a good perception of different aspects of COVID-19 vaccines and vaccination (604 [59.9%] to 1253 [97.9%]). The majority of the patients totally agreed/agreed that they will not get infected with

**Table 1.** Distribution of the main diagnoses from the patients whose data were analyzed (number of patients [%]).

	Overall population n = 1439* (100%)	INCMYn-SZ n = 556* (38.6%)	HGM-EL n = 335* (3.3%)	HG-SZ n = 300* (20.8%)	HU-JEG n = 248* (17.2%)
RA	577 (40.1)	166 (29.9)	145 (43.3)	139 (46.3)	127 (51.2)
SLE	427 (29.7)	243 (43.7)	119 (35.5)	28 (9.3)	37 (14.9)
Osteoarthritis	77 (5.4)	4 (.7)	0	50 (16.7)	23 (9.3)
Primary Sjögren Syndrome	66 (4.6)	39 (7)	6 (1.8)	9 (3)	12 (4.8)
Systemic Sclerosis	66 (4.6)	41 (7.4)	20 (6)	3 (1)	2 (.8)
Spondyloarthritis	57 (4)	18 (3.2)	6 (1.8)	20 (6.7)	13 (5.2)
PAPS	55 (3.8)	45 (8.1)	6 (1.8)	3 (1)	5 (2)
Inflammatory myopathies	44 (3.1)	19 (3.4)	2 (.6)	3 (1)	5 (2)
Systemic vasculitis	39 (2.7)	24 (4.3)	9 (2.7)	2 (.7)	4 (1.6)
Gout	23 (1.6)	4 (.7)	13 (3.9)	6 (2)	0
Juvenile idiopathic arthritis	16 (1.1)	5 (.9)	2 (.6)	6 (2)	3 (1.2)
MCTD	16 (1.1)	14 (2.5)	1 (.3)	1 (.3)	0
Other diagnoses	101 (7)	20 (3.6)	6 (1.8)	40 (13.3)	35 (14.1)

RA=Rheumatoid Arthritis. SLE=Systemic Lupus Erythematosus. PAPS=Primary Anti-Phospholipid Syndrome. MCTD=Mixed Connective Tissue Disease. \*There were 3%-13.3% of the patients with  $\geq 2$  different rheumatic diagnoses.

**Table 2.** Population characteristics and their comparison between patients with and without VA.

	Overall population n = 1439	Patients with VA <sup>2</sup> n = 992 (72.2%)	Patients with VH <sup>2</sup> n = 382 (27.8%)	p
<b>Socio-demographic characteristics</b>				
Age, years	47.4 ( $\pm 14.3$ )	48.2 ( $\pm 14.3$ )	45.7 ( $\pm 14.3$ )	0.004
Females*	1235 (85.8)	846 (85.3)	329 (86.1)	0.733
Formal education, years (16MD)	12.1 ( $\pm 4.4$ )	12.4 ( $\pm 4.4$ )	11.4 ( $\pm 4.3$ )	$\leq 0.001$
Living with a partner*	812 (56.4)	578 (58.3)	202 (52.9)	0.078
Formal and non-formal job*	650 (45.2)	473 (47.7)	158 (41.4)	0.040
Access to Social Security benefits*	751 (52.2)	516 (52)	151 (39.5)	$\leq 0.001$
<b>RD-related characteristics</b>				
RA diagnosis*	577 (40.1)	404 (41)	154 (40.3)	0.854
SLE diagnosis*	427 (29.7)	277 (27.9)	123 (32.2)	0.127
Disease duration, years (5MD)	10.4 ( $\pm 9.4$ )	10.4 ( $\pm 9.6$ )	10.5 ( $\pm 9$ )	0.937
Rheumatic disease comorbidity index score	0.51 ( $\pm 0.79$ )	0.51 ( $\pm 0.8$ )	0.51 ( $\pm 0.78$ )	0.916
Rheumatic disease comorbidity index score $\geq 1$ *	532 (37)	358 (36.1)	145 (38)	0.532
Adequate control of the rheumatic disease* (30MD)	926 (65.7)	657 (67.5)	234 (62.7)	0.107
Remission* (30MD)	868 (61.6)	625 (64.2)	214 (57.4)	0.024
<b>Treatment-related characteristics</b>				
Corticosteroid use*	517 (35.9)	311 (31.4)	170 (44.5)	$\leq 0.001$
Corticosteroids equivalent to $\leq 10$ mg/day of prednisone* <sup>1</sup>	341 (66)	213 (68.5)	110 (64.7)	0.418
cDMARDs use*	1094 (76)	746 (75.2)	300 (78.5)	0.204
bDMARDs use*	70 (4.9)	41 (4.1)	25 (6.5)	0.067
Other immunosuppressive drugs use* <sup>3</sup>	335 (23.3)	203 (20.5)	106 (27.7)	0.005
<b>Treatment recommendation at study entry (30MD)</b>				
No changes*	868 (61.6)	629 (64.6)	203 (54.4)	0.001
Changes due to clinical improvement* <sup>4</sup>	220 (40.7)	155 (45.1)	59 (34.7)	0.029
Changes due to substantial disease-related activity* <sup>4</sup>	277 (51.2)	163 (47.4)	95 (55.9)	0.075

\*Number (%) of patients. Data presented as mean ( $\pm$ SD) unless otherwise indicated. <sup>1</sup>Among those on corticosteroids. MD=Missing data. RA=Rheumatoid arthritis. SLE=Systemic lupus erythematosus. DMARDs=Disease modifying anti-rheumatic drugs. RD=Rheumatic disease. cDMARDs=conventional disease modifying anti-rheumatic drugs. bDMARDs=biologic disease modifying anti-rheumatic drugs. <sup>2</sup>There were 1374 (95.5%) patients in whom the C19VHQ was scored (at least six out of the seven items were scored). <sup>3</sup>Azathioprine, cyclophosphamide, and mycophenolic acid. <sup>4</sup>Among those with treatment changes.

COVID-19 over the next 12 months (604 [59.9%]) and referred to a very high/high perception of the pandemic severity (1302 [90.4%]). In general, patients' perception of their disability related to the underlying RD was low, while their score of comorbid conditions' control showed an area for improvement. A minority of them (471 [32.7%]) referred to a very high/high perception of the (immunosuppressive) treatment impact on their immune system. Finally, most of the patients (1369 [95.1%]) strongly agreed/partially agreed that the COVID-19 vaccine should be offered as a right by health authorities, while 890 patients (61.8%) strongly agreed/partially agreed it should be imposed. A significant proportion of the patients (408 [28.4%]) would change their willingness to get vaccinated if

vaccination becomes an obligation, and half of the patients strongly agreed/agreed on the influence of the vaccine "brand" in the desire to get/not get vaccinated.

There were 328 patients (22.8%) who self-referred influenza vaccination each of the previous 5 years, while 413 (28.7%) denied it (Figure 1).

### Rates of VA

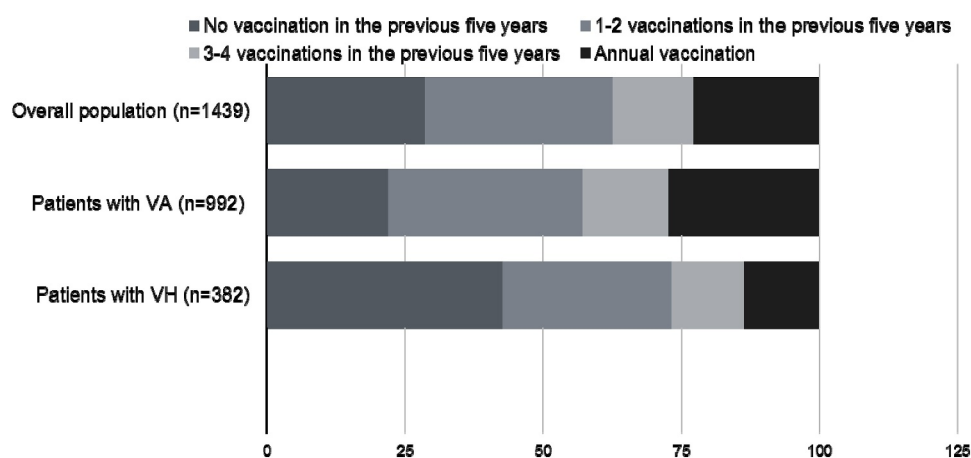
There were 1374 (95.5%) patients in whom the C19VHQ was scored (at least six out of seven items with "I do not know" option not scored), and 992 (72.2%) of them were classified as with VA (C19VHQ score  $\geq 1.86$ ).



**Table 3.** Description of factors associated with vaccine uptake and their comparison between patients with global-VA and their counterparts.

	Overall population n=1439	Patients with VA <sup>1</sup> n=992 (72.2%)	Patients with VH <sup>1</sup> n=382 (27.8%)	p
<b>Patient-doctor relationship component <sup>2</sup></b>				
"I trust my doctor"	1332 (92.6)	928 (93.5)	353 (92.4)	0.472
"My doctor makes an effort to help me"	1337 (92.9)	933 (94.1)	350 (91.6)	0.115
"I can talk to my doctor"	1286 (89.4)	901 (90.8)	332 (86.9)	<b>0.037</b>
<b>Patient' perception of the COVID-19 vaccine component <sup>3</sup></b>				
Do you think you will be infected with COVID-19 over the next 12 months? (29.9%)	604 (59.9)	437 (61.7)	153 (56.7)	0.165
The COVID-19 vaccine is likely to work... (for others) (8.1%)	1016 (76.9)	818 (87)	187 (55.8)	<b>≤0.0001</b>
The COVID-19 vaccine is likely to work... (for me) (11.6%)	1075 (84.5)	849 (91.7)	212 (68.8)	<b>≤0.0001</b>
If I get the COVID-19 vaccine it will be helpful... (for the community) (5.3%)	1307 (95.9)	965 (98.5)	312 (89.9)	<b>≤0.0001</b>
If individuals like me get the COVID-19 vaccine it will... (impact on mortality) (11%)	1253 (97.9)	939 (99.5)	286 (93.5)	<b>≤0.0001</b>
The speed of developing and testing the vaccine means it will be... (goodness/badness) (17.9)	991 (83.8)	794 (91.6)	181 (64)	<b>≤0.0001</b>
The speed of developing and testing the vaccine means it will be... (safe/unsafe) (19.8%)	984 (85.3)	792 (93.2)	178 (65.4)	<b>≤0.0001</b>
If many people do not get the vaccine this... (about danger/good) (7.2%)	1298 (97.2)	955 (98.9)	314 (92.9)	<b>≤0.0001</b>
I expect that receiving the vaccine will be... (about sensations) (13.7)	1001 (80.6)	755 (83.7)	227 (73.7)	<b>≤0.0001</b>
The side effects for people of getting the COVID-19 vaccine will be... (about graduation) (19%) (19%)	817 (70.1)	654 (76.6)	149 (54)	<b>≤0.0001</b>
The COVID-19 vaccine will... (about effects on one's immune system) (21.9%)	1003 (89.2)	791 (93.4)	199 (77.1)	<b>≤0.0001</b>
Taking the COVID-19 vaccine... (about one's freedom) (10.4%)	817 (63.4)	647 (68.8)	153 (48.1)	<b>≤0.0001</b>
Getting the vaccine is a sign of... (about personal strength/weakness) (8%)	955 (72.1)	743 (78.6)	197 (57.6)	<b>≤0.0001</b>
Taking a new COVID-19 vaccine will make me feel like a guinea pig... (9.6%)	226 (17.4)	90 (9.9)	116 (33.5)	<b>≤0.0001</b>
<b>Patient' perception of the pandemic severity component</b>				
Patients with very high/high perception of the pandemic severity	1301 (90.4)	923 (93)	323 (84.6)	<b>≤0.0001</b>
<b>Patient' perception of RD-related disability component (MD=4)</b>				
Mean (±SD) HAQ-DI (adapted versión)	0.51 (±0.79)	0.29 (±0.46)	0.35 (±0.52)	0.081
<b>Patient' perception of comorbid conditions control component (MD=2)</b>				
Mean (±SD) Visual Analogue Scale	50.9 (±36.7)	50.8 (±36.8)	51.7 (±36.8)	0.713
<b>Patient' perception of immunosuppressive treatment impact on immune system</b>				
Patients with very high/high perception of immunosuppressive treatment impact on immune system	471 (32.7)	320 (32.3)	122 (31.9)	0.950
<b>Patient' statement regarding COVID-19 vaccine (Human rights approach)</b>				
The vaccine for COVID-19 should be offered by health authorities as a right... (Strongly agree/partially agree)	1369 (95.1)	960 (96.8)	353 (92.4)	<b>≤0.0001</b>
The vaccine for COVID-19 should be imposed by the health authorities as an obligation (Strongly agree/partially agree)	890 (61.8)	692 (69.8)	183 (47.9)	<b>≤0.0001</b>
Patients who would change their willingness to get the vaccine if vaccination becomes an obligation	408 (28.4)	221 (22.3)	151 (39.5)	<b>≤0.0001</b>
The brand or type of vaccine for COVID-19 influences my desire or not to get vaccinated (Strongly agree/partially agree)	649 (49.5)	418 (42.1)	203 (53.1)	<b>≤0.0001</b>

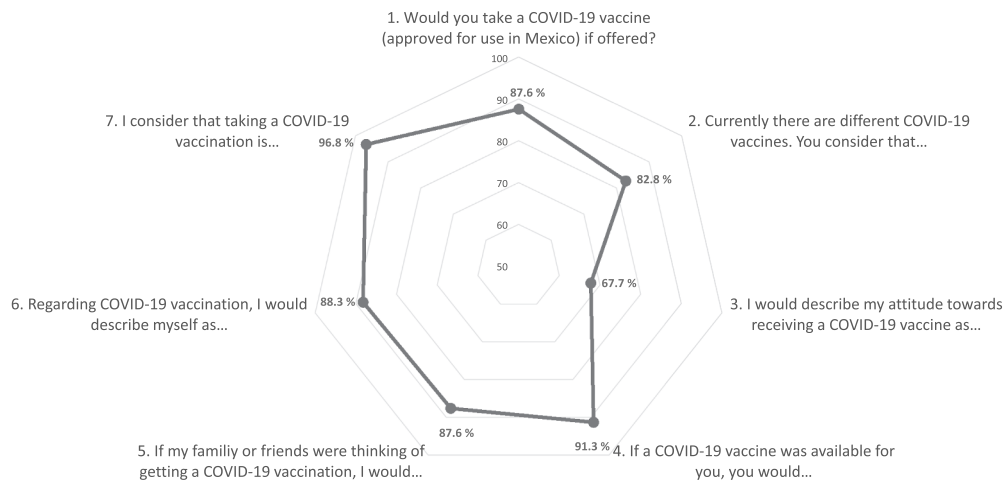
<sup>1</sup>There were 1374 (95.5%) patients in whom the C19VHQ was scored (at least six out of the seven items were scored). <sup>2</sup>Patients who totally agreed/agreed. <sup>3</sup>Patients who scored one of the first two options of the scale response (which translates into a positive perception regarding vaccination and into the perception that they will not get COVID-19 over the next 12 months). Data presented as N° (%) of patients unless otherwise indicated. MD=Missing data.

**Figure 1.** Self-referred influenza vaccination during the previous (to study entry) 5-year period and the comparison between patients with VA and VH.[a]

Also, VA for each individual item of the C19VHQ showed some variations, with the lowest rate for item 3 (n = 974 [67.7%]) and the highest for item 7 (n = 1393 [96.8%]), as summarized in Figure 2.

### Comparison of VA and VH patients

We first compared population characteristics between patients with VA and their counterparts. Patients from the former group were older, more educated, had more frequently a job



**Figure 2.** VA for each individual item (N = 1439, no missing data).

and access to Social Security benefits, and were more frequently assessed by their primary physician as in remission status than patients with VH. Also, they had lesser frequently indicated corticosteroids and immunosuppressive drugs, while a similar tendency was shown regarding bDMARDs. Finally, they had more frequently no changes in their treatment at study entry; meanwhile, among those with treatment changes, the direction was more frequently related to clinical improvement compared to patients with VH (Table 2).

Table 3 compares the patients' responses to the C19FAVUQ between patients with VA and their counterparts. Compared to VH-patients, patients from the former group more frequently totally agreed/agreed with the item "I can talk to my doctor" from the PDR component, had more frequently a favorable perception of different aspects of COVID-19 vaccines and vaccination, more frequently perceived the pandemic as severe/very severe, scored lower on RD-related disability component, and more frequently strongly agreed/partially agreed that the COVID-19 vaccine should be offered as a right by Health authorities and also that it should be an obligation. Meanwhile, these patients less frequently would change their willingness to get vaccinated if vaccination becomes an obligation and less frequently strongly agreed/agreed on the influence of the vaccine "brand" in the desire to get/not get vaccinated, compared to VH patients.

Finally, VA patients more frequently referred previous consistent influenza vaccination (Figure 1).

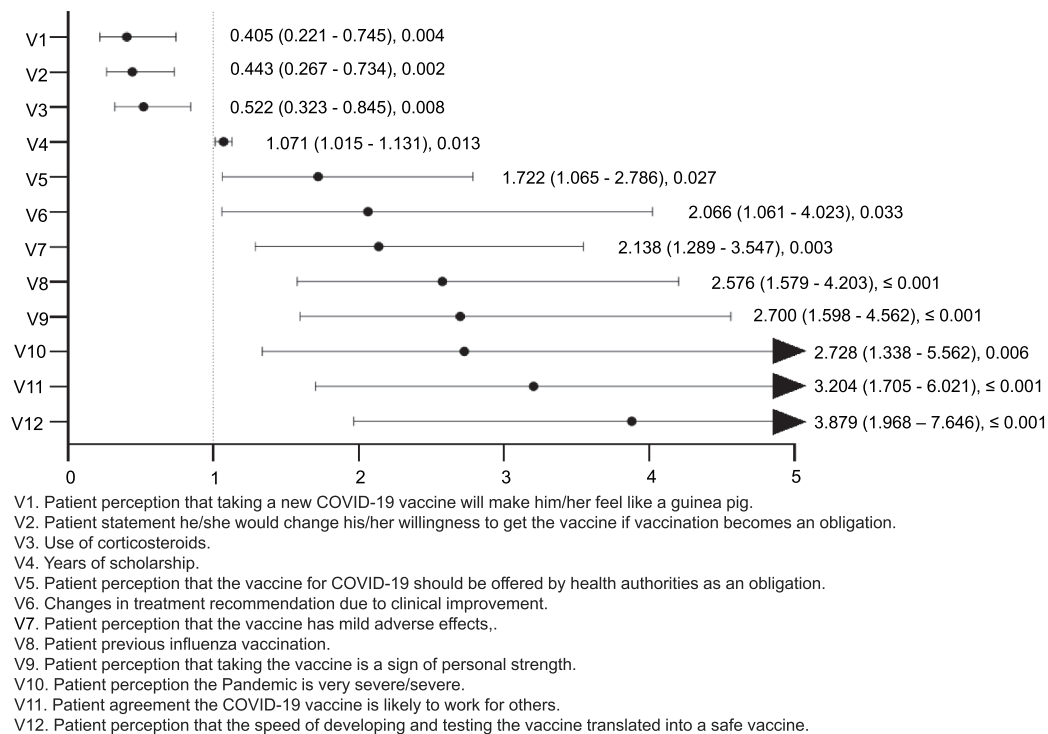
### Factors associated with VA

There were 33 variables included in the initial model (Supplementary Table S3). Figure 3 summarizes results from multivariable logistic regression analysis. Most relevant factors associated with VA were related to a positive patient perception about the COVID-19 vaccine in terms of safety and efficacy, the pandemic severity and previous patient influenza vaccination; additional factors included changes in treatment recommendation due to clinical improvement and corticosteroid use (protective), patient position regarding COVID-19 vaccine from a Civil rights/moral approach, and years of scholarship.

### Discussion

The study revealed that up to 72.2% of Mexican outpatients with RDs rated the C19VHQ with VA, while significant variations were identified when considering individual item responses. The influence of survey designs, question framing, and answer options on individuals' mind-set and COVID-19 vaccine receptivity, has been recently highlighted.<sup>26</sup> In addition, a wide range of COVID-19 VA rates have been described across different populations of patients with RDs, and the studies in which data were analyzed were all survey-based.<sup>5-13,27</sup> In these studies, patients from the Latin-American region were underrepresented,<sup>27,28</sup> while it has emphasized the relevance of addressing the scope of COVID-19 hesitancy in some regions, including Middle and South America.<sup>29</sup> A cluster analysis international study included 53 Mexican patients with RMDs;<sup>28</sup> patients were characterized in three clusters: "Most willing to get vaccinated," "More hesitant," and "Mostly opposed to getting vaccinated," and only five patients (10%) were assigned to the first cluster. Meanwhile, a web-based survey of more than 1000 Brazilian patients with immune-mediated inflammatory diseases found that up to 82% of the patients were willing to get vaccinated.<sup>27</sup> Our rate of VA in patients with RDs was similar to that reported by Lazarus et al.<sup>24</sup> who performed a country-level analysis in 19 countries, in June 2020; authors included 699 Mexican individuals and 76.3% had VA. In January 2021, Argote-Tironi et al.<sup>30</sup> conducted an online survey across six Latin American countries, including Mexico; only 62.5% of the participants strongly agree/agree with the statement, "If a vaccine were available to me now, I would get vaccinated" and this percentage is in accordance with a 62.3% of COVID-19 VA described in a nationally representative sample of the Mexican population.<sup>31</sup>

Relevant factors independently associated with VA were related to individual patient perceptions about the COVID-19 vaccine in terms of safety and efficacy, patient perception of the pandemic severity, patient previous influenza vaccination record, individual factors related to the treatment of the underlying rheumatic disease, the patient civil/moral position



**Figure 3.** Multiple logistic regression for VA in Mexican patients (Pseudo  $R^2 = .219$ ).

regarding COVID-19 vaccine and the patient education level. Overall, these results are generally consistent with those of the existing literature about vaccine uptake.<sup>24,30,32</sup>

A recent systematic review of the factors that contribute to COVID-19 vaccine uptake among the general population across different cultural and geographical contexts identified that individual beliefs and concerns related to vaccine efficacy, safety, and side effects, insufficient vaccine testing, and quick development pace were consistent major themes that contribute to increased VH.<sup>32</sup> In the current study, the patient perception that the speed of developing and testing the vaccine translated into a safe vaccine had the most substantial impact on VA, followed by a patient agreement that the vaccine is likely to work for others. Previous studies showed that the accelerated pace of vaccine development might increase public anxieties and compromise VA.<sup>33</sup> Indeed, individuals are more averse to the risks associated with an action—getting an “unsafe” vaccine, than to the risks associated with inaction—taking a chance of contracting an infection, which is known as the omission bias.<sup>25,34</sup> Also, patients’ perception of vaccine safety and efficacy might be considered a surrogate of trust in vaccines, which is the primary driver of vaccine uptake.<sup>35</sup> Finally, the patient perception that the vaccine has mild adverse effects was associated with VA in the current study; Gauer et al.<sup>11</sup> also found that fear related to vaccine side effects was a common reason for VH in 280 patients with a systemic autoimmune RD and 102 controls from the general population.

Patient perception of the pandemic was very severe/severe and showed a substantial impact on VA. This result aligns with the recognized association between perceived risk and individual vaccination intention, which has been confirmed among individuals who perceived themselves as vulnerable or at

greater susceptibility to COVID-19<sup>36</sup>. Also, in accordance with our results, prior receipt of other vaccines, particularly past influenza vaccination, has been positively associated with COVID-19 VA, as recently highlighted in a systematic review.<sup>36</sup> This association has been confirmed in patients with RDs.<sup>6,7,11</sup>

Two pharmacologic interventions related to the underlying RD impacted COVID-19 VA: corticosteroid use was protective, while change in treatment recommendation due to clinical improvement was a risk factor. A recent web-based survey aimed at identifying predictors of COVID-19 VH in 1000 adult Brazilians with immune-mediated inflammatory diseases identified recent corticosteroid (pulse) independently associated with higher odds of VH.<sup>27</sup> The results described might be related to the association between greater perceived susceptibility to COVID-19 and vaccination intention; previous studies had shown that moderate-to-high glucocorticoid dosages had been associated with unfavorable outcomes of COVID-19 in patients with RDs.<sup>37</sup>

The patient’s perception that health authorities should offer the COVID-19 vaccine as an obligation was associated with VA, while the patient’s statement that they would change their willingness to get the vaccine if vaccination became an obligation was protective. Seeing vaccination as a social norm is a potentially powerful driver of VA, while social norms can also result in social pressure to accept vaccination.<sup>25,38</sup> From another point of view, social responsibility translates into seeing vaccination as an individual’s duty to maintain herd immunity and protect vulnerable individuals and has also been linked with VA.<sup>25,39</sup> The patient’s perception that health authorities should offer the COVID-19 vaccine as an obligation can also be approached from the Moral Foundations Theory framework.<sup>40</sup> The theory maintains that there exist five moral

contents that can be found across cultures, with cultural variations in the importance attached to each:<sup>41</sup> care/harm, fairness/cheating, loyalty/betrayal, authority/subversion, and sanctity/degradation. The patient perspective described in the results might be representative of the authority/subversion moral foundation (which emphasizes concerns related to social order and the obligations of hierarchical relationships such as obedience, respect, and proper role fulfillment), and/or the loyalty/betrayal moral foundation (which emphasizes concerns related to obligations of group membership, such as loyalty, self-sacrifice, and vigilance against betrayal). Individual differences in primary moral concerns have been related to a more significant endorsement of conspiracy theories and VH, and individual behavior was found to contain the pandemic.<sup>42-44</sup> Finally, there is published evidence confirming that mandates could increase resistance to COVID-19 vaccine uptake,<sup>26</sup> even among those with VA as observed in the current study, which should be considered in evaluating local political measures to contain the pandemic.

The low likelihood of getting the COVID-19 vaccine among individuals with lower educational backgrounds has been previously identified and is especially concerning because of their disproportionately higher burden from COVID-19 disease.<sup>36,45</sup> Education has been traditionally described as a strong determinant of differences in health and to determine a remarkably homogeneous gradient of prevalence at the disadvantage of low educated people across age classes for many chronic diseases,<sup>46</sup> including RDs.<sup>47</sup> According to the “layers of vulnerability” framework,<sup>48</sup> lower education confers a vulnerability state, while RDs, COVID-19 pandemic, and female gender (which has been consistently associated with VH) are conditions that contribute to individual accrual vulnerability and increase the risk of adverse outcomes.

Limitations of the study need to be addressed. First, we used the C19FAVUQ to identify VA factors, and this questionnaire lacked a formal validation process. Second, we studied a limited number of potential independent variables associated with VA, while patient’s perception of disease activity level related to the underlying rheumatic disease was not assessed; also, the determinants of attitude formation toward vaccination may range from psychological, moral, cultural, or even societal.<sup>49</sup> Third, we included a large number of RD patients from across the country, but they were primarily followed up in public institutions. Fourth, the study was developed in a particular period, and VH rates varied depending on when studies were conducted.<sup>50</sup> Finally, patient self-reported metrics may not correlate with future behavior.

VH is a complex theoretical construct, whose measurement should ideally involve its operationalization in a defined variable and the development and application of an instrument to its adequate quantification.<sup>21</sup> We previously found the C19VHQ was valid and reliable to assess the VH phenomenon in Mexican patients with RDs;<sup>21</sup> validity and reliability are critical indicators of the quality of a measuring instrument. The current study adds valuable information regarding VH determinants, in a substantial number of Mexican participants with a wide range of different rheumatologic diagnoses, while four public tertiary-care level centers in metropolitan areas contributed with

patients. We consider the results could be generalized to Mexican patients with RDs and populations with similar characteristics and cultural backgrounds.

## Conclusions

The current study identified the participants in COVID-19 VA among Mexican patients with RDs. Positive attitudinal beliefs about the COVID-19 vaccine and the subjective perception of the pandemic severity had the most significant impact, followed by previous individual vaccination record, which can be easily identified as a “red flag” on daily care. VA contextual factors observed were related to the underlying treatment and disease trajectory. Civil/moral factors had an additional impact, and their contribution to the VA phenomenon might be unique to the cultural background of the study population. Finally, education, which confers a consistent vulnerability state across populations, showed a little contribution to VA.<sup>1</sup>

## Note

- [a] Data are presented as number of patients (%). p value  $\leq$ .0001 for comparison of previous influenza vaccination between VA and VH patients.

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