Vaccine effectiveness against SARS-CoV-2 infection and severe outcomes among individuals with immune-mediated inflammatory diseases tested between March 1 and Nov 22, 2021, in Ontario, Canada: a population-based analysis

Jessica Widdifield, Jeffrey C Kwong, Simon Chen, Lihi Eder, Eric I Benchimol, Gilaad G Kaplan, Carol Hitchon, J Antonio Aviña-Zubieta, Diane Lacaille, Hannah Chung, Sasha Bernatsky

Summary

Background We estimated COVID-19 vaccine effectiveness against SARS-CoV-2 infection and severe COVID-19 outcomes among individuals with immune-mediated inflammatory diseases in Ontario, Canada.

Methods In this population-based analysis, we used a test-negative design across four immune-mediated inflammatory disease population-based cohorts, comprising individuals with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease. We identified all SARS-CoV-2 tests done in these populations between March 1 and Nov 22, 2021 (a period in which there was rapid uptake of vaccines, and the alpha [B.1.1.7] and delta [B.1.617.2] SARS-CoV-2 variants were predominantly circulating in Canada) and separately assessed outcomes of SARS-CoV-2 infection and severe COVID-19 outcomes (hospitalisation due to COVID-19 and death due to COVID-19) for each disease group. We used multivariable logistic regression to estimate the effectiveness of one, two, and three doses of mRNA-based COVID-19 vaccine (BNT162b2 [Pfizer–BioNTech], or mRNA-1273 [Moderna]) among individuals at the time of SARS-CoV-2 testing.

Findings Between March 1 and Nov 22, 2021, we identified 2127 (5·9%) test-positive cases among 36 145 individuals (26 476 [73·2%] were female and 9669 [26·8%] were male) with rheumatoid arthritis tested, 476 (6·1%) test-positive cases among 7863 individuals (4130 [52·5%] were female and 3733 [47·5%] were male) with ankylosing spondylitis tested, 3089 (6·5%) test-positive cases among 47 199 individuals (26 062 [55·2%] were female and 21 137 [44·8%] were male) with psoriasis tested, and 1702 (5·4%) test-positive cases among 31 311 individuals (17 716 [56·6%] were female and 13 595 [43·4%] were male) with inflammatory bowel disease tested. Adjusted vaccine effectiveness of two doses against infection was 83% (95% CI 80–86) in those with rheumatoid arthritis, 89% (83–93) among those with ankylosing spondylitis, 84% (81–86) among those with psoriasis, and 79% (74–82) among those with inflammatory bowel disease. After two vaccine doses, effectiveness against infection generally peaked 31–60 days after vaccination and waned gradually with each additional month. Vaccine effectiveness against severe outcomes after two doses was 92% (95% CI 88–95) in those with rheumatoid arthritis, 97% (83–99) among those with ankylosing spondylitis, 92% (86–95) among those with psoriasis, and 94% (88–97) among those with inflammatory bowel disease. Vaccine effectiveness after a third dose against infection was similar to or higher than after the second dose (ranging from 76% [47–89] to 96% [72–99]), although due to a paucity of events, estimates could not be calculated for some subgroups for severe outcomes.

Interpretation Two vaccine doses were found to be highly effective against both SARS-CoV-2 infection and severe COVID-19 outcomes in patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease during the study period. Research is needed to determine the durability of effectiveness of three doses over time, particularly against emerging variants.

Funding Public Health Agency of Canada.

Introduction

Canada's comprehensive universal SARS-CoV-2 testing and surveillance, rapid uptake of COVID-19 vaccines, and population-based linked health datasets have contributed to monitoring of vaccine effectiveness in the general population.[1–5] Less is known about vaccine effectiveness among individuals with immune-mediated inflammatory diseases. Individuals with immune-mediated inflammatory diseases are not only susceptible to severe outcomes associated with SARS-CoV-2,[6–9] but the immunogenicity of mRNA-based COVID-19 vaccines might also be impaired in this patient population.[10–14] Although policy and clinical recommendations on COVID-19 vaccination for people with immune-mediated

Holland Bone & Joint Program, Sunnybrook Research Institute, Toronto ON, Canada (J Widdifield PhD); **ICES, Toronto, Canada** (J Widdifield, Prof J C Kwong MD, S Chen MPH, Prof E I Benchimol MD, H Chung MPH); **Institute of Health Policy, Management and Evaluation** (J Widdifield, Prof E I Benchimol), **Department of Family and Community Medicine, Faculty of Medicine** (Prof J C Kwong), **Dalla Lana School of Public Health** (Prof J C Kwong), **Division of Rheumatology** (L Eder), **and Department of Paediatrics** (Prof E I Benchimol), **University of Toronto, Toronto, ON, Canada; Public Health Ontario, Toronto, Canada** (Prof J C Kwong); **Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada** (L Eder); **SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, ON, Canada** (Prof E I Benchimol); **Child Health Evaluative Sciences, SickKids Research Institute, Toronto, ON, Canada** (Prof E I Benchimol); **Department of Medicine and Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada** (Prof G G Kaplan MD); **Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada** (C Hitchon MD); **Division of Rheumatology,**

Research in context

Evidence before this study
We searched PubMed for studies published in English between Jan 1, 2021, and Mar 1, 2022, using different combinations of the terms "SARS-CoV-2", "COVID-19", "vaccination", "vaccine", "rheumatic diseases", "rheumatoid arthritis", "psoriasis", "inflammatory bowel disease", "ankylosing spondylitis", "immune-mediated Inflammatory diseases", "effectiveness", and "immunogenicity". Vaccine effectiveness studies done on the general population have shown that mRNA-based COVID-19 vaccines are highly protective against infections and severe outcomes, such as admission to hospital and death. Studies have shown than the immunogenicity of mRNA-based COVID-19 vaccines might be impaired among individuals with immune-mediated inflammatory diseases, which could translate into reduced vaccine effectiveness. Sparse information exists on the effectiveness of COVID-19 vaccines in patients with immune-mediated inflammatory diseases.

Added value of this study
To our knowledge, this is the largest population-based study of vaccine effectiveness of mRNA-based COVID-19 vaccines in people with immune-mediated inflammatory diseases. Among

individuals with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease tested for SARS-CoV-2 between March 1 and Nov 22, 2021, we estimated high (92–97%) vaccine effectiveness of two doses of mRNA-based COVID-19 vaccines (BNT162b2 or mRNA-1273) against severe COVID-19 outcomes compared with unvaccinated patients. Estimates of vaccine effectiveness against SARS-CoV-2 infection were numerically lower than for severe outcomes. For the outcome of infection with SARS-CoV-2, overall vaccine effectiveness for two doses exceeded 79% across all four patient populations. After the second dose, vaccine effectiveness against infection peaked 31–60 days after vaccination (82–90%) and waned with each additional month, but effectiveness increased again with third doses.

Implications of all the available evidence
We found high vaccine effectiveness of mRNA vaccines against severe COVID-19 outcomes among individuals with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease, which could help individuals with these diseases, who were largely excluded from vaccine trials, make informed decisions about following vaccination recommendations.

Department of Medicine, University of British Columbia, Vancouver, BC, Canada (J A Aviña-Zubieta MD, Prof D Lacaille MD); **Arthritis Research Canada, Vancouver, BC, Canada** (J A Aviña-Zubieta, Prof D Lacaille); **Divisions of Rheumatology and Clinical Epidemiology, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada** (Prof S Bernatsky MD)

Correspondence to:
Dr Jessica Widdifield, Sunnybrook Research Institute, Toronto ON, M4N 3M5, Canada
jessica.widdifield@utoronto.ca

inflammatory diseases have largely been driven by research on immunogenicity,[15,16] understanding how well these vaccines work in broader immune-mediated inflammatory disease populations remains a priority, especially because they are under-represented in clinical studies. Therefore, we aimed to estimate the vaccine effectiveness of mRNA-based COVID-19 vaccines against SARS-CoV-2 infection and severe COVID-19 outcomes among individuals with a selection of immune-mediated inflammatory diseases in Ontario, Canada, over the period March to November, 2021, during which there was rapid uptake of vaccinations in the province,[17] and the predominant circulating SARS-CoV-2 variants were alpha (B.1.1.7; March to June, 2021) and delta (B.1.617.2; June to November, 2021).[1]

Methods

Study design and setting

In this population-based study, we used a common protocol that was used to estimate vaccine effectiveness within the general Ontario population to help facilitate comparisons.[1–3]

To assess vaccine effectiveness, we used a test-negative design across four separate population-based cohorts of people with immune-mediated inflammatory diseases. Within each cohort, individuals tested for SARS-CoV-2 served as the nested cohort, whereby vaccine status was compared between SARS-CoV-2 test-positive cases versus test-negative controls.

Our study period was from March 1 to November 22, 2021. The details of the immunisation rollout in Ontario has

been previously reported.[17] Briefly, due to low vaccine supply, Ontario initially had a slow and low vaccine uptake between December, 2020, and March, 2021, during which time vaccines were prioritised for residents and staff of long-term care and retirement homes, health-care workers, and adults aged 80 years and older. By March, 2021, vaccination of residents was largely prioritised by age (in decreasing age group increments) in rapid succession, resulting in a rapid increase in vaccine uptake of one and two doses among all age groups between March and July, 2021.[17] Administration of third doses started in September, 2021.[18] Most people with immune-mediated inflammatory diseases in Ontario were given the BNT162b2 (Pfizer–BioNTech) vaccine (>70%) and the mRNA-1273 (Moderna) vaccine (>18%) as part of their initial two doses, and few patients (<10%) received the Covishield vaccine (also known as ChAdOx1 nCoV-19; Oxford–AstraZeneca).[17] The pandemic's third wave occurred in the country between March and June, 2021, with a lower incidence of SARS-CoV-2 infections observed between June and November, 2021.[19]

This study was approved by a privacy impact assessment at ICES (formerly called the Institute for Clinical Evaluative Sciences). The use of the data in this project was authorised under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. Datasets were linked using unique encoded identifiers and analysed at ICES. ICES is a prescribed entity under Personal Health Information Protection Act. Section 45 of the Personal Health Information Protection Act

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authorises ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system.

Data sources and definitions

We collected patient-level data on SARS-CoV-2 testing and COVID-19 vaccination for patients with immune-mediated inflammatory diseases. Ontario residents, comprising approximately 40% of Canada's population of 35 million people, are insured under a single payer health-care system (Ontario's Health Insurance Plan) that covers all medically necessary health services. These contacts for health services are recorded in administrative databases and linked using unique encoded identifiers. We assembled four separate population-based cohorts of individuals aged 16 years or older with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease using established disease-specific case definitions applied to health administrative data (appendix p 1). These case definitions require multiple health-care contacts for diagnosis codes related to the condition of interest (a minimum of three to five diagnosis codes, often involving a health-care contact with a specialist) and are based on validation studies involving medical chart review.[20–22] These population-based cohorts have been extensively used for previous research, including assessments of SARS-CoV-2 testing and risks of infection, and severe COVID-19 outcomes.[6,17,23–27]

From within each cohort, we identified all individuals who had real-time RT-PCR tests for SARS-CoV-2 during the study period. Data on SARS-CoV-2 tests (sample collection date and results) were collected from the Ontario Laboratories Information System. The study accrual period ended on Nov 22, 2021, when the first cases of infection with the omicron (B.1.1.529) variant were detected in Ontario (to limit misclassification of variants).

We excluded long-term care residents because they undergo frequent testing, are more frail than other individuals, and have a different threshold for admission to hospital; individuals who received out-of-province vaccinations; and individuals who had received two doses of ChAdOx1 nCoV-19 because effectiveness for that schedule is known to be lower than for mRNA-based vaccines[1–3] and most of the study population received mRNA-based COVID-19 vaccines.[17]

For vaccine effectiveness against infection, cases were defined as individuals with a laboratory-confirmed positive PCR test for SARS-CoV-2 between March 1 and Nov 22, 2021. The index date was the sample collection date. We identified the first positive test for the individual, and individuals who tested negative were treated as controls. For controls with multiple negative tests, we used the date of a randomly selected negative test as their index date.

Severe outcomes were defined as an admission to hospital (ie, hospitalisation) or death attributed to SARS-CoV-2 infection in test-positive individuals. Severe outcomes were ascertained from an integrated dataset linking Public Health Ontario's Case and Contact Management (CCM) dataset (which contains information on the clinical course of patients with SARS-CoV-2 infection [including hospitalisations and deaths]), the Canadian Institute for Health Information Discharge Abstract Database (as a secondary source to identify hospitalisations and inpatient deaths in individuals with a diagnosis of COVID-19 [ie, an International Classification of Diseases 10th edition code U07.1], and a positive test result within 14 days before or 3 days after admission), and the Ontario Registered Persons Database (as a secondary source for deaths, in which a positive test result must have occurred within 30 days before death or within 7 days post-mortem if COVID-19 was suspected). Infections that occurred during hospital stay for another reason were not considered a severe outcome for the purposes of this analysis. We used the earliest date of sample collection or hospital admission or death as the index date.

At the time of testing, we assessed whether or not individuals had one, two, or three vaccine doses before their testing date. COVID-19 vaccination status, including vaccine product, date of administration, and dose number were determined from COVaxON, a centralised COVID-19 vaccine registry in Ontario.

Statistical analysis

We did analyses separately for each of the four study populations (rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease). To compare characteristics between test-positive cases and test-negative controls and between those vaccinated with at least one dose of mRNA-based vaccine and unvaccinated individuals, we did descriptive analyses and calculated standardised differences (with a standardised difference of >0·10 considered to be a clinically relevant difference).[28,29]

We separately estimated overall vaccine effectiveness (for infection and severe outcomes) for one dose of vaccine at least 14 days before testing date, and at least 7 days before testing date for two and three doses, using multivariable logistic regression to compare the odds of vaccination in test-positive cases with the odds of vaccination among test-negative controls, adjusting for covariates that are associated with SARS-CoV-2 infection and vaccination. We estimated vaccine effectiveness as $(1 - \text{odds ratio}) \times 100\%$. Subsequently, we estimated vaccine effectiveness against infection for each subsequent month after receipt of two doses of vaccine. We also separately estimated adjusted vaccine effectiveness against SARS-CoV-2 infection by vaccine product after one and two doses. We adjusted estimates of vaccine effectiveness for patient age (using age bands as a categorical variable), sex, public health unit

region of residence, biweekly period of test (to account for temporal variations in viral activity and regional vaccine roll-out), number of PCR tests for each individual in the 3 months before the start of Ontario's COVID-19 immunisation programme (a proxy for individuals who are at increased risk of SARS-CoV-2 exposure and undergo frequent testing), previous SARS-CoV-2 infection more than 90 days before the index date, presence of any comorbidity that increases the risk of severe COVID-19 (ie, chronic respiratory diseases, chronic heart disease, hypertension, diabetes, chronic kidney disease, other immunosuppressive conditions including receipt of a transplant, other immune disorders, active cancer, advanced liver disease, dementia, frailty, or history of transient ischaemic attack or stroke), a previous influenza vaccination (within the past 2 years, a proxy for health behaviours), and census dissemination area-level quintiles of household income, proportion of people employed as non-health-care-based essential workers (proxy of individuals unable to work from home), average number of people per dwelling, and proportion of self-identified minorities. Full details regarding these covariates are provided in the appendix (pp 2–7).

Because of the length of the study period with changes over time in SARS-CoV-2 infection incidence, PCR testing volumes (ie, higher volumes early on due to higher incidence of infection), and vaccination status (ie, increased vaccination coverage later in the time course) in the underlying population, we did a sensitivity analysis to assess potential bias in patient selection by using the last negative testing episode (rather than a random selection among those with multiple negative tests).

All tests were two-sided and a p value of less than 0·05 was considered to be significant. We do not report estimates of vaccine effectiveness after three doses of vaccine in situations where there were very few individuals with three doses among the test-positive cases, because vaccine effectiveness approximates 100% on the basis of near-zero vaccinated test-positive cases and the 95% CIs were essentially infinite or extremely imprecise.

We did all analyses using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among 36 145 individuals with rheumatoid arthritis tested for SARS-CoV-2 during the study period, we identified 2127 (5·9%) test-positive cases (appendix p 8). For ankylosing spondylitis, we identified 476 (6·1%) positive cases among 7863 individuals with ankylosing spondylitis tested (appendix p 9). For psoriasis, we identified 3089 (6·5%) positive cases among 47 199 individuals with

	Rheumatoid arthritis			Ankylosing spondylitis			Psoriasis			Inflammatory bowel disease		
	SARS-CoV-2 positive (n=2127)	SARS-CoV-2 negative (n=34 018)	Standardised difference*	SARS-CoV-2 positive (n=476)	SARS-CoV-2 negative (n=7387)	Standardised difference*	SARS-CoV-2 positive (n=3089)	SARS-CoV-2 negative (n=44 110)	Standardised difference*	SARS-CoV-2 positive (n=1702)	SARS-CoV-2 negative (n=29 609)	Standardised difference*
Age, years	57·4 (16·1)	61·4 (16·5)	0·25	50·4 (14·3)	52·6 (15·8)	0·15	49·4 (16·6)	53·6 (17·5)	0·24	46·8 (16·8)	51·1 (17·4)	0·25
Sex												
Male	564 (26·5%)	9105 (26·8%)	0·01	252 (52·9%)	3481 (47·1%)	0·12	1567 (50·7%)	19 570 (44·4%)	0·13	860 (50·5%)	12 735 (43·0%)	0·15
Female	1563 (73·5%)	24 913 (73·2%)	0·01	224 (47·1%)	3906 (52·9%)	0·12	1522 (49·3%)	24 540 (55·6%)	0·13	842 (49·5%)	16 874 (57·0%)	0·15
Number of tests in past 3 months†												
0	1776 (83·5%)	25 520 (75·0%)	0·21	381 (80·0%)	5467 (74·0%)	0·14	2533 (82·0%)	32 877 (74·5%)	0·18	1318 (77·4%)	21 549 (72·8%)	0·11
1	250 (11·8%)	5202 (15·3%)	0·10	70 (14·7%)	1267 (17·2%)	0·07	416 (13·5%)	7169 (16·3%)	0·08	274 (16·1%)	5186 (17·5%)	0·04
≥2	101 (4·7%)	3296 (9·7%)	0·19	25 (5·3%)	653 (8·8%)	0·14	140 (4·5%)	4064 (9·2%)	0·19	110 (6·5%)	2874 (9·7%)	0·12
Previous positive test >90 days since testing date‡	16 (0·8%)	639 (1·9%)	0·10	0	134 (1·8%)	0·19	15 (0·5%)	882 (2·0%)	0·14	12 (0·7%)	471 (1·6%)	0·08
Any comorbidity§	1473 (69·3%)	25 165 (74·0%)	0·10	270 (56·7%)	4569 (61·9%)	0·10	1781 (57·7%)	27 058 (61·3%)	0·08	938 (55·1%)	17 714 (59·8%)	0·10
Previous influenza vaccination¶	862 (40·5%)	18 373 (54·0%)	0·27	186 (39·1%)	3460 (46·8%)	0·16	993 (32·1%)	19 706 (44·7%)	0·26	555 (32·6%)	13 504 (45·6%)	0·27
Neighbourhood income quintile‖												
1 (lowest)	526 (24·7%)	6787 (20·0%)	0·11	98 (20·6%)	1219 (16·5%)	0·11	708 (22·9%)	7754 (17·6%)	0·13	301 (17·7%)	4814 (16·3%)	0·04
2	429 (20·2%)	6625 (19·5%)	0·02	91 (19·1%)	1323 (17·9%)	0·03	615 (19·9%)	8389 (19·0%)	0·02	357 (21·0%)	5575 (18·8%)	0·05
3	457 (21·5%)	6653 (19·6%)	0·05	102 (21·4%)	1455 (19·7%)	0·04	620 (20·1%)	8614 (19·5%)	0·01	354 (20·8%)	5981 (20·2%)	0·01
4	386 (18·1%)	6826 (20·1%)	0·05	94 (19·7%)	1571 (21·3%)	0·04	619 (20·0%)	9269 (21·0%)	0·02	356 (20·9%)	6193 (20·9%)	0·00
5 (highest)	319 (15·0%)	7004 (20·6%)	0·15	86 (18·1%)	1787 (24·2%)	0·15	515 (16·7%)	9932 (22·5%)	0·15	328 (19·3%)	6949 (23·5%)	0·10

Data are mean (SD) or n (%), unless otherwise stated. Proportions might not add up to 100% due to rounding. Additional patient characteristics are provided in the appendix (pp 12–14). *Values of >0·10 are considered to be clinically relevant differences. †In the 3 months before COVID-19 immunisation programme started on Dec 14, 2020. ‡Previous positive tests by PCR before study period (before March 1, 2021). §Comorbidities include chronic respiratory diseases, chronic heart diseases, hypertension, diabetes, chronic kidney disease, other immunocompromising illness, active cancer, advanced liver disease, dementia, frailty, and history of stroke or transient ischaemic attack (appendix pp 12–14). ¶Influenza vaccination during 2019–20 or 2020–21 influenza season, or both. ‖The sum of counts does not equal the column total because of individuals with missing information (<1·0%) for this characteristic.

Table 1: Characteristics of individuals with immune-mediated inflammatory diseases, by SARS-CoV-2 test result, at time of testing between March 1 and Nov 22, 2021

	Rheumatoid arthritis			Ankylosing spondylitis			Psoriasis			Inflammatory bowel disease		
	Unvaccinated (n=11238)	At least one dose of mRNA-based vaccine (n=22990)	Standardised difference*	Unvaccinated (n=2857)	At least one dose of mRNA-based vaccine (n=4470)	Standardised difference*	Unvaccinated (n=17338)	At least one dose of mRNA-based vaccine (n=26693)	Standardised difference*	Unvaccinated (n=11246)	At least one dose of mRNA-based vaccine (n=18159)	Standardised difference*
Tested positive for SARS-CoV-2†	1332 (11.9%)	720 (3.1%)	0.34	320 (11.2%)	140 (3.1%)	0.32	2083 (12.0%)	887 (3.3%)	0.33	1084 (9.6%)	554 (3.1%)	0.27
Age, years	55.9 (15.9)	63.9 (16.7)	0.50	48.6 (14.3)	54.5 (16.6)	0.38	48.1 (16.0)	56.2 (18.4)	0.47	46.4 (15.6)	53.1 (18.6)	0.39
Sex												
Male	3062 (27.2%)	5985 (26.0%)	0.03	1421 (49.7%)	2012 (45.0%)	0.09	8129 (46.9%)	11268 (42.2%)	0.09	5169 (46.0%)	7489 (41.2%)	0.10
Female	8176 (72.8%)	17005 (74.0%)	0.03	1436 (50.3%)	2458 (55.0%)	0.09	9209 (53.1%)	15425 (57.8%)	0.09	6077 (54.0%)	10670 (58.8%)	0.10
Number of tests in past 3 months‡												
0	8752 (77.9%)	17028 (74.1%)	0.09	2188 (76.6%)	3229 (72.2%)	0.10	13396 (77.3%)	19464 (72.9%)	0.10	8419 (74.9%)	12953 (71.3%)	0.08
1	1726 (15.4%)	3404 (14.8%)	0.02	492 (17.2%)	760 (17.0%)	0.01	2820 (16.3%)	4261 (16.0%)	0.01	2018 (17.9%)	3132 (17.2%)	0.02
≥2	760 (6.8%)	2558 (11.1%)	0.15	177 (6.2%)	481 (10.8%)	0.16	1122 (6.5%)	2968 (11.1%)	0.16	809 (7.2%)	2074 (11.4%)	0.15
Previous positive test >90 days since testing date	161 (1.4%)	473 (2.1%)	0.05	35 (1.2%)	93 (2.1%)	0.07	253 (1.5%)	599 (2.2%)	0.06	134 (1.2%)	329 (1.8%)	0.05
Any comorbidity§	7556 (67.2%)	17685 (76.9%)	0.22	1609 (56.3%)	2896 (64.8%)	0.17	9367 (54.0%)	17528 (65.7%)	0.24	6061 (53.9%)	11367 (62.6%)	0.18
Prior influenza vaccination¶	4467 (39.7%)	13568 (59.0%)	0.39	1019 (35.7%)	2310 (51.7%)	0.33	5329 (30.7%)	13498 (50.6%)	0.41	3621 (32.2%)	9287 (51.1%)	0.39
Neighbourhood income quintile‖												
1 (lowest)	2555 (22.7%)	4433 (19.3%)	0.08	534 (18.7%)	715 (16.0%)	0.07	3340 (19.3%)	4684 (17.5%)	0.04	2036 (18.1%)	2800 (15.4%)	0.07
2	2229 (19.8%)	4467 (19.4%)	0.01	564 (19.7%)	775 (17.3%)	0.06	3415 (19.7%)	5134 (19.2%)	0.01	2217 (19.7%)	3412 (18.8%)	0.02
3	2224 (19.8%)	4527 (19.7%)	0.00	608 (21.3%)	851 (19.0%)	0.06	3474 (20.0%)	5180 (19.4%)	0.02	2317 (20.6%)	3672 (20.2%)	0.01
4	2151 (19.1%)	4699 (20.4%)	0.03	575 (20.1%)	982 (22.0%)	0.05	3570 (20.6%)	5597 (21.0%)	0.01	2345 (20.9%)	3822 (21.0%)	0.00
5 (highest)	2033 (18.1%)	4784 (20.8%)	0.07	562 (19.7%)	1126 (25.2%)	0.13	3475 (20.0%)	6008 (22.5%)	0.06	2294 (20.4%)	4395 (24.2%)	0.09

Data are n (%) or mean (SD), unless otherwise stated. Proportions might not add up to 100% due to rounding. Additional patient characteristics in the appendix (pp 15–17). *Values of >0·10 are considered to be clinically relevant differences. †Positive test by PCR at index test between March and November, 2021. ‡In the previous 3 months before COVID-19 immunisation programme started (on Dec 14, 2020). §Comorbidities include chronic respiratory diseases, chronic heart diseases, hypertension, diabetes, chronic kidney disease, other immunocompromising illness, active cancer, advanced liver disease, dementia, frailty, and history of stroke or transient ischaemic attack. ¶Influenza vaccination during 2019–20 or 2020–21 influenza season, or both. ‖The sum of counts does not equal the column total because of individuals with missing information (<1.0%) for this characteristic.

Table 2: Characteristics of individuals with immune-mediated inflammatory diseases, by vaccination status, at time of testing between March 1 and Nov 22, 2021

psoriasis tested (appendix p 10). And for inflammatory bowel disease, we identified 1702 (5·4%) positive cases among 31 311 individuals with inflammatory bowel disease tested (appendix p 11).

Among 36 145 individuals with rheumatoid arthritis, the mean age was 61·2 years (SD 16·5), 20 682 (57·2%) were aged 60 years or older, 26 476 (73·2%) were female, and 9669 (26·8%) were male. Among 7863 individuals with ankylosing spondylitis, the mean age was 52·5 years (SD 15·7), 2615 (33·3%) were aged 60 years or older, 4130 (52·5%) were female, and 3733 (47·5%) were male. Among 47 199 individuals with psoriasis, the mean age was 53·3 years (SD 17·5), 17 954 (38·0%) were aged 60 years or older, 26 062 (55·2%) were female, and 21 137 (44·8%) were male. And among 31 311 individuals with inflammatory bowel disease, the mean age was 50·9 years (SD 17·4), 10 043 (32·1%) were 60 years or older, 17 716 (56·6%) were female, and 13 595 (43·4%) were male. No data were captured on race or ethnicity.

Across all four immune-mediated inflammatory disease groups, test-positive cases were more likely to be younger and reside in neighbourhoods with lower income, and were less likely to have had any PCR tests during the 3 months before the start of Ontario's immunisation programme than were test-negative controls (table 1; appendix pp 12–14).

Among test-positive cases and test-negative controls, 1917 with rheumatoid arthritis, 536 with ankylosing spondylitis, 3168 with psoriasis, and 1906 with inflammatory bowel disease received out-of-province or ChAdOx1 nCoV-19 vaccines and were excluded from the subsequent analyses.

Across all four immune-mediated inflammatory disease groups, at the time of the index test date, unvaccinated patients were generally younger, less likely to have had previous testing, and less likely to have a comorbidity than were patients who had received at least one dose of mRNA-based COVID-19 vaccine (table 2; appendix pp 15–17).

Overall adjusted vaccine effectiveness of two doses of mRNA-based COVID-19 vaccine against SARS-CoV-2 infection was 83% (95% CI 80–86) in patients with rheumatoid arthritis, 89% (83–93) in patients with ankylosing spondylitis, 84% (81–86) in patients with psoriasis, and 79% (74–82) in patients with inflammatory bowel disease (table 3). Effectiveness against infection peaked 31–60 days after two doses (adjusted vaccine effectiveness 82–92% across immune-mediated inflammatory disease groups) and overall waned gradually with each additional month (figure). Estimates of adjusted vaccine effectiveness against infection after three doses of vaccine were near equivalent or higher than those after two doses, although less precise due to fewer patients having received three doses (table 3). Because few test-positive cases had received a third dose of vaccine and due to insufficient follow-up time, we
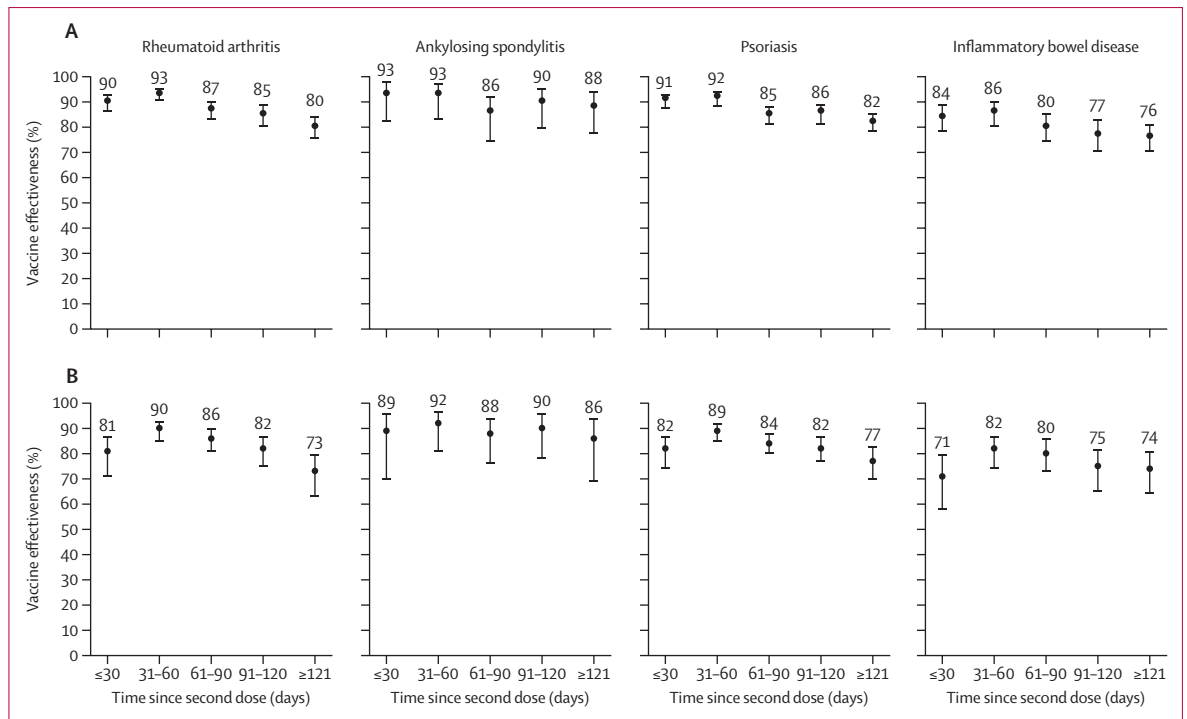
could not assess waning of vaccine effectiveness after third doses over time.

Across all four immune-mediated inflammatory disease groups, adjusted vaccine effectiveness estimates against SARS-CoV-2 infection were higher for mRNA-1273 than for BNT162b2 after one and two doses (appendix p 18). Estimates for vaccine effectiveness after three doses could not be precisely determined and so are not presented here.

	Test-positive cases	Test-negative controls	Unadjusted vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)*
SARS-CoV-2 infection				
Rheumatoid arthritis				
First dose ≥14 days	311/1801 (17·3%)	6005/17 393 (34·5%)	60% (55–65)	53% (45–59)
Second dose ≥7 days	244/1734 (14·1%)	14 330/25 718 (55·7%)	87% (85–89)	83% (80–86)
Third dose ≥7 days	7/1497 (0·5%)	453/11 841 (3·8%)	88% (75–94)	86% (70–94)
Ankylosing spondylitis				
First dose ≥14 days	62/421 (14·7%)	1074/3902 (27·5%)	55% (40–66)	49% (30–63)
Second dose ≥7 days	37/396 (9·3%)	2876/5704 (50·4%)	90% (86–93)	89% (83–93)
Third dose ≥7 days	<6/361 (<1·7%)	89/2917 (3·1%)	NR	82% (20–96)
Psoriasis				
First dose ≥14 days	334/2655 (12·6%)	6548/23 586 (27·8%)	63% (58–67)	55% (48–60)
Second dose ≥7 days	314/2635 (11·9%)	17 230/34 268 (50·3%)	87% (85–88)	84% (81–86)
Third dose ≥7 days	<6/2322 (<0·3%)	245/17 283 (1·4%)	NR	96% (72–99)
Inflammatory bowel disease				
First dose ≥14 days	202/1400 (14·4%)	4570/15 907 (28·7%)	58% (51–64)	49% (40–57)
Second dose ≥7 days	231/1429 (16·2%)	11 560/22 897 (50·5%)	81% (78–84)	79% (74–82)
Third dose ≥7 days	7/1205 (0·6%)	300/11 637 (2·6%)	78% (53–90)	76% (47–89)
Severe outcomes				
Rheumatoid arthritis				
First dose ≥14 days	53/305 (17·4%)	6005/17 393 (34·5%)	60% (46–70)	74% (63–81)
Second dose ≥7 days	35/287 (12·2%)	14 330/25 718 (55·7%)	89% (84–92)	92% (88–95)
Third dose ≥7 days	<6/254 (<2·4%)	453/11 841 (3·8%)	NR	88% (48–97)
Ankylosing spondylitis				
First dose ≥14 days	6/46 (13·0%)	1074/3902 (27·5%)	61% (7–83)	76% (35–91)
Second dose ≥7 days	<6/42 (<14·3%)	2876/5704 (50·4%)	NR	97% (83–99)
Third dose ≥7 days	<6/41 (<14·6%)	89/2917 (3·1%)	NR	NR†
Psoriasis				
First dose ≥14 days	37/269 (13·8%)	6548/23 586 (27·8%)	59% (41–71)	72% (59–82)
Second dose ≥7 days	25/257 (9·7%)	17 230/34 268 (50·3%)	89% (84–93)	92% (86–95)
Third dose ≥7 days	<6/232 (<2·6%)	245/17 283 (1·4%)	NR	NR†
Inflammatory bowel disease				
First dose ≥14 days	30/173 (17·3%)	4570/15 907 (28·7%)	48% (23–65)	65% (44–78)
Second dose ≥7 days	14/157 (8·9%)	11 560/22 897 (50·5%)	90% (83–94)	94% (88–97)
Third dose ≥7 days	<6/145 (<4·1%)	300/11 637 (2·6%)	NR	NR†

Data are n/N (%), where n is number vaccinated, and N is total cases, unless otherwise stated. Exact patient numbers and unadjusted vaccine estimates cannot be provided for groups containing fewer than six patients to maintain patient anonymity. Vaccine effectiveness is (1–odds ratio) × 100%. Severe outcome is defined as hospitalisation or death attributed to SARS-CoV-2 infection. NR=not reportable. *Adjusted for age, sex, region, biweekly period of test, number of previous SARS-CoV-2 tests, past SARS-CoV-2 infection, presence of any comorbidity, previous receipt of influenza vaccine, and area-level sociodemographic variables. †Not reported due to extremely imprecise 95% confidence intervals due to near zero exposures among test-positive cases.

Table 3: **Estimated vaccine effectiveness of mRNA-based COVID-19 vaccines against SARS-CoV-2 infection and severe outcome, by time between vaccination and testing date**

Figure: **Unadjusted (A) and adjusted* (B) vaccine effectiveness against SARS-CoV-2 infection by time since second dose for those tested for SARS-CoV-2 between March 1 and Nov 22, 2021**
Datapoints are vaccine effectiveness, with whiskers showing 95% CIs. *Adjusted for age, sex, region, biweekly period of test, number of previous SARS-CoV-2 tests, past SARS-CoV-2 infection, presence of any comorbidity, previous receipt of influenza vaccine, and area-level sociodemographic variables.

For rheumatoid arthritis, among 2127 test-positive cases, 352 (16·5%) had a severe outcome including 16 (0·8%) deaths attributed to COVID-19. For ankylosing spondylitis, among 476 test-positive cases, 50 (10·5%) had a severe outcome. For psoriasis, among 3089 test-positive cases, 298 (9·6%) had a severe outcome, of whom 13 (0·4%) died. For inflammatory bowel disease, among 1702 test-positive cases, 196 (11·5%) had a severe outcome. Fewer than six patients died in each group of ankylosing spondylitis and inflammatory bowel disease; therefore, we cannot report the exact numbers due to privacy protection regulations.

Adjusted vaccine effectiveness of two doses against severe outcome was high across all four immune-mediated inflammatory disease groups: 92% (95% CI 88–95) in patients with rheumatoid arthritis, 97% (83–99) in patients with ankylosing spondylitis, 92% (86–95) in patients with psoriasis, and 94% (88–97) in patients with inflammatory bowel disease (table 3). Among test-positive patients who had a severe outcome, there were too few patients who had received three doses of vaccine to precisely estimate vaccine effectiveness for patients with ankylosing spondylitis, psoriasis, and inflammatory bowel disease.

The assessment of potential selection bias through the sensitivity analysis did not change study findings (data not shown).

Discussion

Over a 9 month period in 2021, we assessed the initial vaccine effectiveness of mRNA-based COVID-19 vaccines in patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease. We found high (92–97%) adjusted vaccine effectiveness of two doses of an mRNA-based COVID-19 vaccines (BNT162b2 or mRNA-1273) against severe COVID-19 outcomes compared with unvaccinated patients. Although vaccine effectiveness estimates against infection were lower than for severe outcomes, COVID-19 vaccines still offered very good protection against infection during the study period. For second doses, adjusted vaccine effectiveness against infection peaked at 31–60 days after vaccination (82–92%) and waned with each additional month but rebounded for those who received three doses. Because administration of third doses only commenced on Sept 14, 2021, in Ontario, Canada, and our study accrual period was only up to Nov 22, 2021, we were unable to assess waning of third dose effectiveness in this study.

We found high vaccine effectiveness against severe outcomes in individuals with immune-mediated inflammatory diseases that are similar to those found in the larger general population in Ontario.[1–3] However, vaccine effectiveness against infection among people with immune-mediated inflammatory diseases was slightly lower than that estimated for the general population, which was estimated to be above 90% for symptomatic

infection shortly after two doses of vaccine (and rebound to >90% after a third dose) during a similar study time frame.[1,3] We were unable to estimate vaccine effectiveness for symptomatic infection, which might also explain differences in estimates of vaccine effectiveness compared with the general population. Possibly the increased age, altered immune response, high burden of comorbidities, and use of immunosuppressant therapy in people with immune-mediated inflammatory diseases reduces vaccine effectiveness against infection.[6,9,30] People with immune-mediated inflammatory diseases might also be more likely to get tested for SARS-CoV-2 infection than people in the general population because they know they are more clinically vulnerable, leading to higher detection of infections than in the general population.

Estimates of COVID-19 vaccine effectiveness against infection and seroconversion rates are generally lower in people with immune-mediated inflammatory diseases than in the general population.[11,12,31–34] Two systematic reviews reported that immunocompromised groups, including people with immune-mediated inflammatory diseases, had lower seroconversion and antibody titres after first and second doses of COVID-19 vaccines than did immunocompetent controls.[11,35] Studies have also found that additional doses of vaccine and temporary discontinuation of immunosuppressant therapy might improve immunogenicity.[10,13,14] Thus, the reduced immune response to COVID-19 vaccines that has been observed in clinical studies is probably translates to slightly lower vaccine effectiveness in the larger population of people with immune-mediated inflammatory diseases, as we found in our study. We also found that adjusted vaccine effectiveness estimates against SARS-CoV-2 infection were generally higher for mRNA-1273 than for BNT162b2, for both one and two doses; a finding that has been signalled in other studies[1,36] and is potentially a result in differences in the mRNA content and higher dose of mRNA-1273 than BNT162b2.

By linking a centralised vaccine registry with laboratory and health administrative data, we created large cohorts to study vaccine effectiveness, overcoming the sample size challenges faced by clinical studies. We used a test-negative study design to enable us to do comparative assessments with the general population estimates of vaccine effectiveness from previous Ontario reports that used a similar protocol.[1–3] The test-negative design in traditional case-control studies is purported to reduce selection bias associated with differential health care-seeking behaviour between cases and controls, and reduce misclassification of cases,[37–39] resulting in comparable estimates with those of case-control and cohort studies (although all might underestimate true vaccine effectiveness) and randomised controlled trials.[38,40] However, bias might still occur due to unmeasured differences between vaccinated and unvaccinated patients, and testing patterns might also differ between vaccinated and unvaccinated patients.

The preferred approach in test-negative designs is to sample patients who present for testing with symptomatic disease, otherwise including patients with asymptomatic disease can create a downward bias resulting in underestimation of vaccine effectiveness. Unfortunately, information on symptoms (at the time of testing) was only available on a subset of patients and so we were unable to estimate vaccine effectiveness against symptomatic infection. This approach might have resulted in lower estimates of vaccine effectiveness for the outcome of infection than for the outcome of symptomatic infection.

Ontario's centralised vaccine registry minimised misclassification of vaccination status, and during our study period there were no changes in PCR testing eligibility. Even with the increased use of rapid antigen tests (which were not captured in our datasets), all individuals who tested positive with rapid antigen tests were advised to obtain PCR tests for confirmation throughout our study period. The proportion of SARS-CoV-2 infections that are not confirmed by PCR is unclear; however, our estimates of vaccine effectiveness against severe outcomes are not biased by this uncertainty because, for this measure, all individuals would have received a PCR test upon hospital admission.

Another potential limitation of our study is misclassification error using administrative data to identify people with immune-mediated inflammatory diseases. Our immune-mediated inflammatory disease case definitions were previously validated by medical chart reviews, yielding high specificity (approximately 99%) and positive predictive values (rheumatoid arthritis: 78%, inflammatory bowel disease: 71–81%).[20,22,41] Misclassified patients (false positives) usually have a similar immune-mediated inflammatory disease diagnosis.[20,21] Because of the population-based nature of our data, the patients with immune-mediated inflammatory diseases in our study encompass a wide spectrum of disease states that are likely to be highly generalisable to real-world populations across different settings; however, we were not able to assess phenotype, disease activity, or severity. Heterogeneity in vaccine effectiveness might exist across different risk groups, such as those receiving pharmacological therapy.[9,30,42–48] We did not assess the effects or control for immunosuppressant therapies because prescription drug data were limited to a subset of patients who qualify for the publicly funded drug programme in the province (primarily those aged ≥65 years). Therefore, despite controlling for potential confounders, residual confounding might have affected our results.

Finally, we restricted our study period to predate the omicron SARS-CoV-2 variant for several methodological reasons. The omicron variant has shown differences in disease severity for both vaccinated and unvaccinated individuals within Canada[49] and other countries,[50,51] which could confound our results. Moreover, because of

the high vaccine coverage in our population with immune-mediated inflammatory diseases by the time omicron was circulating[17] and strict public health measures among unvaccinated individuals, estimating vaccine effectiveness for only the initial part of the omicron wave could lead to downward bias. Although the dominant circulating variants of SARS-CoV-2 are changing over time, we postulated a priori that any differences observed (comparing estimates of vaccine effectiveness within Ontario's population with immune-mediated inflammatory diseases within Ontario's general population[1–3]) will probably hold true for omicron and future variants. Early general population-based analyses (up to Dec 26, 2021) from Ontario reported that vaccine effectiveness against infection with the omicron variant has been lower than that observed against infection with the delta variant, but still remains high against severe outcomes for omicron.[3] Unfortunately, universal PCR testing in Ontario is no longer available, restricting our ability to replicate our analyses in Ontario's population with immune-mediated inflammatory diseases for the outcome of infection with the omicron variant.

In summary, between March and November, 2021, we estimated high vaccine effectiveness of mRNA-based COVID-19 vaccines against severe outcomes and infection among individuals with immune-mediated inflammatory diseases. These findings are crucial to help these individuals, who were excluded from vaccine trials, make informed decisions about following vaccine recommendations and to inform future vaccine strategies. Future research is needed to understand how long effectiveness of three doses of these vaccines remains durable, particularly against emerging variants.

Contributors

JW contributed to study design, data acquisition, statistical analysis, interpretation of data, manuscript writing, and is responsible for the overall content as guarantor. JCK contributed to study design, statistical analysis, interpretation of data, and manuscript editing. SC contributed to data acquisition, data preparation, statistical analysis, and manuscript editing. LE, EIB, GGK, CH, JAA-Z, and DL contributed to study design, interpretation of data, and manuscript editing. HC contributed to study design, data preparation, interpretation of data, and manuscript editing. SB contributed to study design, data acquisition, statistical analysis, interpretation of data, and manuscript editing. All authors had final responsibility for the decision to submit for publication. JW, SC, HC, and SB accessed and verified the underlying study data.

Declaration of interests

GGK has received honoraria for speaking or consultancy from AbbVie, Janssen, Pfizer, and Takeda; has received research support from Janssen, AbbVie, GlaxoSmithKline, Merck, Ferring, and Shire; has been a consultant for Gilead; and shares ownership of two patents (Treatment of inflammatory disorders, autoimmune disease, and PBC, UTI Limited Partnership, assignee. patent WO2019046959A1. PCT/CA2018/051098. Sept 7, 2018). EIB has acted as a legal consultant for Hoffman La-Roche and Peabody & Arnold, and consultant for McKesson Canada for matters unrelated to a medication used to treat inflammatory bowel disease or COVID-19 (ie, unrelated to the submitted work). LE reports grants from AbbVie, Novartis, UCB, Pfizer, and Eli Lilly. All other authors declare no competing interests.

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