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Predictors of Influenza Vaccination in Early Rheumatoid Arthritis 2017-2021: Results From the Canadian Early Arthritis Cohort

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Objective. Adults with rheumatoid arthritis (RA) are at a higher risk for infections, including influenza and related complications. We identified influenza vaccination coverage in adults newly diagnosed with RA and examined sociodemographic RA characteristics and attitudes associated with vaccination.

Methods. We used data from patients enrolled in the Canadian Early Arthritis Cohort between September 2017 and February 2021. At enrollment, participants reported their vaccination status in the previous year and completed the Beliefs About Medicines Questionnaire (BMQ). Clinical data were obtained from medical records. Logistic regression was used to identify predictors of vaccination in the year after RA diagnosis.

Results. The baseline analytic sample of 431 patients were mostly White (80%) women (67%) with a mean age of 56 (SD 14) years. Prediagnosis, influenza vaccine coverage was 38%, increasing to 46% post diagnosis in the longitudinal sample (n = 229). Participants with previous influenza vaccination (odds ratio [OR] 15.33; 95% confidence interval [CI] 6.37-36.90), on biologics or JAKs (OR 5.42; 95% CI 1.72-17.03), and with a higher change in BMQ Necessity-Concerns Differential scores (OR 1.08; 95% CI 1.02-1.15) had greater odds, whereas women (OR 0.32; 95% CI 0.14-0.71), participants with a non-White racial background (OR 0.13; 95% CI 0.04-0.51), and participants currently smoking (OR 0.09; 95% CI 0.02-0.37) had lower odds of influenza vaccine coverage.

Conclusion. Influenza vaccination coverage in patients with early RA remains below national targets in adults living with a chronic condition. Discussing vaccine history and medication attitudes at initial clinic visits with new patients with RA may enhance vaccine acceptance and uptake.

INTRODUCTION

Seasonal influenza is an acute respiratory infection that ranks sixth (along with pneumonia) among the top 10 leading causes of death in Canada (1). Despite the accessibility and affordability of effective vaccines, influenza significantly contributes to the mortality rate and health care burden in Canada, with yearly estimates of 12,000 hospitalizations and 3500 deaths (2,3). The incidence of influenza is higher in adults with rheumatoid arthritis (RA) than in the general population (4).

RA is the most common type of immune-mediated inflammatory arthritis, affecting 1% of Canadians. Patients with newly diagnosed RA benefit from being treated aggressively, generally with combinations of pharmacotherapies, with the aim of reaching a state of remission or low disease activity within 6 months to

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SIGNIFICANCE & INNOVATIONS

- Among newly diagnosed adults with rheumatoid arthritis (RA), influenza vaccination coverage remains suboptimal.
- Vaccination prior to RA diagnosis, being on advanced biologics, and having a higher change in RA medication necessity beliefs versus concerns predicted vaccination in the first year of RA.
- Those with a non-White racial background, women, and smokers were less likely to get an influenza vaccination.
- Assessing vaccination history and RA medication beliefs and concerns may help identify and attenuate vaccination hesitancy.

reduce the risk of permanent joint damage and disability [5]. However, the disease itself and treatment also place patients at greater risk of infections [6]. When infected with influenza, adults with RA have nearly a threefold greater risk of developing influenza-related complications as a potential result of immune dysfunction, the immunosuppressant effects of RA medications, and other factors [4,7].

Because annual influenza vaccination reduces morbidity and mortality from influenza, it has been recommended for adults with RA and is often emphasized in periodic updates of RA treatment guidelines [8–10]. Although influenza vaccination is best administered when disease activity is low or prior to immunosuppressant use, adequate influenza vaccine response has been found in patients using DMARDs and TNF-α inhibitors except rituximab [8,11–13]. Yet influenza vaccination coverage in adults with established RA in parts of Canada and elsewhere remains suboptimal [10,14–16]. Perceived risks associated with vaccination and risk tolerance vary considerably across individuals and strongly influence decision-making around vaccination. Given that beliefs and attitudes about medicines predict adherence more strongly than sociodemographic or clinical factors across multiple chronic diseases, including RA [17], medication beliefs and attitudes may offer insight into risk perceptions and concerns about vaccinations. For example, Wood et al [18] found that antivaccination attitudes in UK adults were associated with medical mistrust and general concerns about medications.

Notably, only one published cross-sectional report in Brazil has examined vaccination coverage in 68 adults with RA for up to 1 year and reported 42% had been vaccinated [19]. Around the time of diagnosis, there is an optimal opportunity to verify vaccination history and ensure patients are aware of the importance of preventive measures. In this study, we describe influenza vaccination coverage in a nationwide Canadian cohort of patients with early RA and identify factors associated with influenza vaccination. We hypothesized that influenza vaccination coverage would be similar to that in the general Canadian population in the year prior to RA diagnosis and would increase in the year post diagnosis but fall short of recommended levels. We also hypothesized that individuals reporting higher concerns about RA medications would be less likely to be vaccinated before and after RA diagnosis.

PATIENTS AND METHODS

Study setting and participants. The present study analyzed data at baseline and 1-year follow-up from the Canadian Early Arthritis Cohort (CATCH) study between September 2017 and February 2021. CATCH recruitment and study methods have been detailed elsewhere [20]. In brief, CATCH is a prospective inception cohort of real-world patients with early RA (<1 year of symptoms) treated by rheumatologists as part of usual care. Patients diagnosed with early RA for the first time by a CATCH rheumatologist at 1 of 17 academic and community clinics across Canada are eligible to enroll in the CATCH study and complete repeat clinical assessments, study questionnaires, serologic tests, and x-ray assessments at predetermined intervals. All CATCH participants provided signed informed consent, the data were anonymized, and the CATCH study was approved by each local site's research ethics board. Additionally, the study was conducted according to the Declaration of Helsinki.

Outcomes and covariates. We included data on sociodemographic variables collected at enrollment and RA clinical status, medication use, vaccination status for influenza in the previous 12 months, and Beliefs About Medicine Questionnaire–Specific (BMQ) scores at enrollment and 1-year follow-up. BMQ consists of two scales, Necessity and Concerns, and has been validated in RA [21]. The 5-item Necessity scale measures perceived necessity of RA medications, and the 5-item Concerns scale measures perceived RA medications worries. Items from both scales are rated using a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). A Necessity-Concerns Differential (NCD) score is calculated as the difference between Necessity and Concerns subscale scores; higher scores reflect stronger beliefs about perceived benefits versus risks of RA medications. RA characteristics were collected from physician assessments.

Statistical analysis. Descriptive statistics were used to summarize patient characteristics and calculate influenza vaccine coverage in the year prior to and year after RA. Groups were compared using t-tests and χ^2 tests. Multivariable logistic regression was used to identify predictors of influenza vaccination coverage at 12 months. Variables were selected for inclusion based on review of the literature, factors found to be significant at $P < 0.20$ in univariate analyses, and expert opinion. We conducted a separate sensitivity analysis by sex. Data were analyzed using SAS v9.4 and P values less than 0.05 were considered significant.

Ethics approval. Ethics approval was obtained at each site, and written informed consent was obtained from participants at enrollment.

RESULTS

Between September 1, 2017, and February 24, 2021, 611 patients were enrolled in CATCH; 431 (71%) had completed the BMQ and had information available about influenza vaccination in the previous year. The final baseline analytic sample of 431 patients were mostly White (80%) women (67%) with a mean age of 56 (SD 14) years and symptom duration of 5 (SD 3) months.

Individuals excluded from the baseline sample were similar to those included, except excluded participants were younger (mean age 52 vs. 56 years) and more likely to be White (14% vs. 17% non-White racial background; see Supplementary Table 1). A total of 317 participants had been in follow-up for at least a year (the others had not yet been enrolled for 1 year), and influenza vaccination information and BMQ scores were available for 229 (72%), which formed the longitudinal analytic sample. As compared with those excluded from the longitudinal sample, included participants were similar in all characteristics examined, except they were less likely to have had cancer (18% vs. 6%,

respectively; Supplementary Table 1). Figure 1 shows the flow diagram for study participants.

Influenza vaccine coverage. Among the final longitudinal analytic sample (n = 229), at 12 months, 105 (46%) reported receiving an influenza vaccination; 69 of the 105 (66%) had also been vaccinated prior to RA diagnosis. Of the 124 not vaccinated at 12 months, 20 (16%) reported influenza vaccine coverage prior to RA diagnosis.

Characteristics associated with vaccination. At baseline, participants who were vaccinated were more likely to be older, be nonsmokers, have more comorbidities (specifically cardiovascular disease, hypertension, diabetes, stomach problems and/or ulcers, and cancer; Table 1). Groups did not differ significantly by other sociodemographic or RA characteristics examined.

At baseline, on the BMQ Necessity scale, the items with the highest levels of endorsement (agree and strongly agree) included protection from worsening RA and impact on current and future health (Figure 2). The most common concerns included worries about taking RA medications and their long-term safety and becoming too dependent on RA medications. The mean BMQ NCD score was higher in vaccinated versus unvaccinated individuals.
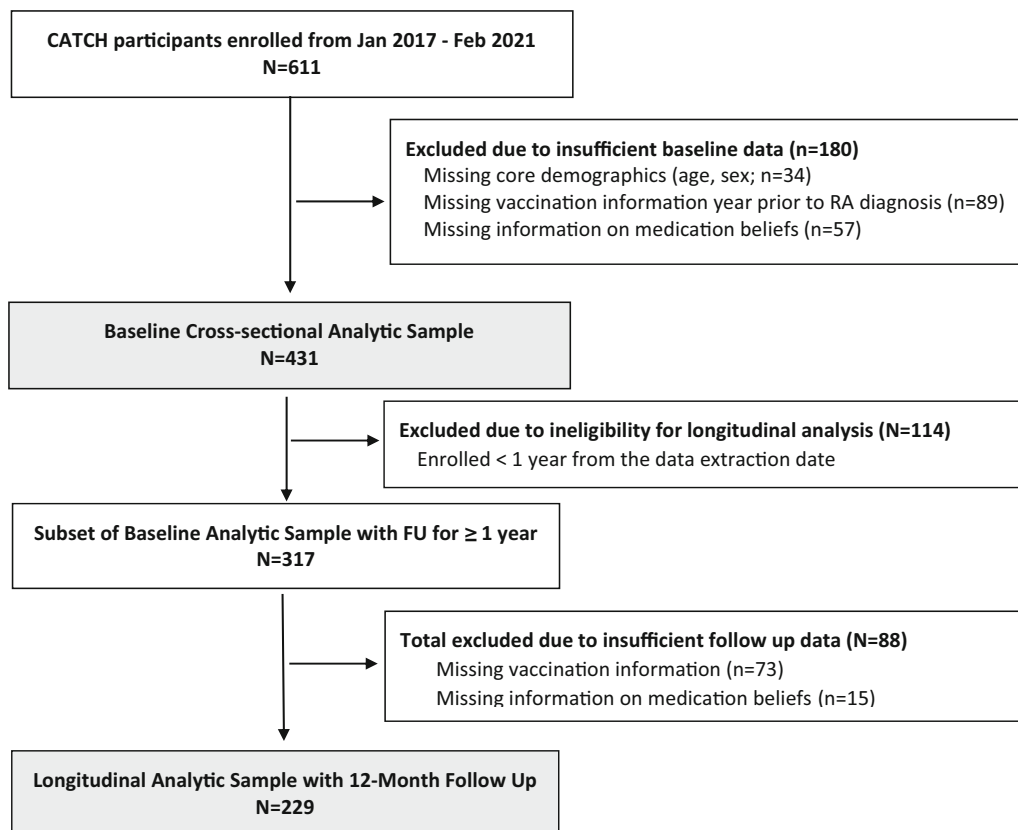

Figure 1. Study flowchart. CATCH, Canadian Early Arthritis Cohort; FU, follow up; RA, rheumatoid arthritis.
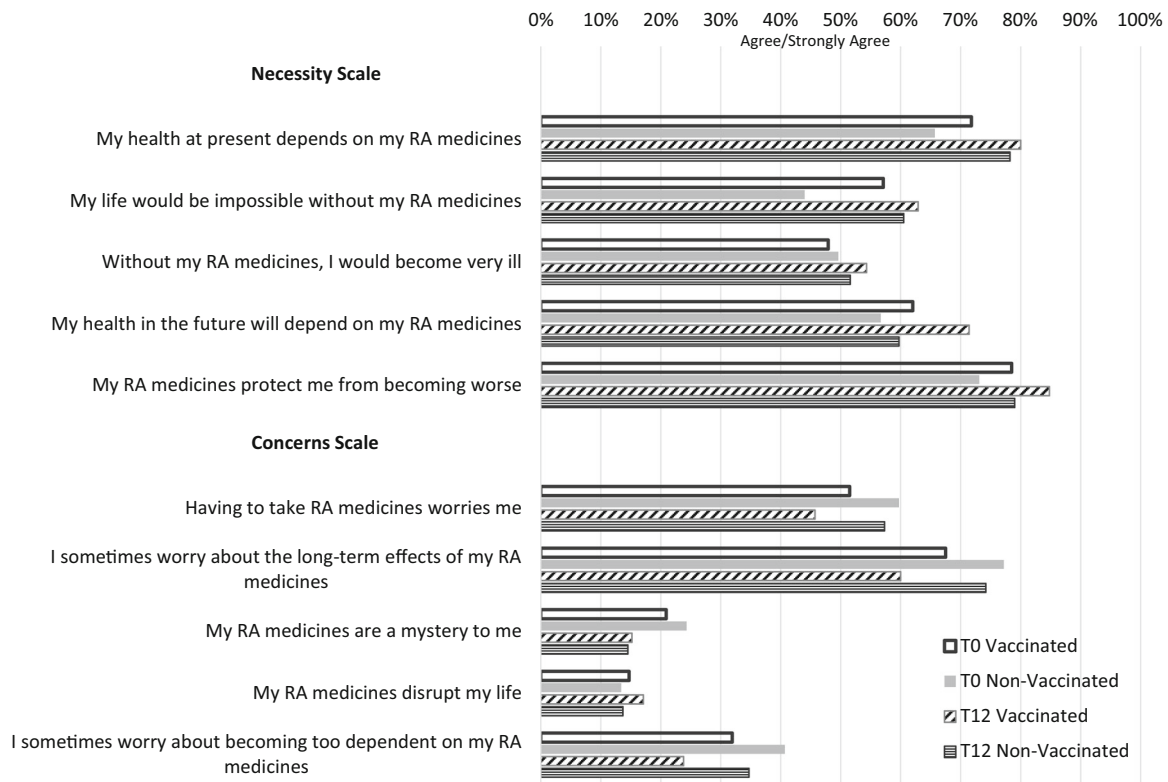
Figure 2. Proportions of patients who agree or strongly agree with Beliefs About Medicines items by vaccination status prior to (T0) and post diagnosis (T12). RA, rheumatoid arthritis.

At 12 months, patients with RA who were vaccinated were more likely to be older, White, male, and nonsmokers; more likely to be treated with biologics or JAKs in the first year and oral corticosteroids in the first 3 months; and more likely to have been vaccinated in the year prior to RA diagnosis (Table 1). Vaccinated patients also had a larger BMQ NCD score (ie, 12 months [baseline]) than patients who were unvaccinated. In adjusted analyses, patients with RA who had been vaccinated prior to diagnosis, had used biologics and JAKs in the first year, and had a higher change in the BMQ NCD score between baseline and 12 months had a higher odds of influenza vaccination; women, racial and ethnic minority groups, and smokers had a lower odds of influenza vaccination (Table 2). Results were essentially unchanged when models were examined by sex in sensitivity analyses (data not shown).

DISCUSSION

We examined data from CATCH, the largest pan-Canadian early RA cohort, to describe influenza vaccine coverage and identify factors associated with influenza vaccination in the year prior to and post RA diagnosis. Our results suggest that vaccine coverage increased by 8% (ie, from 38% to 46%) after RA diagnosis yet remained well below national goals. The vaccination coverage at both time points was similar to the coverage of 36% to 42% in other Canadian adults from 2017 to 2020 (22,23), although lower overall than coverage in the United States (46%) during the 2017-2018 season (24). Post diagnosis, vaccination coverage was comparable to the 37% to 44% coverage of Canadian adults aged 18 to 64 years with a chronic medical condition (22,23). Although similar influenza coverage has been reported among individuals with other immune-mediated inflammatory diseases, such as inflammatory bowel disease and multiple sclerosis, in one Canadian province where coverage is available for the entire population at no cost (16), coverage remains substantially lower than estimates from the US National Health Interview Survey 2017-2018 season. Among US adults aged 19 years and older at high risk for influenza-related complications (eg, diabetes, chronic obstructive pulmonary disease, heart disease, specific cancer or recent diagnosis, chronic bronchitis, failing kidneys, recent asthma attack), vaccination coverage was estimated at 61% (24). Generally, vaccination coverage increased as the number of physician contacts increased, regardless of whether they had health insurance (24).

Globally, vaccination coverage of patients with RA remains suboptimal and varies widely. Among 3290 patients with RA across 17 countries in Europe, Africa, Asia, the United States, and South America involved in the Comorbidities in RA (COMORA) cohort, influenza vaccination coverage ranged from less than 1% in Morocco and Egypt to 66% in Japan and was

Table 1. Patient characteristics by influenza vaccination status at initial and 12-month visits

Characteristics	Baseline (n = 431)			12-month follow-up (n = 229)		
	Vaccinated prior to RA diagnosis			Vaccinated post RA diagnosis		
	Yes	No	P	Yes	No	P
n (%)	163 (38%)	268 (62%)		105 (46%)	124 (54%)	
Sociodemographic						
Age, mean (SD)	62 (14)	53 (14)	<0.001	60 (12)	53 (13)	<0.001
18-64	81 (50%)	218 (81%)	<0.001	62 (59%)	104 (84%)	<0.001
≥65	82 (50%)	50 (19%)		43 (41%)	20 (16%)	
Women	109 (67%)	185 (69%)	0.641	59 (56%)	90 (73%)	0.001
Non-White racial background	20 (12%)	54 (20%)	0.028	8 (8%)	24 (19%)	0.010
Education, ≤HS degree	64 (39%)	87 (32%)	0.197	35 (33%)	43 (35%)	0.849
Private insurance	86 (53%)	158 (59%)	0.260	67 (64%)	71 (57%)	0.346
Current smoker	14 (9%)	45 (17%)	0.016	5 (5%)	29 (23%)	<0.001
Body mass index, mean (SD)	28.5 (7.1)	28.1 (6.1)	0.547	27.3 (6.1)	28.9 (7.2)	0.091
RDCI, mean (SD)	1.7 (1.6)	1.1 (1.3)	<0.001	1.5 (1.6)	1.1 (1.2)	0.035
Cardiovascular disease	27 (17%)	23 (9%)	0.012	15 (14%)	8 (6%)	0.049
Hypertension	55 (34%)	51 (19%)	0.001	34 (32%)	25 (20%)	0.035
Lung disease	35 (21%)	46 (17%)	0.225	19 (18%)	24 (19%)	0.808
Fracture	26 (16%)	43 (16%)	0.979	21 (20%)	17 (14%)	0.202
Depression	27 (17%)	35 (13%)	0.315	16 (15%)	14 (11%)	0.378
Diabetes	35 (21%)	23 (9%)	<0.001	14 (13%)	13 (10%)	0.505
Stomach problem or ulcer	7 (4%)	2 (1%)	0.013	3 (3%)	1 (1%)	0.238
Cancer	24 (15%)	15 (6%)	0.001	8 (8%)	6 (5%)	0.382
RA clinical, mean (SD)						
Symptom duration (months)	5.4 (3.0)	5.4 (3.0)	0.791	5.1 (3.0)	5.4 (3.0)	0.046
CDAI	25.4 (14.1)	25.3 (13.5)	0.960	27.3 (13.8)	25.9 (13.8)	0.456
RA medications[a]						
csDMARDs or MTX	153 (94%)	250 (93%)	0.812	99 (94%)	118 (95%)	0.767
Biologics or JAKs	18 (11%)	26 (10%)	0.656	21 (20%)	11 (9%)	0.016
Corticosteroids (oral)	51 (31%)	80 (30%)	0.753	39 (37%)	28 (23%)	0.016
Vaccinated prior to diagnosis	–	–	–	105 (46%)	124 (54%)	<0.001
BMQ Necessity score, mean (SD)	18.5 (4.0)	18.0 (4.2)	0.161	19.9 (3.8)	18.8 (4.4)	0.054
BMQ Concerns score, mean (SD)	14.8 (4.0)	15.5 (3.8)	0.077	13.7 (4.4)	14.8 (3.9)	0.050
BMQ Necessity-Concerns Differential score, mean (SD)	3.7 (5.3)	2.5 (5.2)	0.016	6.2 (5.9)	4.1 (5.6)	0.005

Abbreviations: BMQ, Beliefs About Medicines Questionnaire; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; HS, high school; JAK, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index.
[a] csDMARD, MTX, and corticosteroid (oral) use in the first 3 months; biologic, JAK and advanced therapy use in the first 12 months of follow-up.

largely explained by differences in vaccine policies (25). Considerable variation has also been reported, with some US and UK academic arthritis centers reporting coverage of 79% or more (26–28). Fragoulis et al (29) recently reported that influenza vaccination rates increased from 76% to 83% in response to the COVID-19 pandemic in autoimmune patients seen at specialty clinics in Greece. In a survey of 157 countries, Palache et al (30) noted that policies that directly impacted patients (eg, reimbursement, communication) increased vaccine coverage, whereas public health recommendations alone were necessary but not sufficient to drive higher coverage. Coverage within countries can also vary; for example, an analysis of claims data showed coverage was twice as high in eastern Germany (49%-59%) as compared with southern Germany (26%-27%) (31). In recent studies of Ontario, Quebec, and Manitoba, less than half of adults

receiving care for their RA from rheumatologists had received the influenza vaccine (10,14–16). We also found regional differences in influenza vaccination within Canada. Although there are differences in health care coverage (influenza vaccination is offered at no cost to all individuals living in Ontario, whereas it is offered only to individuals at high risk [including individuals with RA] in Quebec), it is unclear why patients with early RA in Quebec were more likely to be vaccinated than those living in Ontario (55% vs. 39%, respectively).

Despite the large variability in coverage between and within countries, influenza vaccination coverage is still generally low, making it essential to improve vaccination acceptance as part of RA care. Identifying characteristics related to vaccination hesitancy can help target interventions to vulnerable patients. Not surprisingly, we found that individuals who had previously been

Table 2. Characteristics associated with influenza vaccination in the year following RA diagnosis

	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age 18-64 (vs. ≥65)	0.31	0.16-0.59	0.86	0.36-2.08	0.87	0.36-2.11	0.80	0.32-1.97
Women (vs. men)	0.58	0.32-1.06	0.35	0.16-0.77	0.35	0.16-0.79	**0.32**	**0.14-0.71**
Education ≤high school			0.97	0.43-2.19	0.95	0.42-2.16	1.03	0.45-2.38
Non-White racial background			0.14	0.04-0.53	0.16	0.04-0.59	**0.13**	**0.04-0.51**
Currently smoking[a]			0.11	0.03-0.43	0.12	0.03-0.45	**0.09**	**0.02-0.37**
Rheumatic Disease Comorbidity Index			0.98	0.75-1.27	0.98	0.76-1.27	0.99	0.75-1.30
CDAI at baseline			1.00	0.97-1.02	1.00	0.97-1.02	1.00	0.97-1.03
RA medications in first year								
Biologics or JAKs			4.59	1.54-13.74	4.42	1.47-13.23	**5.42**	**1.72-17.03**
Corticosteroids (oral)[b]			1.19	0.50-2.84	1.18	0.49-2.82	1.23	0.50-2.98
Vaccination previous year			13.04	5.65-30.12	12.87	5.57-29.76	**15.33**	**6.37-36.90**
BMQ Necessity-Concerns Differential at baseline					1.03	0.96-1.11		
Change in BMQ Necessity-Concerns Differential (12 months – baseline)							**1.08**	**1.02-1.15**

Abbreviations: BMQ, Beliefs About Medicines Questionnaire; CI, confidence interval; CDAI, Clinical Disease Activity Index; JAK, Janus kinase; OR, odds ratio.
Bolded values indicate $p < .05$.
[a]Versus former and never smoking.
[b]Use of corticosteroids (oral) in the first 3 months. Akaike information criteria: model 1, 271.4; model 2, 213.1; model 3, 214.4; model 4, 208.9.

vaccinated, were on advanced RA therapies, and held stronger beliefs about the need for RA medications along with fewer concerns were more likely to report receiving an influenza vaccination, whereas women, smokers, and racial and ethic minority groups were less likely to do so. There is initial evidence that attitudes toward vaccination overlap with attitudes toward medications; for example, Wood et al [18] reported that higher medication concerns on the BMQ scores correlated moderately and directly with higher influenza antivaccination scores on the Vaccination Attitudes Examination scale, even with adjustment for education and medical mistrust. In the COMORA cohort, adults with RA who were taking daily medicine for conditions other than RA were 60% more likely to have been vaccinated against influenza in the year prior to enrollment [25]. Together, these findings suggest that beliefs about medications and vaccines, which in turn influence medication adherence and uptake, may reflect general concerns and mistrust of pharmacotherapeutic agents. Better understanding is needed of the specific knowledge, attitudes, and beliefs about influenza vaccines of people with early RA. Additionally, studies should examine the extent to which these factors impact the acceptance of other vaccines (eg, pneumococcal, zoster, COVID-19).

Previous studies that examined predictors of influenza vaccine coverage in established RA have reported a moderate-strong positive relationship between vaccination and previous influenza [32] or pneumococcal vaccinations [14,32,33] and being advised to be vaccinated by a physician [14,15,32,34] or rheumatologist [32,34]. A recent review supports the important role rheumatologists play on reducing vaccine hesitancy [35]. Although several studies [14,27,32,36] reported that most (71%-96%) patients with RA discussed whether or not to be vaccinated, lack of awareness and no physician recommendation remained commonly cited reasons for nonvaccination [15,28,33,34,36–38]. This gap speaks to the need to clearly allocate the responsibility of influenza vaccination discussions to specific health providers and to improve communication among providers, as suggested by Qendro et al [14], because influenza vaccination may be assumed to be the responsibility of rheumatologists but is mostly prescribed by general practitioners or recommended by others such as pharmacists [31,33]. In Canada and elsewhere, it is often assumed that general practitioners should take responsibility for discussing annual influenza vaccinations [39]. Researchers have noted that as compared with primary care providers, subspecialists are less likely to assess for, recommend, stock, or refer patients for vaccination [40]. Nonetheless, conversations about the importance of influenza vaccination in patients with RA provide a critical opportunity to improve vaccination uptake because 69% of Canadians state that recommendations by their doctor are an important part of their decision to get vaccinated [22].

Strengths of our study include the use of a well-characterized cohort of individuals captured around the time of RA diagnosis. There are also limitations. Vaccination status was self-reported, although we note that the Centers for Disease Control and Prevention, the Public Health Agency of Canada, and the World Health Organization often rely on self-reported vaccination to establish vaccine coverage. Self-reports have been shown to be a good proxy of coverage according to vaccination records, although they may overestimate coverage by about 10% [41].

Vaccination information post diagnosis was incomplete; however, the comparison of characteristics between those included and excluded showed the groups were very similar. Some CATCH sites offer influenza vaccinations to patients at study visits (ie, after questionnaires are completed); of 21 participants who had been vaccinated prior to diagnosis but reported no current vaccination, nine (43%) visits were scheduled between November 1 and January 30. Findings may also represent a best case scenario because many of the rheumatologists in CATCH helped develop the Canadian RA treatment guidelines, and provider awareness and perceived responsibility are important contributors to higher vaccination coverage in RA (35).

Similar to patients with established RA, our results indicate that influenza vaccination coverage in patients with early RA remains suboptimal. Previous vaccination, selected RA treatments (being on advanced therapeutics), sociodemographic characteristics (White, male), lifestyle (not smoking), and a stronger belief in the necessity of medications to control RA relative to medication concerns are markers of individuals more likely to be vaccinated. Having conversations about the vaccination history and attitudes toward RA medications and influenza vaccination offers a potential opportunity to increase both RA medication adherence and vaccine uptake in adults with newly diagnosed RA.

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. Bartlett 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. Ta, Schieir, Hitchon, Bessette, Hazlewood, Thorne, Pope, Boire, Tin, Keystone, Bykerk, Bartlett.
Acquisition of data. Schieir, Hitchon, Bessette, Hazlewood, Thorne, Pope, Boire, Tin, Keystone, Bykerk, Bartlett.
Analysis and interpretation. Ta, Schieir, Valois, Colmegna, Bartlett.

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