


# Influenza Vaccine Hesitancy and Its Determinants Among Rheumatology Patients

Valeria Valerio,<sup>1</sup> Marie Hudson,<sup>2</sup> Mianbo Wang,<sup>3</sup> Sasha Bernatsky,<sup>4</sup>  Elizabeth M. Hazel,<sup>5</sup> Brian Ward,<sup>4</sup> and Inés Colmegna<sup>4</sup> 

**Objective.** Patients with rheumatic disease (RD) have an increased risk of influenza and its complications. Despite inactivated influenza vaccine (IIV) recommendations, IIV uptake in patients with RD is suboptimal, a problem of increasing importance in the COVID-19 era. We estimated the frequency of IIV hesitancy and associated factors among Canadian patients with RD.

**Methods.** A cross-sectional vaccine hesitancy survey was completed by rheumatology clinic patients (November 2019 to January 2020). Patients rated their likelihood of receiving the influenza vaccine (scale of 0–10). We categorized these as follows: likely to refuse (scale of 0–2), uncertain (scale of 3–7), or likely to accept (scale of 8–10). Multivariate logistical regression was used to evaluate factors associated with vaccine hesitancy.

**Results.** A total of 282 patients (63.5% of those approached) completed the survey, with 165 (58.5%) being likely to accept, 67 (23.8%) being likely to refuse, and 50 (17.7%) uncertain. Uncertain patients were younger and more likely to be employed than those in the other two groups. No previous influenza vaccination (odds ratio [OR] 36.6, 95% confidence interval [CI] 5.3–252.9), belief that vaccination should not be mandatory (OR 0.1, 95% CI 0.0–0.7), unwillingness to take time off work to be vaccinated (OR 6.8, 95% CI 1.5–30.6), and distrust in pharmaceutical companies (OR 41.0, 95% CI 5.6–301.5) predicted likeliness to refuse. Reluctance to pay for vaccination (OR 2.8, 95% CI 1.1–7.5) and no previous influenza vaccination (OR 18.9, 95% CI 3.3–109.7) predicted uncertainty.

**Conclusion.** More than 40% of rheumatology patients are either likely to refuse or uncertain about receiving IIV. This contributes to suboptimal vaccine coverage in this population. Interventions addressing these concerns are needed, particularly in the COVID-19 era.

## INTRODUCTION

Influenza and pneumonia are among the top 10 leading causes of death in North America (1,2). Influenza's annual global attack rate (i.e., percentage of an at-risk population contracting the disease during a specified time interval) is ~10% in adults (3). Influenza's estimated respiratory-associated mortality is 300,000 to 650,000 deaths per year globally (4.0–8.8 per 100,000 individuals) (4). Most patients with rheumatic disease (RD) have an increased influenza risk compared with the general population (eg, first severe influenza and pneumonia infection in patients with antineutrophil-cytoplasmic-antibody-associated

vasculitis [unadjusted rate ratio 3.3, 95% confidence interval (CI) 2.2–4.8]; rheumatoid arthritis [RA] adjusted incidence rate of influenza: 1.22, 95% CI 1.05–1.41) (5,6). In addition, patients with RA have a higher risk of influenza-related complications (incidence rate ratio adjusted for baseline characteristics 1.82, 95% CI 1.16–2.81), including pneumonia, stroke, and myocardial infarction (6). The inactivated influenza vaccine (IIV) reduces the incidence, complications, hospitalizations, and mortality from influenza in patients with RD (7,8). Hence, influenza vaccination is of high importance in this at-risk population.

Multiple rheumatology societies recommend annual IIV for patients with autoimmune inflammatory RD on immunosuppressants

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<sup>1</sup>Valeria Valerio, MD: The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada; <sup>2</sup>Marie Hudson, MD, MPH: Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada; <sup>3</sup>Mianbo Wang, MSc: Lady Davis Institute, Montreal, Quebec, Canada; <sup>4</sup>Sasha Bernatsky, MD, PhD, Brian Ward, MSc, MDCM, Inés Colmegna, MD: The Research Institute of the McGill University Health Centre and McGill University, Montreal, Quebec, Canada; <sup>5</sup>Elizabeth M. Hazel, MD: McGill University, Montreal, Quebec, Canada.

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Address correspondence to Inés Colmegna, MD, The Research Institute of the McGill University Health Centre, Office EM2-3238, 1001 Decarie Boulevard, Montreal, Quebec H4A 3J1, Canada. Email: [ines.colmegna.med@sss.gouv.qc.ca](mailto:ines.colmegna.med@sss.gouv.qc.ca).

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(7,9). Moreover, IIV is a quality indicator in some rheumatology settings (10). Despite current recommendations, IIV uptake in patients with RD is suboptimal, with coverage rates of 32% to 49% (11). This falls well below the influenza immunization target of 75% to 80% established by different health organizations for adults with chronic medical conditions (12,13).

Delay in acceptance or refusal of vaccination despite the availability of vaccination services, known as vaccine hesitancy, is multifactorial, encompassing cultural, psychosocial, spiritual, political, and cognitive factors (14,15). According to the World Health Organization Strategic Advisory Group of Experts (WHO-SAGE), vaccine hesitancy is influenced by three types of determinants: (a) contextual: historical, sociocultural, environmental, health system or institutional, economic, or political factors; (b) individual or group dependent: personal perception of the vaccine or influences of the social or peer environment; and (c) vaccine or vaccination specific (16). Vaccine hesitancy is highly variable across time, place, and vaccine and represents one of the main threats to global health (17).

Understanding the frequency and determinants of IIV hesitancy in rheumatology is key to increasing IIV coverage. We report the results of a self-administered questionnaire completed by patients with RD to evaluate IIV hesitancy in this vulnerable population.

## MATERIAL AND METHODS

**Study design.** Between November 1, 2019, and January 1, 2020, adults with RD presenting to the outpatient rheumatology specialty clinics (ie, inflammatory arthritis clinic, systemic lupus erythematosus [SLE] or vasculitis clinic) of the Montreal General Hospital for routine evaluation were asked to complete a one-time self-administered vaccine hesitancy questionnaire. This was a pen-and-paper survey administered prior to the rheumatology visit. This study was approved by the Research Ethics Board of the McGill University Health Centre (protocol number MP-37-2017-2794).

**Measurement and variables.** The survey consisted of three sections: (a) demographics, (b) influenza vaccine uptake, and (c) determinants of influenza vaccine hesitancy (questions proposed by the WHO-SAGE) (18,19). The data collected in each section included the following:

a. Demographics: sex, age, highest level of education, current employment, civil status, RD diagnosis (RA; spondyloarthritis [SpA]; systemic autoimmune rheumatic diseases [SARDs], which included systemic vasculitis, SLE, immunoglobulin-G4-related disease, Sjögren syndrome, antiphospholipid syndrome, Cogan syndrome, relapsing polychondritis, inflammatory myositis, and mixed connective tissue disease; osteoarthritis [OA] and fibromyalgia [FM]; and other diseases), RD duration, current treatment, and smoking status.

b. Influenza vaccine uptake: previous acceptance of IIV, reasons for nonvaccination in the 2018-2019 influenza season, and influenza vaccine acceptance by family members. The likelihood of receiving IIV was assessed on a 0 to 10 Likert scale (0: “I definitely will not get the flu vaccine”; 10: “I unquestionably will get the flu vaccine”).

c. Factors associated with influenza vaccine hesitancy: WHO-SAGE questions about most and least trustworthy sources of information on vaccines; the influence of leadership on vaccine acceptance (eg, celebrities, religious leaders); trust in government, pharmaceutical companies, and health care providers; barriers to vaccination (eg, vaccine-related costs, distance to vaccine provider, time off work, fear of needles); influence of personal or third-party negative experiences with vaccination; beliefs about disease prevention; influenza vaccine and influenza disease; satisfaction about available vaccine information; and opinion on whether IIV should be mandatory.

The questionnaire did not contain identifiers, it was available in English and French, and participants chose to complete it in their preferred language. The questionnaire was initially developed in English, and the French version was developed by systematic question-by-question translation with adaptation notes that were discussed, tested, implemented, and confirmed with back translation.

**Statistical analysis.** Baseline characteristics of the study group and distributions of responses were reported using descriptive statistics. Categorical variables were presented as frequency and percentage relative to the total participants from whom data were available, and continuous variables were expressed as mean  $\pm$  standard deviation. On the basis of self-reported willingness to receive IIV, three groups were defined: (a) likely to refuse (values 0-2), (b) uncertain (values 3-7), and (c) likely to accept (values 8-10). Baseline characteristics were compared between groups. Univariate logistical regression models were generated to assess factors associated with IIV uncertainty and refusal. All multivariate models included sex, age, and RD diagnosis, as well as univariate predictors below the  $P < 0.05$  level of significance. A sensitivity analysis using different cutoffs (likely to refuse [value 0], uncertain [values 1-9], and likely to accept [value 10]) was performed (Supplementary Tables 1-3).

## RESULTS

**Study population.** Four hundred forty-four rheumatology outpatients were approached, and 282 (63.5%) completed the survey. Most were middle-aged (mean age  $\pm$  SD: 51.5  $\pm$  17.3; minimum 18, maximum 91) English speakers ( $n = 189$ , 67%) and women ( $n = 178$ , 64.5%) (Table 1). Most patients had education beyond high school ( $n = 180$ , 65.2%), were married or living in common-law relationships ( $n = 160$ , 57.1%), and were employed

**Table 1.** Participants general characteristics (n = 282) according to likelihood of receiving IIV

Variable	Whole population (N = 282)	Likely to refuse (n = 67)	Uncertain (n = 50)	Likely to accept (n = 165)
Sex, n (%)				
Female	178 (64.5)	42 (63.6)	32 (64.0)	104 (65.0)
Male	98 (35.5)	24 (36.4)	18 (36.0)	56 (35.0)
Age, <sup>a,b</sup> mean ± SD	51.5 ± 17.3	52.5 ± 15.0	44.4 ± 16.3	53.2 ± 18.0
Marital status, n (%)				
Single	77 (27.5)	15 (22.7)	14 (28.0)	48 (29.3)
Married or common law	160 (57.1)	34 (51.5)	30 (60.0)	96 (58.5)
Widowed	14 (5.0)	5 (7.6)	1 (2.0)	8 (4.9)
Divorced	29 (10.4)	12 (18.2)	5 (10.0)	12 (7.3)
Language of preference, n (%)				
English	189 (67.0)	39 (58.2)	34 (68.0)	116 (70.3)
French	93 (33.0)	28 (41.8)	16 (32.0)	49 (29.7)
School degree, n (%)				
No certificate, diploma, or degree	19 (6.9)	4 (6.0)	2 (4.2)	13 (8.1)
Secondary or high school graduate	77 (27.9)	19 (28.4)	19 (39.6)	39 (24.2)
Apprenticeship or trades certificate or diploma	34 (12.3)	13 (19.4)	4 (8.3)	17 (10.6)
College diploma or other nonuniversity certificate	10 (3.6)	2 (3.0)	1 (2.1)	7 (4.4)
University certificate, diploma, or degree at bachelor level or above	136 (49.3)	29 (43.3)	22 (45.8)	85 (52.8)
Employment status, <sup>d</sup> n (%)				
Not employed	45 (16.1)	7 (10.4)	11 (22.0)	27 (16.6)
Employed	152 (54.3)	40 (59.7)	33 (66)	79 (48.4)
Retired	83 (29.6)	20 (29.9)	6 (12.0)	57 (35.0)
Diagnosis, n (%)				
Rheumatoid arthritis	87 (30.9)	24 (35.8)	12 (24.0)	51 (30.9)
Systemic autoimmune rheumatic diseases	107 (37.9)	23 (34.3)	22 (44.0)	62 (37.6)
Spondyloarthropathies	54 (19.1)	12 (17.9)	11 (22.0)	31 (18.8)
Mechanical or crystal or fibromyalgia	28 (9.9)	7 (10.5)	3 (6.0)	18 (10.9)
Other <sup>c</sup>	6 (2.1)	1 (1.5)	2 (4.0)	3 (1.8)
Disease duration, mean ± SD	9.8 ± 10.4	8.6 ± 7.5	7.7 ± 9.8	11.0 ± 11.5
Treatment, n (%)				
No immunosuppressant treatment	121 (43.8)	34 (52.3)	22 (44.9)	65 (40.1)
DMARDs <sup>d</sup>	62 (22.5)	17 (26.2)	14 (28.6)	31 (19.1)
Biologics	68 (24.6)	9 (13.9)	12 (24.5)	47 (29.0)
Immunosuppressants <sup>e</sup>	25 (9.1)	5 (7.7)	1 (2.0)	19 (11.7)
Smoking status, n (%)				
Yes	250 (90.3)	6 (9.2)	5 (10.0)	16 (9.9)
No	27 (9.7)	59 (90.8)	45 (90.0)	146 (90.1)

Abbreviations: DMARD, disease-modifying antirheumatic drug; IIV, inactivated influenza vaccine.

<sup>a</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were uncertain about receiving it was statistically significant ( $P \leq 0.05$ ).

<sup>b</sup> The comparison between participants who were uncertain about receiving the influenza vaccine and those who were likely to accept it was statistically significant ( $P \leq 0.05$ ).

<sup>c</sup> Idiopathic erythema nodosum and polymyalgia rheumatica.

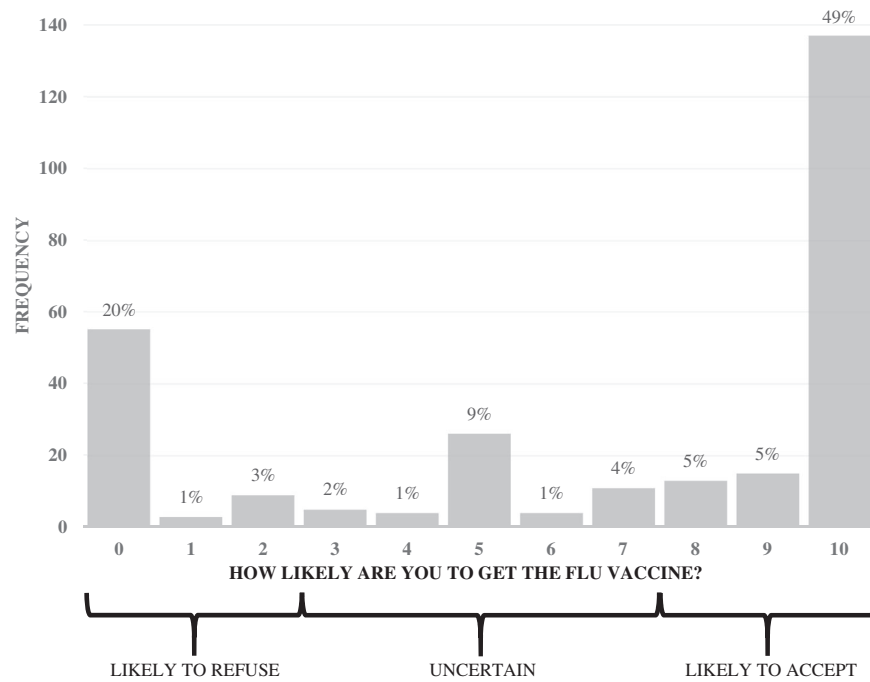
<sup>d</sup> Methotrexate, hydroxychloroquine, sulfasalazine, tofacitinib, and apremilast.

<sup>e</sup> Azathioprine, mycophenolate mofetil, and cyclosporine.

(n = 152, 54.3%). RD diagnoses included SARDs (n = 107, 37.9%), RA (n = 87, 30.9%), SpA (n = 54, 19.1%), OA and FM (n = 28, 9.9%), and other diagnoses (eg, polymyalgia rheumatica, erythema nodosum) (n = 6, 2.1%). The overall disease duration was  $9.8 \pm 10.4$  years, and most patients were treated (n = 155, 56.2%; most commonly with disease-modifying antirheumatic drugs [n = 62, 22.5%], biologics [n = 68, 24.6%], and other immunosuppressants [eg, mycophenolate mofetil] [n = 25, 9.1%]). Most participants (n = 250, 90.3%) were nonsmokers.

Most patients with RD reported being likely to accept IIV (n = 165, 58.5%), 23.8% (n = 67) were likely to refuse it, and 17.7% (n = 50) were uncertain about receiving IIV (Figure 1).

Uncertain patients were younger (uncertain vs likely to accept:  $44.4 \pm 16.3$  vs  $53.2 \pm 18.0$ ,  $P = 0.003$ ; uncertain vs likely to refuse:  $44.4 \pm 16.3$  vs  $52.5 \pm 15.0$ ,  $P = 0.01$ ), and they were more frequently employed than those likely to accept IIV (uncertain vs likely to accept: 66% vs 48.4%,  $P = 0.02$ ). No other differences between groups were found.



**Figure 1.** Participants’ self-reported willingness to receive inactivated influenza vaccine (IIV). Distribution of the willingness to receive IIV on a scale of 0 to 10 (0 = “I definitely will not get the flu vaccine,” and 10 = “I unquestionably will get the flu vaccine”). The graph also shows the cutoffs used to classify patients with rheumatic diseases in three categories: (a) likely to refuse, (b) uncertain, and (c) likely to accept.

**Vaccination status.** Overall, most participants with RD (n = 226, 80.4%) had previously received IIV (Table 2). Patients likely to refuse less frequently reported having previously received IIV (likely to refuse vs uncertain: 46.3% vs 67.3%, *P* = 0.02; likely to refuse vs likely to accept: 46.3% vs 98.2%, *P* < 0.001). Characteristics of patients with RD who had previously received IIV are summarized in Supplementary Table 4. Forty-one percent of participants (n = 114) did not receive IIV in 2018-2019, and 43 patients (37.7%) reported the reasons for this. Those included the belief that IIV was not needed (27.9%), personal reasons (eg,

forgot, did not have the chance, etc) (27.9%), negative past experiences (14%), uncertainty about vaccine efficacy (14%), lack of health care professional (HCP) recommendation (7%), fear of side effects (4.7%), and difficulties to access IIV (4.7%). Past negative experiences with vaccination and doubts about vaccine efficacy were more frequently reported by patients likely to refuse IIV, whereas lack of HCP recommendation was more commonly reported by those who were uncertain (likely to refuse vs uncertain: bad past experiences: 23.1% vs 0%; vaccine efficacy uncertainty: 19.2% vs 0%; lack of HCP recommendation: 0% vs 25%,

**Table 2.** Vaccination status according to vaccine hesitancy

Vaccination status	Whole population (N = 282), n (%)	Likely to refuse (n = 67), n (%)	Uncertain (n = 50), n (%)	Likely to accept (n = 165), n (%)
Previous IIV <sup>a,b,c</sup>				
No	55 (19.6)	36 (53.7)	16 (32.7)	3 (1.8)
Yes	226 (80.4)	31 (46.3)	33 (67.3)	162 (98.2)
IIV last year (2018-2019) <sup>a,b,c</sup>				
No	114 (40.6)	62 (92.5)	35 (71.4)	17 (10.3)
Yes	167 (59.4)	5 (7.5)	14 (28.6)	148 (89.7)
IIV every year since the RD diagnosis <sup>a,b,c</sup>				
No	144 (54.1)	63 (96.9)	38 (84.4)	43 (27.6)
Yes	122 (45.9)	2 (3.1)	7 (15.6)	113 (72.4)

Abbreviations: IIV, inactivated influenza vaccine; RD, rheumatic disease.

<sup>a</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were likely to accept it was statistically significant (*P* < 0.001).

<sup>b</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were uncertain about receiving it was statistically significant (*P* ≤ 0.05).

<sup>c</sup> The comparison between participants who were uncertain about receiving the influenza vaccine and those who were likely to accept it was statistically significant (*P* < 0.001).

**Table 3.** WHO-SAGE questions to assess vaccine hesitancy in rheumatology patients according to likelihood to receive IIV

Variables	Whole population (N = 282), n (%)	Likely to refuse (n = 67), n (%)	Uncertain (n = 50), n (%)	Likely to accept (n = 165), n (%)
<b>Contextual influences</b>				
The most trusted source of information on vaccines				
Health care professionals	173 (62.7)	37 (59.7)	29 (58)	107 (65.2)
Health authorities	17 (6.2)	3 (4.8)	3 (6)	11 (6.7)
Social media and Internet	1 (0.4)	1 (1.6)	0	0
Family and friends and other patients	9 (3.3)	5 (8.1)	1 (2)	3 (1.8)
Pharmaceutical companies	1 (0.4)	1 (1.6)	0	0
>1 of those mentioned above	75 (27.2)	15 (24.2)	17 (34)	43 (26.2)
Least trusted source of information on vaccines <sup>a</sup>				
Health care professionals	25 (9.2)	6 (9.4)	7 (14)	12 (7.6)
Health authorities	5 (1.8)	1 (1.6)	1 (2)	3 (1.9)
Social media and Internet	135 (49.8)	24 (37.5)	20 (40)	91 (58)
Family and friends and other patients	17 (6.3)	3 (4.7)	3 (6)	11 (7)
Pharmaceutical companies	16 (5.9)	9 (14.1)	3 (6)	4 (2.5)
>1 of those mentioned above	73 (26.9)	21 (32.8)	16 (32)	36 (22.9)
Doubts triggered if a celebrity advocates against influenza vaccine				
No	261 (97.4)	62 (95.4)	47 (97.9)	152 (98.1)
Yes	7 (2.6)	3 (4.6)	1 (2.1)	3 (1.9)
Imam, priest, or rabbi has ever advocated against vaccination				
No	237 (99.2)	58 (100)	43 (97.7)	136 (99.3)
Yes	2 (0.8)	1 (1.6)	1 (2.3)	1 (0.7)
Religion, philosophy, or culture recommends against influenza vaccine				
No	253 (100)	60 (100)	45 (100)	148 (100)
Yes	0	0	0	0
Trust pharmaceutical company to provide safe and effective influenza vaccines <sup>b,c</sup>				
No	39 (14.8)	27 (45)	4 (8.3)	8 (5.1)
Yes	114 (43.2)	10 (16.7)	20 (41.7)	84 (53.8)
Not sure	111 (42.0)	23 (38.3)	24 (50)	64 (41)
Trust that the government is making decisions in best interest of patients with RD with respect to influenza vaccines <sup>b,d</sup>				
No	58 (22.8)	23 (43.4)	11 (23.9)	24 (15.5)
Yes	196 (77.2)	30 (56.6)	35 (76.1)	131 (84.5)
The government is pushed by the industry to recommend certain influenza vaccines <sup>a</sup>				
No	59 (22.6)	12 (20.3)	8 (16.7)	39 (25.3)
Yes	65 (24.9)	23 (39)	12 (25)	30 (19.5)
Not sure	137 (52.5)	24 (40.7)	28 (58.3)	85 (55.2)
IIV should be compulsory <sup>b,c,e</sup>				
No	90 (33.2)	45 (70.3)	12 (24.5)	33 (20.9)
Yes	84 (31.0)	1 (1.6)	7 (14.3)	76 (48.1)
Not sure	97 (35.8)	18 (28.1)	30 (61.2)	49 (31)
Factors that prevented influenza vaccination				
Distance to vaccine provider	2 (2.1)	0	0	2 (3.9)
Time to vaccine provider	21 (21.9)	2 (11.8)	9 (32.1)	10 (19.6)
Waiting time at vaccine provider	16 (16.7)	1 (5.9)	2 (7.1)	13 (25.5)
Cost and/or parking at vaccine provider	6 (6.3)	1 (5.9)	1 (3.6)	4 (7.8)
Effort of traveling to vaccine provider	12 (12.5)	3 (17.6)	1 (3.6)	8 (15.7)
>1 factor	22 (22.9)	3 (17.6)	10 (35.7)	9 (17.6)
<b>Individual and group influences</b>				
Previous adverse reaction to influenza vaccine (personal or in someone close)made you reconsider receiving IIV <sup>b,d</sup>				
No	206 (74.9)	33 (51.6)	39 (78)	134 (83.2)
Yes	69 (25.1)	31 (48.4)	11 (22)	27 (16.8)
Previously rejected IIV <sup>b,c</sup>				
No	236 (87.7)	40 (64.5)	46 (93.9)	150 (94.9)
Yes	33 (12.3)	22 (35.5)	3 (6.1)	8 (5.1)
IIV overloads the immune system <sup>b,d,f</sup>				
No	114 (42.1)	11 (16.9)	14 (29.2)	89 (56.3)
Yes	30 (11.1)	19 (29.2)	3 (6.3)	8 (5.1)

(Continued)

**Table 3.** (Cont'd)

Variables	Whole population (N = 282), n (%)	Likely to refuse (n = 67), n (%)	Uncertain (n = 50), n (%)	Likely to accept (n = 165), n (%)
Not sure	127 (46.8)	35 (53.8)	31 (64.6)	61 (38.6)
There are better ways to avoid vaccine-preventable diseases <sup>b,d,e</sup>				
No	179 (75.9)	25 (46.3)	29 (67.4)	125 (89.9)
Yes	57 (24.1)	29 (53.7)	14 (32.6)	14 (10.1)
Receive enough information about IIV				
No	87 (32.7)	16 (27.1)	18 (40)	53 (32.7)
Yes	179 (67.3)	43 (72.9)	27 (60)	109 (67.3)
Trust the information received from health care providers about IIV				
No	21 (8.0)	7 (12.1)	4 (8.7)	10 (6.3)
Yes	243 (92.0)	51 (87.9)	42 (91.3)	150 (93.8)
Vaccine benefits, in general, are larger than their risks				
No	15 (5.6)	5 (8.5)	4 (8.5)	6 (3.7)
Yes	184 (68.4)	41 (69.5)	28 (59.6)	115 (70.6)
Not sure	70 (26)	13 (22)	15 (31.9)	42 (25.8)
IIV is safe for patients with RD <sup>b,f</sup>				
No	36 (13.3)	17 (28.3)	9 (19.1)	10 (6.1)
Yes	167 (61.6)	33 (55)	25 (53.2)	109 (66.5)
Not sure	68 (25.1)	10 (16.7)	13 (27.7)	45 (27.4)
Concerned about IIV safety				
Not concerned at all	153 (57.7)	36 (63.2)	26 (55.3)	91 (56.5)
A little concerned	90 (34.0)	15 (26.3)	15 (31.9)	60 (37.3)
Very concerned	22 (8.3)	6 (10.5)	6 (12.8)	10 (6.2)
Influenza disease can be serious				
No	10 (3.7)	4 (6.8)	1 (2.1)	5 (3)
Yes	232 (85.9)	48 (81.4)	40 (85.1)	144 (87.8)
Not sure	28 (10.4)	7 (11.9)	6 (12.8)	15 (9.1)
Social pressure to receive IIV				
No	215 (80.2)	52 (86.7)	37 (78.7)	126 (78.3)
Yes	39 (14.6)	8 (13.3)	6 (12.8)	25 (15.5)
Not sure	14 (5.2)	0	4 (8.5)	10 (6.2)
Vaccine/vaccination-specific issues				
Experiences with pain or fear of needles with past IIV prevent receiving it <sup>a</sup>				
No	255 (93.4)	56 (87.5)	45 (91.8)	154 (96.3)
Yes	18 (6.6)	8 (12.5)	4 (8.2)	6 (3.8)
Not sure	26 (9.7)	2 (3.4)	7 (14.9)	17 (10.5)
Willing to take time off from work to receive IIV <sup>b,c,f</sup>				
No	137 (57.1)	52 (92.9)	30 (65.2)	55 (39.9)
Yes	103 (42.9)	4 (7.1)	16 (34.8)	83 (60.1)
Willing to pay for IIV <sup>b,e</sup>				
No	146 (55.9)	51 (85)	36 (78.3)	59 (38.1)
Yes	115 (44.1)	9 (15)	10 (21.7)	96 (61.9)

Abbreviations: IIV, inactivated influenza vaccine; RD, rheumatic diseases; WHO-SAGE, World Health Organization Strategic Advisory Group of Experts.

<sup>a</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were likely to accept it was statistically significant ( $P \leq 0.05$ ).

<sup>b</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were likely to accept it was statistically significant ( $P < 0.001$ ).

<sup>c</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were uncertain about receiving it was statistically significant ( $P < 0.001$ ).

<sup>d</sup> The comparison between participants who were likely to refuse the influenza vaccine and those who were uncertain about receiving it was statistically significant ( $P \leq 0.05$ ).

<sup>e</sup> The comparison between participants who were uncertain about receiving the influenza vaccine and those who were likely to accept it was statistically significant ( $P < 0.001$ ).

<sup>f</sup> The comparison between participants who were uncertain about receiving the influenza vaccine and those who were likely to accept it was statistically significant ( $P \leq 0.05$ ).

$P = 0.01$ ). Characteristics of patients with RD who received IIV in the 2018-2019 influenza season are summarized in Supplementary Table 5. Most participants did not receive IIV on a yearly basis

since the RD diagnosis ( $n = 144$ , 54.1%). Patients with RD likely to refuse IIV, as well as those uncertain, less frequently received IIV annually since their diagnosis (likely to refuse vs likely to accept:

3.1% vs 72.4%,  $P < 0.001$ ; uncertain vs likely to accept: 15.6% vs 72.4%,  $P < 0.001$ ).

**Determinants of influenza vaccine hesitancy among patients with RD.** Factors associated with vaccine hesitancy are classified on the basis of contextual or individual and/or group influences and vaccine/vaccination-specific issues and summarized in Table 3.

*Contextual influences.* The most trusted source of information on vaccines among patients with RD was HCPs ( $n = 173$ , 62.7%), whereas the least trusted sources were social media and the Internet ( $n = 135$ , 49.8%). Twenty-seven percent of participants had more than one preferred or least preferred source of information on vaccines.

Participants likely to refuse IIV had less trust in pharmaceutical companies and were more likely to trust social media and the Internet. Most patients with RD did not feel influenced by celebrities who advocated against IIV ( $n = 261$ , 97.4%); most of them also indicated that religious leaders (imam, priest, or rabbi) ( $n = 237$ , 99.2%) or their religion, philosophy, and culture were not opposed to IIV uptake ( $n = 253$ , 100%). Although less than half of patients with RD ( $n = 114$ , 43.2%) trusted pharmaceutical companies to provide safe and effective vaccines, most of them ( $n = 196$ , 77.2%) believed that the government was making decisions in the best interest of the citizens concerning IIV. Only 25% ( $n = 65$ ) considered that industry pushes the government to recommend certain influenza vaccines. Patients likely to refuse IIV were less likely to trust the government (likely to refuse vs likely to accept: 56.6% vs 84.5%,  $P < 0.001$ ; likely to refuse vs uncertain: 56.6% vs 76.1%,  $P = 0.04$ ) and pharmaceutical companies (likely to refuse vs likely to accept: 16.7% vs 53.8%,  $P < 0.001$ ; likely to refuse vs uncertain: 16.7% vs 41.7%,  $P < 0.001$ ) and were more likely to believe that industry forces the government to recommend certain influenza vaccines (likely to refuse vs likely to accept: 39% vs 19.5%,  $P = 0.01$ ). Almost a third of patients with RD ( $n = 84$ , 31%) considered that IIV should be mandatory, and 35.8% ( $n = 97$ ) were uncertain about this. Patients likely to refuse IIV tended to oppose compulsory IIV (likely to refuse vs likely to accept: 70.3% vs 20.9%,  $P < 0.001$ ; likely to refuse vs uncertain: 70.3% vs 24.5%,  $P < 0.001$ ), whereas uncertain patients were more likely to be unsure of whether IIV should be mandatory (uncertain vs likely to refuse: 61.2% vs 28.1%,  $P < 0.001$ ; uncertain vs likely to accept: 61.2% vs 31%;  $P < 0.001$ ).

Geographical barriers prevented 28% of patients with RD from receiving IIV, and 22.9% of them reported more than one barrier. The time needed to get to the vaccine provider (21.9%) and waiting time at the vaccine provider (16.7%) were the barriers most frequently reported (Table 3).

*Individual and group influences.* Twelve percent of study participants ( $n = 33$ ) reported previously rejecting vaccination against seasonal influenza. Previous bad reactions to IIV, either personal

or in someone close, made a quarter of patients reconsider being vaccinated. Other reported reasons for rejecting IIV in the past included fear of side effects, uncertainty of effectiveness, considering vaccination not necessary, medical contraindications, fear of needles, and refusal because of peer or authority pressure. Patients likely to refuse IIV tended more often to reconsider receiving it after a personal or third-party bad experience with IIV (likely to refuse vs uncertain: 48.4% vs 22%,  $P = 0.004$ ; likely to refuse vs likely to accept: 48.4% vs 16.8%,  $P < 0.001$ ) and reported more frequently having previously rejected IIV (likely to refuse vs uncertain: 35.5% vs 6.1%,  $P < 0.001$ ; likely to refuse vs likely to accept: 35.5% vs 5.1%,  $P < 0.001$ ). Only 11% ( $n = 30$ ) of the patients with RD considered that IIV overloads the immune system, and 46.8% ( $n = 127$ ) were uncertain about this. Patients likely to refuse IIV more often had the misconception that IIV overwhelms the immune system (likely to refuse vs likely to accept: 29.2% vs 5.1%,  $P < 0.001$ ; likely to refuse vs uncertain: 29.2% vs 6.3%,  $P = 0.007$ ), whereas those who were uncertain were unsure about this (uncertain vs likely to refuse: 64.6% vs 53.8%,  $P = 0.007$ ; uncertain vs likely to accept: 64.6% vs 38.6%,  $P = 0.04$ ). Fifty-seven patients with RD (24.1%) considered that there are better ways to prevent diseases than a vaccine, such as healthy lifestyles and good hygiene. Patients likely to refuse IIV more often considered that there are better ways to avoid vaccine-preventable diseases than vaccines (likely to refuse vs likely to accept: 53.7% vs 10.1%,  $P < 0.001$ ; likely to refuse vs uncertain: 53.7% vs 32.6%,  $P = 0.04$ ). Most patients ( $n = 179$ , 67.3%) felt they received enough information about IIV, 92% ( $n = 243$ ) trusted in the information about IIV provided by HCPs, and 68.4% ( $n = 184$ ) considered that vaccine benefits outweigh the risks. A quarter of patients with RD ( $n = 68$ ) were uncertain whether IIV was safe, and 13.3% ( $n = 36$ ) believed that it was not. Less than 10% of patients with RD ( $n = 22$ ) were severely worried about IIV safety to the point of not receiving it, whereas 34% ( $n = 90$ ) were somewhat concerned. Patients with RD likely to refuse IIV and those uncertain were more likely to deem IIV as not safe for themselves (likely to refuse vs likely to accept: 28.3% vs 6.1%,  $P < 0.001$ ; uncertain vs likely to accept: 19.1% vs 6.1%,  $P = 0.02$ ). Two hundred thirty-two patients (85.9%) viewed influenza disease as serious, but 215 (80.2%) did not perceive social pressure to receive IIV.

*Vaccine/vaccination-specific issues.* Having experienced severe pain after vaccination or fear of needles prevented 6.6% ( $n = 18$ ) of patients with RD from receiving IIV, and 26 were unsure about this (9.7%). Patients likely to refuse IIV indicated more often that this was a barrier for them to accept the vaccine (likely to refuse vs likely to accept: 12.5% vs 3.8%,  $P = 0.03$ ). Most of the patients ( $n = 137$ , 57.1%) would not take time off work to receive IIV, and most ( $n = 146$ , 55.9%) would reject paying for IIV. Patients likely to refuse or uncertain about receiving IIV reported more frequently that they would not take time off from work to receive the vaccine (likely to refuse vs likely to accept: 92.2% vs 39.9%,

**Table 4.** Predictors of vaccine hesitancy (vaccine acceptance as reference group)

Predictors	Likely to refuse, OR (95% CI)	Uncertain, OR (95% CI)
Sex		
Female	0.36 (0.11-1.19)	0.57 (0.22-1.50)
Male	Reference	Reference
Age	1.01 (0.97-1.05)	0.98 (0.95-1.01)
Employment		
Not employed or retired	2.06 (0.56-7.56)	1.24 (0.42-3.64)
Employed	Reference	Reference
Previous IIV		
No	<b>36.61 (5.30-252.93)</b>	<b>18.90 (3.26-109.70)</b>
Yes	Reference	Reference
Trust that the government is making decisions in best interest of patients with RD with respect to influenza vaccines		
No	Reference	Reference
Yes	0.88 (0.24-3.21)	0.64 (0.20-2.02)
IIV should be compulsory		
No	Reference	Reference
Yes	<b>0.07 (0.01-0.68)</b>	0.58 (0.15-2.27)
Not sure	0.39 (0.11-1.35)	1.71 (0.58-5.06)
Willing to take time off from work to receive IIV		
No	<b>6.77 (1.50-30.62)</b>	1.89 (0.70-5.05)
Yes	Reference	Reference
Willing to pay for IIV		
No	1.79 (0.52-6.10)	<b>2.80 (1.05-7.45)</b>
Yes	Reference	Reference
Trust pharmaceutical company to provide safe and effective influenza vaccines		
No	<b>41.03 (5.58-301.47)</b>	4.40 (0.70-27.80)
Yes	Reference	Reference
Not sure	1.86 (0.52-6.64)	1.17 (0.44-3.11)
Previous adverse reaction to influenza vaccine (personal or in someone close) made you reconsider receiving IIV		
No	Reference	Reference
Yes	3.01 (0.90-10.06)	1.55 (0.52-4.66)
RD		
Rheumatoid arthritis	Reference	
Systemic autoimmune RDs	0.79 (0.21-3.03)	2.02 (0.63-6.48)
Spondyloarthropathies	0.62 (0.10-3.92)	1.40 (0.34-5.79)
Mechanical or crystal or fibromyalgia	3.39 (0.32-35.45)	2.01 (0.28-14.60)
Other <sup>a</sup>	<0.01 (<0.01-999.99)	9.96 (0.61-162.86)

**Note:** Data in bold represent the predictors of vaccine hesitancy.

Abbreviations: CI, confidence interval; IIV, inactivated influenza vaccine; OR, odds ratio; RD, rheumatic disease.

<sup>a</sup> Idiopathic erythema nodosum and polymyalgia rheumatica.

$P < 0.001$ ; uncertain vs likely to accept: 65.2% vs 39.9%,  $P = 0.003$ ) and that they would not pay for IIV (likely to refuse vs likely to accept: 85% vs 38.1%,  $P < 0.001$ ; uncertain vs likely to accept: 78.3% vs 38.1%,  $P < 0.001$ ).

**Multivariate predictors of vaccine hesitancy.** No previous vaccination with IIV (odds ratio [OR] 36.61, 95% CI 5.30-252.93), the perception that IIV should not be mandatory (OR 0.07, 95% CI 0.01-0.68), unwillingness to take time off work to receive the vaccine (OR 6.77, 95% CI 1.50-30.62), and distrust in pharmaceutical companies (OR 41.03, 95% CI 5.58-301.47) were independent predictors of IIV refusal. Independent predictors of IIV uncertainty were no previous vaccination with IIV (OR 18.90, 95% CI 3.26-109.70) and reluctance to pay for the vaccine (OR 2.80, 95% CI 1.05-7.45) (Table 4). A multivariate model including only five variables is presented as Supplementary Table 6.

**Sensitivity analysis.** The results of a sensitivity analysis using different cutoffs for vaccine hesitancy (likely to refuse [value 0], uncertain [values 1-9], and likely to accept [value 10]) were consistent with the determinants of vaccine hesitancy among patients with RD identified in the main analysis. Previous IIV (OR 95.66, CI 95% 8.85- >999.99) and lack of trust in the pharmaceutical industry (OR 81.26, 95% CI 8.26-799.33) were independent predictors of vaccine refusal, whereas no previous IIV (OR 17.04, 95% CI 1.99-145.93) was a predictor of vaccine hesitancy. In addition, uncertainty about trusting in pharmaceutical companies was included among the predictors of vaccine refusal (OR 7.51, 95% CI 1.56-36.15) and hesitancy (OR 2.30, 95% CI 1.04-5.07).

## DISCUSSION

IIV is recommended for patients with RD; however, its uptake in this population is low, below the recommended 80%



vaccination coverage goal for the seasonal influenza vaccine established by the Government of Canada and the World Health Organization (7,9,11,12,20–23). Vaccine hesitancy and prolonged vaccine deliberation (ie, the act of thinking about or discussing something and deciding carefully) delay vaccine uptake and contribute to the low IIV coverage in patients with RD (14,24,25). This cross-sectional study evaluated participants' willingness to receive IIV and the determinants of vaccine hesitancy among patients with RD at a McGill-University-affiliated hospital. This study was performed before the first case of COVID-19 was diagnosed in Canada (January 27, 2020). In our study, 17.7% of patients with RD were uncertain about accepting IIV, and 23.8% were likely to refuse it. Of interest, 67% of patients with RD who were uncertain had received at least one dose of IIV previously. This highlights that vaccine hesitancy does not necessarily lead to rejection of a vaccine because many individuals who have concerns about a vaccine take it nonetheless (15).

Overall, more than 40% of patients with RD had doubts about IIV and could benefit from interventions addressing vaccine hesitancy. IIV hesitancy among patients with RD is a problem of increasing importance in the COVID-19 era. In addition to preventing influenza infections, IIV also reduces intensive care admissions and duration of hospitalizations (26). Therefore, high IIV coverage is expected to reduce the burden of health care use by influenza-related admissions and allow for the care of patients with severe COVID-19 (27). Moreover, a possible association between IIV and decreased risk of COVID-19 mortality, decreased need for intensive care treatment and invasive respiratory support, and improved clinical outcomes has been suggested (28–30), emphasizing the relevance of addressing IIV hesitancy.

HCPs were recognized by patients with RD as the most trusted source of information on vaccines, whereas social media and the Internet were the least trustworthy sources. Previous studies have highlighted the importance of HCP recommendation and its association with IIV uptake in patients with RD (11,21,31). Moreover, HCP reminders to recommend IIV to patients with RD enhance vaccine uptake (31,32). Despite the finding that social media and the Internet were not trustworthy sources of information among patients with RD, their influence on vaccine decisions in the general population is well-established (32). As in previous studies, our data linked negative attitudes toward vaccination to mistrust in government and scientists (33–35).

Most patients acknowledged that influenza-related disease could be severe. However, misconceptions such as vaccines overloading the immune system, concerns about vaccine safety, and beliefs that healthy lifestyles and good hygiene are better ways to avoid vaccine-preventable diseases were common among patients likely to refuse or uncertain about IIV. Previous data confirm that people are more likely to accept vaccination when they trust in the safety of the vaccine and in the system that delivers it and if they recognize the risk from the disease and consider vaccination as an effective solution to that risk (36,37).

Therefore, educational interventions addressing misconceptions among patients with RD may help promote IIV uptake.

Fear of pain or needle phobia is a barrier for a minority of patients likely to refuse the vaccine. The prevalence of IIV avoidance due to fear of needles in our study is similar to that previously described in the literature (6%-16%) (38). Effective, simple, non-costly, and age-specific evidence-based strategies to mitigate pain at the time of vaccination are described (39,40). Although decreasing pain during vaccine injection might reduce distress during vaccination and improve the immunization experience, further studies on the impact of these interventions on vaccine hesitancy are needed (32,39). Alternative approaches to vaccination by needle and syringe (eg, oral formulations, jet injectors) could also potentially address this barrier (41,42).

Previous studies showed people are more prone to accept vaccination when vaccine access is convenient, free, and easy (32,43). Ways to improve IIV uptake supported by the data presented in this study include administering IIV for free at work or other convenient locations (ie, rheumatology clinics). We previously showed that a multimodal strategy that provided IIV at no cost in the rheumatology clinics increased its uptake by 14% in patients with RA, emphasizing the importance of facilitating access (31).

Our study has a number of limitations, including the following: (i) it was based at a single university center among patients with RD who attended a rheumatology clinic, and thus its results may not represent the views and behaviors of people living with RD in other settings or countries; (ii) data were self-reported and therefore at risk of reporting bias; (iii) bias in estimates (sparse data bias) could explain large CIs given that for some combinations of risk factors and outcome levels, there were a small number of observations; and (iv) it assessed the likelihood of accepting IIV but not whether patients actually received IIV, which is relevant because vaccine uptake is usually lower than vaccine intention.

This study also informs clinicians of ways to identify patients with RD more likely to refuse IIV. Those include patients who have not previously received that vaccine, those who oppose IIV being mandatory, those who are not willing to take time off work to receive IIV, and those who distrust pharmaceutical companies. These results also highlight the opportunity to ask about previous influenza vaccination and reluctance to pay for the vaccine because these questions are associated with uncertainty about accepting IIV. Finally, whether the determinants of IIV hesitancy among patients with RD can be extrapolated to other vaccines, in particular COVID-19 vaccines, remains to be defined.

In summary, IIV is a priority as part of the care of patients with RD to decrease influenza incidence and prevent influenza-related complications. Vaccine hesitancy is multifactorial and contributes to low IIV uptake in this population. Interventions and strategies that facilitate access to vaccination, strengthen confidence in public health decisions, and educate patients with RD on

influenza virus and the risks and benefits of IIV may enhance vaccine acceptance and increase IIV coverage rates in this population.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Colmegna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Valerio, Hudson, Ward, Colmegna.

**Acquisition of data.** Valerio, Bernatsky, Hazel, Colmegna.

**Analysis and interpretation of data.** Valerio, Wang, Colmegna.

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