Low Uptake of Influenza Vaccination in Immune-mediated Inflammatory Diseases: A Cohort Study

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Title: 92 characters
Abstract: 249
Text: 2490
References: 39
Tables: 4
Figures: 2
Supplemental: 3 Tables, 1 figure

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Abstract

Background: We examined influenza vaccination uptake in inflammatory bowel disease (IBD), multiple sclerosis (MS) and rheumatoid arthritis (RA), as compared to persons without these immune-mediated inflammatory diseases (IMID), and evaluated the influence of psychiatric comorbidity on vaccine uptake.

Methods: Using administrative data from 1984-2015, we conducted a retrospective cohort study in Manitoba, Canada. We identified 10,148 persons with IBD, 6,158 with MS, 16,975 with RA, and 164,152 controls matched on age, sex and region. We identified cohort members with any mood or anxiety disorder (MAD; depression, anxiety disorders, bipolar disorder). We identified influenza vaccinations using tariff (i.e., billing) codes. Using log-binomial regression, we modeled the difference in the proportion of the IMID and matched cohorts vaccinated annually, adjusting for sociodemographics, comorbidity and immune therapy use. We tested additive interaction effects between cohort and psychiatric status.

Results: In 2015, 41.3% (40.6-42.0%) of IMID cases received an influenza vaccination, 7.6% more than matched controls (33.7%; 33.4-34.0). After adjustment, participants with an IMID but no MAD had 6.44% (5.79-7.10%) more uptake of vaccination than participants without an IMID. Among participants without an IMID, having a MAD was associated with 4.54% (4.20-4.89%) greater uptake of vaccination. However, we observed a less than additive interaction between IMID and psychiatric status (-1.38%; -2.26 -0.50%).

Interpretation: Influenza vaccination uptake is consistently low in IMID populations. While psychiatric morbidity is associated with greater vaccine uptake in Manitobans, it negatively interacts with IMID to reduce uptake. Changes in care delivery are needed to mitigate this gap in care.

Introduction

Immune-mediated inflammatory diseases (IMID), such as inflammatory bowel disease (IBD), multiple sclerosis (MS) and rheumatoid arthritis (RA), are prevalent in Canada.[1-3] Affected individuals share an increased risk for influenza and related complications.[4] Among 140,480 persons with and without IBD, those with IBD had a 54% increased incidence of influenza, and were more likely to require hospitalization.[5] Persons with MS are more likely to be hospitalized for influenza than persons without MS,[6,7] and influenza increases relapse risk.[8]

Given the elevated risks and adverse impact of influenza in persons with IMID, influenza prevention is important. Effective implementation of influenza vaccination strategies require knowledge of vaccine uptake, and how this varies across population subgroups. However, our understanding of influenza vaccine uptake in IMID populations has been limited by the use of small samples, selection biases, cross-sectional designs, and variable study durations and time periods. Prior findings regarding vaccine uptake in IMID are highly variable.[9-14] A population-based assessment of influenza vaccine uptake in IMID is needed to clarify the extent of this important gap in preventive care.

Serious psychiatric disorders such as schizophrenia are associated with lower uptake of preventive health care such as cervical cancer screening and vaccinations.[15,16] Psychiatric disorders, mainly mood and anxiety disorders (MAD), affect people with IMID more often than people without IMID.[17] While MAD are known to adversely affect health outcomes in IMID, it is unknown whether MAD affect preventive health behaviors such as influenza vaccination. Small studies have suggested that the presence of any comorbidity may increase vaccination uptake,[14] while others have reported no association.[14,18]

We examined uptake of influenza vaccination in population-based cohorts with IBD, MS and RA, as compared to persons without these IMID. We also evaluated the influence of MAD on vaccine uptake in

these populations. We focused on IMID that are highly prevalent in Canada, affect individuals across the age spectrum, affect different organ systems and cared for by different specialists. We considered that if vaccine uptake is uniformly low across these IMID, this would suggest our findings generalize to other IMID.

Methods

Data Sources

This retrospective cohort study was conducted in Manitoba, Canada, which has a population of about 1.3 million. Universal health care is publicly funded, and provided for medically necessary services. Manitoba Health, the provincial health department, maintains a population registry and health services databases. We accessed four databases housed in the Manitoba Population Research Data Repository at the Manitoba Centre for Health Policy including the population registry, Discharge Abstract Database (DAD), medical services database, and the Drug Program Information Network (DPIN) database. We linked these databases at the individual level using an encrypted unique identifier. The population registry captures sex; dates of birth, death and health care coverage; and region of residence (postal code) for all provincial residents eligible to receive health services. The DAD captures hospitalizations, admission and discharge dates, and up to 25 diagnoses. Until March 31, 2004, diagnoses were recorded using the International Classification of Diseases (ICD), 9th revision, Clinical Modification (ICD-9-CM) codes, and by ICD 10th revision, Canadian version (ICD-10-CA) codes thereafter. The medical services database captures the service date, one diagnosis assigned using ICD-9-CM codes, and tariff (i.e., billing) codes (including for vaccinations). Since 1995, DPIN has captured outpatient prescription dispensations, including the drug name, drug identification number (DIN) and date; the DIN links to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System.[12] Except for DPIN, we accessed data for the period April 1, 1984-March 31, 2016. The University of Manitoba Health Research

Ethics Board approved the study. Manitoba's Health Information Privacy Committee approved data access.

Study populations

Using validated case definitions, we identified Manitobans with IBD, MS and RA.[19-21] For each case, we defined the first health claim (hospital, physician, prescription) as the index date. Next, as described elsewhere,[17] we identified a general population cohort which excluded anyone with ICD-9-CM/ICD-10-CA codes for IBD, MS or RA, or use of any MS-specific disease-modifying therapies, as these were part of the MS case definition. Then, we selected up to 5 controls for each case, matched on sex, year of birth within ± 5 years, and forward sortation area (first 3 digits of postal code). We assigned controls the index date of their matched cases.

Comorbidity

We applied validated case definitions developed in Manitoba to identify members of each cohort affected by any MAD (which included ≥1 of depression, anxiety disorders, bipolar disorders) and the individual disorders comprising MAD.[22] We classified the date of the first claim for each condition as the diagnosis date. We identified physical comorbidity using the John Hopkins Adjusted Clinical Group System Aggregated Diagnosis Groups (ADGs), specifically using major physical ADGs which were not time-limited (ADGs 9, 11, 16, 22 and 32).

Covariates

We included the following covariates in the regression models: sex (male as reference group), age (updated annually), socioeconomic status (SES) at the index date, region of residence at the index date, physical comorbidity (updated annually), IMID-specific procedures (ever), and disease-modifying therapy use (updated annually). We categorized age as 18-24 [reference group], 25-44, 45-64, and ≥65

years reflecting the emphasis on immunizing individuals in the latter age group. To determine SES we linked postal code to dissemination-area level census data then calculated the Socioeconomic Factor Index version 2 (SEFI-2), which incorporates information regarding average household income, percent of single parent households, unemployment rate and high school education rate; scores less than zero indicate higher SES.[13] We categorized SES into quintiles (lowest quintile of SES as reference group). Regions were classified as urban (Winnipeg, population >600,000 and Brandon, population >47,000). Physical comorbidity was based on ADG scores and categorized as 0 (reference group), 1 or ≥2, with higher scores indicating greater comorbidity. IMID-specific procedures were included as a measure of disease severity. For IBD these included surgical procedures related to the gastrointestinal resections or ostomy placement (Table e1), and for RA these included joint-related surgical procedures (Table e2); there were no relevant procedures for MS. Annually for IBD and RA, immune therapies were categorized as none (reference group), any biologic (alone or in combination), or any anti-inflammatory or traditional immunosuppressive therapy or corticosteroids. For MS, disease-modifying therapies were categorized as none, first-line, or second-line (Table e3).

Influenza Vaccination

Annually, we identified influenza vaccinations using tariff codes 8791, 8792 or 8799, which are used by primary care and pharmacy providers to bill for their services.

Analysis

We summarized the characteristics of the cohort using descriptive statistics, including mean (standard deviation [SD]), median (interquartile range [IQR]), and frequency (percent [%]). We report the crude percentage of each cohort who had the influenza vaccination annually, along with a 95% confidence interval (95%CI) based on the binomial distribution. We also report percentages standardized by age and sex to the 2010 Canadian Census population. Although we accessed data for the period April 1, 1984-

March 31, 2016 initially, for regression analyses, we limited the time period to 2006-2016 to reduce secular trends. We modeled the difference in the proportion immunized annually so that we could estimate the absolute effects of cohort (IMID vs. matches), and psychiatric comorbidity on this outcome, as this is more useful for policymakers than relative effects. We used a log-binomial regression model with generalized estimating equations, accounting for differences in follow-up time by including the log of person-years as the model offset. Covariates included those defined above. Also, we tested for the presence of additive interaction effects between cohort and MAD status, where a positive (synergistic interaction) would indicate the joint effects of cohort and MAD exceeded the sum of their individual effects, while a negative interaction would indicate the joint effect was less than the sum of their individual effects. We report differences in percentages and 95%CI. We repeated these analyses for each cohort (IBD, MS, RA) separately.

Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary NC).

Results

Cohorts

We identified 10,148 persons with IBD, 6,158 with MS, and 16,975 with RA and a total of 164,152 matched controls (Table 1). Their characteristics were similar to those of the IMID populations for the period 2006-2016. Two-thirds of the combined IMID cohort was female. Cases and controls were well-matched with respect to age, sex, and SES at the index date.

Influenza vaccination

The percentage of the combined IMID cases and matched controls who received influenza vaccination rose over time (Figure 1). However, the percentage of IMID cases who received an influenza vaccination

was low regardless of the year, and was comparable across IMIDs after age and sex-standardization (Figure 2). In 2015, the crude percentage of IMID cases who received an influenza vaccination was 41.3% (95%CI: 40.6-42.0%), 7.6% more than matched controls (33.7%; 95%CI: 33.4-34.0%).

Among IMID cases, those with any MAD (43.7%; 95%CI: 42.8-44.6%) had greater vaccine uptake than those without a MAD (38.3%; 95%CI: 37.3-39.3%). Similarly, among the matched controls those with a MAD (37.5%; 95%CI: 37.1-37.9%) had greater vaccine uptake than those without (30.5%; 95%CI: 30.1-30.9). The percentage of people immunized increased with age, and was highest among those aged ≥65 years (Figure e1).

Multivariable analysis

On multivariable analysis, participants with an IMID but no MAD had 6.44% (95%CI: 5.79-7.10) more vaccination uptake than participants without an IMID (Table 2). Among participants without an IMID, having a MAD was associated with a 4.54% (95%CI: 4.20-4.89%) more vaccination uptake. However, we observed a less than additive interaction effect between IMID and MAD status (-1.38%; 95%CI: -2.26- -0.50%). As compared to the highest quintile of SES, participants of lower SES had lower vaccination uptake. Female as compared to male sex, older age, living in an urban rather than rural region, and an increased number of physical comorbidities were associated with increased vaccination uptake. Prior disease-specific surgery (IBD, RA), and use of immune therapies were also associated with increased uptake.

When we conducted analyses for depressive and anxiety disorders, findings were similar to those for any MAD (Tables 3-4). When we conducted analyses for individual IMIDs, findings in the RA cohort were similar to those for the combined IMID cohort. Findings in the IBD cohort were similar in magnitude and direction those in the IMID cohort but did not reach statistical significance. We did not observe a departure from additivity between the specific IMID diagnosis and MAD in the MS cohort (Tables 2-4).

Discussion

In this population-based study, vaccination uptake increased over the thirty-year study period in three IMID cohorts, and a matched cohort without IMID, in concert with programmatic changes. In 1999, vaccinations became publicly funded for Manitobans aged ≥65 years, those with some chronic conditions, and health care workers. In 2005, funding was extended to chronic respiratory disease. However, despite universal vaccination coverage as of 2010, and access via pharmacists as of 2014, vaccination rates in the IMID and matched populations remain much lower than desired. In 2015 only four in ten persons with IMID was vaccinated annually, only slightly better than the three in ten persons without IMID vaccinated. In the matched population, having a MAD was associated with increased vaccination uptake. However, the joint effect of an IMID and comorbid MAD on increasing uptake was negative (less than effect of either factor alone).

The target vaccination rate for high-risk populations and adults aged ≥65 years in Canada is 80%; vaccination is also recommended in IMID guidelines.[23-25] We found vaccination rates well below this target. In the 2013/2014 Canadian Community Health Survey only 37.8% of adults aged 18-64 years with a chronic medical condition were vaccinated.[26] Findings from prior studies in IBD, MS and RA have been inconsistent. A Polish survey found a 6% uptake of annual influenza vaccination among hospitalized IBD patients,[9] whereas an internet cohort of 958 patients in the Crohn's and Colitis Foundation of America Partners Program self-reported 80% uptake in 2012.[10] Investigation of temporal changes in vaccine uptake has been limited. In Israel, 16.1% of persons with Crohn's disease were vaccinated in 2006; this increased to 38.3% by 2012.[27] Findings were similar in persons with ulcerative colitis, increasing from 21.5% in 2006 to 37.9% in 2012.[28] Reported influenza vaccine uptake also ranges widely in RA,[14,29-31] from 26.6% in a German outpatient clinic in 2011[31] to 85% in two specialty

rheumatology centers in the United Kingdom.[14] Comparable findings are more limited in MS. In a questionnaire-based study in Israel, 37.6% of 101 participants with MS reported receiving the seasonal flu vaccine during the winter of 2009-2010.[11] In Norway, an immunization register-based study found that 60.7% of persons with MS received the pandemic (H1N1) vaccine in 2009-2010.[32]

We observed a less than additive (negative) interaction between IMID and psychiatric comorbidity on vaccination uptake in the combined IMID cohort, and in the IBD and RA cohorts. This may reflect competing demands during physician visits,[33] or reduced adherence to treatment recommendations by persons with psychiatric disorders, whether pharmacologic,[34-36] or health behaviors.[37] However, we did not observe a negative interaction in the MS cohort, which may reflect differences in provincial programs of care for IMID, which are more centralized for MS. Sociodemographic factors associated with greater vaccine uptake included older age, female sex, higher SES, and urban residence. Greater disease severity, as evidenced by prior surgeries, medical comorbidities, and use of immune therapies were also associated with greater uptake. These findings are consistent with those in the Canadian general population,[26] and earlier studies in IMID populations.[10,27,28]

Interventions to improve vaccination rates in IMID populations have been tested. Use of electronic medical record alerts improved vaccination rates in immunosuppressed rheumatology patients; making the process nurse-led improved vaccination rates further.[38] A quality improvement project in an IBD clinic showed that distributing a vaccine questionnaire before clinic, and offering recommended vaccinations if due increased influenza vaccine uptake from 54% to 81%.[39] Future studies aimed at improving implementation of such strategies are needed.

Study strengths included the population-based design, application of validated case definitions for IMID and psychiatric comorbidity, and extended time period. Conduct of the study in one province was a limitation. However, in the 2013/2014 Canadian Community Health Survey, the proportion of individuals

vaccinated was similar across provinces, apart from Nova Scotia (47.9%), Quebec (25.4%) and Newfoundland (27.6%). This suggests that our findings are generalizable in Canada although they may not be generalizable to jurisdictions with alternate models of health care delivery. We may not have identified all vaccinations administered due to use of tariff codes, but under-ascertainment is likely to be non-differential between cohorts, and would be insufficient to fully account for our findings. We lacked clinical characteristics regarding the IMID, but included some measures of disease severity and treatment status.

Influenza vaccination uptake is lower than desired in vulnerable IMID populations. Given the increased susceptibility of IMID populations to influenza and related complications, it is essential that action be taken to ameliorate this gap in preventive care. Although having a MAD was associated with increased influenza vaccine uptake in Manitobans without IMID, comorbid MAD interacted negatively with IMID. This suggests that the association of psychiatric comorbidity with other preventive health behaviors should also be evaluated in IMID.

Acknowledgement

This study was funded by the Canadian Institutes of Health Research (THC-135234), Crohn's and Colitis Canada and the Waugh Family Chair in Multiple Sclerosis (to RAM). Dr Bernstein is supported in part by the Bingham Chair in Gastroenterology. Dr. Sareen is supported by CIHR #333252. Dr. Lix is supported by a Canada Research Chair. Dr. El-Gabalawy is supported by University of Manitoba Start-Up Funding.

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The use of Aggregated Diagnosis Groups™ (ADGs™) codes for risk adjustment in regression models were created using The Johns Hopkins Adjusted Clinical Group® (ACG®) Case-Mix System version 9. The authors

acknowledge the Manitoba Centre for Health Policy for use of the Population Health Research Data Repository under project #2014-030 (HIPC #2014/2015-19A). The results and conclusions presented are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

Members of the CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease are: Ruth Ann Marrie, James M Bolton, Jitender Sareen, John R Walker‡, Scott B Patten, Alexander Singer, Lisa M. Lix, Carol A Hitchon, Renée El-Gabalawy, PhD, Alan Katz, John D Fisk, Charles N Bernstein, Lesley Graff, Lindsay Berrigan, Ryan Zarychanski, Christine Peschken, James J Marriott

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Author Contributions

RAM, JB, JS, SB, LML, CAH, JJM, AK, JDF and CNB obtained study funding and designed the study. RW analyzed the data and all authors interpreted the data. RAM drafted the manuscript. All other authors revised the manuscript and approved submission.

Competing Interests

Ruth Ann Marrie receives research funding from: CIHR, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC. She is supported by the Waugh Family Chair in Multiple Sclerosis.

Randy Walld reports no disclosures.

James Bolton receives research funding from CIHR, Brain and Behavior Research Foundation and the MS Society of Canada.

Jitender Sareen receives research funding from CIHR and holds stocks in Johnson and Johnson.

Scott Patten receives research funding from CIHR, the MS Society of Canada, Roche, Biogen and the Government of Alberta.

Alexander Singer has received financial and in-kind support from an IBM/CIMVHR Advanced Analytics Grant and Calian Inc.

Lisa Lix receives research funds from CIHR and the Arthritis Society.

Carol Hitchon has research funds for unrelated studies from UCB Canada and Pfizer.

Renee El-Gabalawy receives research funds from CIHR, University of Manitoba Start-Up Funds.

Alan Katz receives research funds from CIHR, the Heart and Stroke Foundation and Research Manitoba.

John Fisk receives research funds from CIHR, the MS Society of Canada, the Nova Scotia Health Authority Research Fund and the Dalhousie Medical Fund.

James Marriott has conducted clinical trials for Biogen Idec and Roche, and receives research funding from the MS Society of Canada, the MS Scientific Foundation and Research Manitoba.

Charles Bernstein has consulted to Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada, and has received unrestricted educational grants from Abbvie Canada, Janssen Canada, Shire Canada and Takeda Canada. He has been on speaker's bureaus of Abbvie Canada and Shire Canada.

Data Sharing

As we are not the data custodians, we are not authorized to make the data used in this study available. With the appropriate approvals, the data can be accessed through the Manitoba Centre for Health Policy.

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Table 1. Characteristics of prevalent disease cohorts at the time of diagnosis, and matched cohorts at the matched index date.

Characteristic	IBD matches (n = 50704)	IBD (n = 10148)	MS matches (n = 30690)	MS (n = 6158)	RA matches (n = 84756)	RA (n = 16975)	IMID[a] (n = 32880)	IMID matches (n = 164152)
Whole population, 1984-2015								
Female, n (%)	27663 (54.6)	5536 (54.6)	21564 (70.3)	4322 (70.2)	61231 (72.2)	12263 (72.2)	21841 (66.4)	65185 (66.7)
Age at diagnosis, mean (SD)	41.7 (17.0)	41.7 (17.0)	42.1 (13.5)	42.1 (13.5)	54.0 (16.1)	54.0 (16.1)	48.0 (17.1)	48.0 (17.1)
Duration of follow-up from the index date (years), median (IQR)	11.9 (4.92, 21.8)	13.3 (5.93, 22.8)	13.9 (5.91, 23.6)	13.9 (6.28, 22.5)	11.1 (4.93, 19.3)	11.4 (5.51, 19.0)	12.4 (5.79, 20.7)	11.9 (5.12, 20.8)
Urban region of residence, n (%)	33799 (66.7)	6763 (66.6)	20685 (67.4)	4154 (67.5)	50281 (59.3)	10070 (59.3)	20727 (63.0)	103468 (63.0)
Socioeconomic status[a]	-0.23 (0.88)	-0.26 (0.91)	-0.22 (0.88)	-0.25 (0.91)	0.06 (1.01)	0.03 (1.03)	-0.11 (0.99)	-0.08 (0.96)
Comorbidity status at study start, n (%)								
No. ADGs								
0	42318 (83.5)	6749 (66.5)	26373 (85.9)	4389 (71.3)	65883 (77.7)	11216 (66.1)	22275 (67.7)	133038 (81.0)
1	7246 (14.3)	2789 (27.5)	3763 (12.3)	1392 (22.6)	15605 (18.4)	4643 (27.4)	8561 (26.0)	26227 (16.0)
≥2	1140 (2.2)	610 (6.0)	554 (1.8)	377 (6.1)	3268 (3.9)	1116 (6.6)	2044 (6.2)	4887 (3.0)
Any Common Mental Disorder	10979 (21.7)	3147 (31.0)	7431 (24.2)	2485 (40.4)	22078 (26.1)	5735 (33.8)	11171 (34.0)	39911 (24.3)
Depression	9590 (18.9)	2764 (27.2)	6546 (21.3)	2197 (35.7)	18853 (22.2)	4864 (28.7)	9645 (29.3)	34480 (21.0)
Anxiety disorder	13438 (26.5)	3453 (34.0)	8931 (29.1)	2378 (38.6)	25922 (30.6)	6074 (35.8)	11707 (35.6)	47639 (29.0)

Bipolar disorder	1562 (3.1)	548 (5.4)	1151 (3.8)	368 (6.0)	2963 (3.5)	716 (4.2)	1602 (4.9)	5583 (3.4)

	Population, 2006-2016							
	IBD matches (n = 40364)	**IBD (n = 8458)**	**MS matches (n = 24154)**	**MS (n = 4748)**	**RA matches (n = 64510)**	**RA (n = 12714)**	**IMID matches (n = 127310)**	**IMID (n = 25832)**
Female, n (%)	22207 (55.0)	4623 (54.7)	17247 (71.4)	3399 (71.6)	47102 (73.0)	9458 (72.8)	85349 (67.0)	8602 (33.3)
Age at diagnosis, mean (SD)	41.2 (16.2)	41.0 (16.2)	40.9 (12.2)	40.2 (11.9)	51.8 (15.2)	51.4 (15.4)	46.4 (16.0)	45.9 (16.0)
Urban region of residence, n (%)	26558 (65.8)	5574 (65.9)	15925 (65.9)	3153 (66.4)	37559 (58.2)	7609 (58.6)	78949 (62.0)	16104 (62.3)
Socioeconomic status[a]	-0.22 (0.85)	-0.26 (0.89)	-0.21 (0.85)	-0.25 (0.89)	0.06 (1.0)	0.04 (1.0)	-0.08 (0.95)	-0.11 (0.98)
Comorbidity status at the index date, n (%)								
No. ADGs								
0	33895 (84.0)	5546 (65.6)	20903 (86.5)	3371 (71.0)	51284 (79.5)	8594 (66.2)	104753 (82.3)	17434 (67.5)
1	5638 (14.0)	2390 (28.2)	2892 (12.0)	1089 (22.9)	11140 (17.3)	3577 (27.5)	19340 (15.2)	6827 (24.2)
≥2	831 (2.0)	522 (6.2)	359 (1.5)	288 (6.1)	2086 (3.2)	813 (6.3)	3217 (2.5)	1571 (6.1)
Any Mood and Anxiety Disorder	9108 (22.6)	2669 (31.6)	6119 (25.3)	1985 (41.8)	17008 (26.4)	4490 (34.6)	31739 (24.9)	8960 (34.7)
Depression	7992 (19.8)	2343 (27.7)	5410 (22.4)	1742 (36.7)	14548 (22.6)	3808 (29.3)	27517 (21.6)	7723 (29.)
Anxiety disorder	11444 (28.4)	2980 (35.2)	7543 (31.2)	1983 (41.8)	21332 (33.1)	5063 (39.0)	39735 (31.2)	9839 (38.1)
Bipolar disorder	1326 (3.3)	465 (5.5)	968 (4.0)	301 (6.3)	2347 (3.6)	575 (4.4)	4559 (3.6)	1312 (5.1)

IBD = inflammatory bowel disease, MS = multiple sclerosis, RA = rheumatoid arthritis, IMID = immune-mediated inflammatory disease, combining IBD, MS and RA cohorts; a-Socioeconomic status = Socioeconomic Factor Index scores; values less than zero indicate higher

socioeconomic status; a- A small number of individuals met the case definitions for more than one of the IMIDs of interest. We did not exclude them to ensure generalizability of our findings but only allowed them to account once in the IMID cohort. In this situation, there were classified on the basis of the IMID with the earliest index date in the coverage period.

Table 2. Association of immune-mediated inflammatory disease (IMID), any mood or anxiety disorder (MAD) and uptake of influenza vaccination (Percentage; 95% confidence interval)

Variable	IMID	IBD	MS	RA
Cohort effect, absent a MAD effect	6.44 (5.79, 7.10)	7.19 (6.12, 8.26)	6.70 (5.13, 8.27)	5.61 (4.64, 6.59)
MAD effect absent a cohort effect	4.54 (4.20, 4.89)	5.10 (4.52, 5.68)	5.31 (4.53, 6.09)	3.74 (3.23, 4.26)
Joint effect (cohort & MAD)*	5.06[a] (4.39, 5.74)	5.76[b] (4.55, 6.98)	6.78[c] (5.29, 8.27)	3.72[d] (2.76, 4.68)
Age				
18-24	0	0	0	0
25-44	6.12 (5.59, 6.64)	5.61 (4.98, 6.24)	6.94 (5.47, 8.40)	5.56 (4.41, 6.71)
45-64	15.1 (14.6, 15.7)	14.0 (13.3, 14.7)	15.2 (13.7, 16.6)	15.0 (13.8, 16.1)
≥65	33.3 (32.7, 33.9)	33.8 (32.9, 34.7)	32.6 (31.0, 34.3)	32.3 (31.1, 33.5)
Sex				
Male	0	0	0	0
Female	4.97 (4.64, 5.29)	4.92 (4.41, 5.43)	3.66 (2.90, 4.42)	4.61 (4.09, 5.13)
Region				
Rural	0	0	0	0
Urban	2.16 (1.83, 2.49)	1.88 (1.35, 2.40)	2.28 (1.52, 3.04)	2.56 (2.06, 3.06)
Socioeconomic status				
Quintile 1 (lowest)	-4.69 (-5.19, -4.19)	-4.66 (-5.48, -3.84)	-3.38 (-4.52, -2.23)	-6.03 (-6.82, -5.25)
Quintile 2	-3.74 (-4.25, -3.23)	-4.00 (-4.79, -3.22)	-3.45 (-4.57, -2.34)	-4.01 (-4.83, -3.18)
Quintile 3	-3.09 (-3.61, -2.58)	-3.40 (-4.18, -2.61)	-2.74 (-3.85, -1.63)	-3.39 (-4.23, -2.55)
Quintile 4	-2.25 (-2.75, -1.75)	-2.16 (-2.93, -1.39)	-2.21 (-3.30, -1.12)	-2.66 (-3.49, -1.84)
Quintile 5 (highest)	0	0	0	0
Comorbidity				
0	0	0	0	0
1	4.77 (4.32, 5.22)	3.43 (2.69, 4.16)	3.78 (2.68, 4.87)	5.66 (5.01, 6.30)
≥2	8.67 (7.60, 9.74)	8.64 (6.61, 10.7)	8.96 (6.10, 11.8	8.34 (6.95, 9.72)
IMID-specific procedure	4.94 (4.21, 5.67)	6.90 (5.58, 8.22)	-	4.00 (3.12, 4.88)
Immune therapy				
None	0	0	0	0
Anti-inflammatory/immune-modulatory therapy	3.09 (2.73, 3.46)	2.95 (2.39, 3.52)	4.43 (2.53, 6.32)	3.07 (2.58, 3.56)

Any biologic	9.08 (7.92, 10.2)	9.11 (7.09, 11.1)	5.60 (2.17, 9.03)	9.45 (7.93, 11.0)

IMID = Immune-mediated inflammatory disease; IBD = inflammatory bowel disease; MS = multiple sclerosis; RA = rheumatoid arthritis; MAD= mood or anxiety disorder; a-IMID*MAD interaction -1.38 (-2.26, -0.50); b-IBD* MAD interaction -1.43 (-2.90, 0.05); c-MS* MAD interaction 0.08 (-1.97, 2.13); d-RA* MAD interaction -1.89 (-3.16, -0.63)

Table 3. Association of immune-mediated inflammatory disease (IMID), depressive disorder, and uptake of influenza vaccination (Percentage; 95% confidence interval)

Variable	IMID	IBD	MS	RA
Cohort effect, absent a depressive disorder effect	6.08 (5.49, 6.66)	6.81 (5.82, 7.80)	5.81 (4.45, 7.18)	5.52 (4.65, 6.38)
Depressive disorder effect absent a cohort effect	4.15 (3.75, 4.56)	5.11 (4.40, 5.82)	4.28 (3.39, 5.17)	3.41 (2.82, 4.00)
Joint effect (cohort & depressive disorder)*	5.09[a] (4.29, 5.90)	5.78[b] (4.30, 7.26)	8.24[c] (6.52, 9.96)	2.99[d] (1.83, 4.14)
Age				
18-24	0	0	0	0
25-44	6.36 (5.83, 6.89)	5.87 (5.24, 6.51)	7.33 (5.90, 8.77)	5.74 (4.58, 6.90)
45-64	15.5 (14.9, 16.0)	14.4 (13.7, 15.1)	15.7 (14.2, 17.1)	15.2 (14.0, 16.4)
≥65	33.8 (33.1, 34.4)	34.3 (33.4, 35.2)	33.2 (31.6, 34.9)	32.6 (31.4, 33.8)
Sex				
Male	0	0	0	0
Female	5.19 (4.87, 5.52)	5.12 (4.62, 5.63)	3.96 (3.21, 4.72)	4.80 (4.28, 5.32)
Region				
Rural	0	0	0	0
Urban	2.28 (1.95, 2.61)	1.99 (1.47, 2.52)	2.47 (1.71, 3.23)	2.67 (2.17, 3.16)
Socioeconomic status				
Quintile 1 (lowest)	-4.71 (-5.21, -4.20)	-4.69 (-5.51, -3.87)	-3.41 (-4.56, -2.27)	-6.03 (-6.82, -5.25)
Quintile 2	-3.81 (-4.32, -3.29)	-4.15 (-4.94, -3.36)	-3.57 (-4.58, -2.45)	-4.02 (-4.85, -3.19)
Quintile 3	-3.14 (-3.65, -2.62)	-3.47 (-4.26, -2.68)	-2.83 (-3.94, -1.72)	-3.40 (-4.24, -2.56)
Quintile 4	-2.27 (-2.77, -1.77)	-2.19 (-2.97, -0.64)	-2.29 (-3.38, -1.19)	-2.66 (-3.48, -1.84)
Quintile 5 (highest)	0	0	0	0
Comorbidity				
0	0	0	0	0
1	4.86 (4.41, 5.31)	3.53 (2.80, 4.27)	3.89 (2.79, 4.98)	5.73 (5.09, 6.37)
≥2	8.73 (7.65, 9.80)	8.65 (6.62, 10.7)	9.04 (6.18, 11.9)	8.41 (7.02, 9.79)
IMID-specific procedure	4.96 (4.23, 5.69)	6.95 (5.63, 8.27)	-	4.01 (3.13, 4.89)
Immune therapy				
None	0	0	0	0
Anti-inflammatory/immune-modulatory therapy	3.10 (2.74, 3.47)	2.97 (2.40, 3.54)	4.40 (2.51, 6.29)	3.06 (2.57, 3.55)

Any biologic	9.08 (7.92, 10.2)	9.08 (7.06, 11.1)	5.54 (2.11, 8.96)	9.46 (7.94, 11.0)

IMID = Immune-mediated inflammatory disease; IBD = inflammatory bowel disease; MS = multiple sclerosis; RA = rheumatoid arthritis; a-IMID*Depression interaction -0.98 (-1.93, -0.04); b-IBD* Depression interaction -1.03 (-2.70, 0.64); c-MS* Depression interaction 2.43 (0.36, 4.49); d-RA* Depression interaction -2.53 (-3.88, -1.18)

Table 4. Association of immune-mediated inflammatory disease (IMID), anxiety disorder and uptake of influenza vaccination (Percentage; 95% confidence interval)

Variable	IMID	IBD	MS	RA
Cohort effect, absent an anxiety disorder effect	6.58 (5.96, 7.19)	6.89 (5.86, 7.91)	7.78 (6.35, 9.21)	5.72 (4.80, 6.64)
Anxiety disorder effect absent a cohort effect	4.41 (4.05, 4.77)	4.93 (4.32, 5.53)	4.95 (4.65, 5.75)	3.75 (3.22, 4.27)
Joint effect (cohort & anxiety disorder)*	4.84[a] (4.12, 5.56)	6.10[b] (4.81, 7.40)	6.25[c] (6.52, 9.96)	3.37[d] (2.34, 4.40)
Age				
18-24	0	0	0	0
25-44	6.22 (5.70, 6.74)	5.72 (5.09, 6.35)	7.12 (5.67, 8.58)	5.62 (4.47, 6.77)
45-64	15.2 (14.7, 15.8)	14.1 (13.4, 14.8)	15.4 (13.9, 16.8)	15.0 (13.9, 16.2)
≥65	33.4 (32.8, 34.0)	33.9 (33.0, 34.8)	32.8 (31.2, 34.5)	32.4 (31.2, 33.6)
Sex				
Male	0	0	0	0
Female	5.10 (4.78, 5.42)	5.06 (4.55, 5.57)	3.86 (3.10, 4.62)	4.69 (4.17, 5.21)
Region				
Rural	0	0	0	0
Urban	2.20 (1.87, 2.53)	1.91 (1.38, 2.43)	2.32 (1.56, 3.09)	2.59 (2.09, 3.09)
Socioeconomic status				
Quintile 1 (lowest)	-4.70 (-5.21, -4.20)	-4.69 (-5.51, -3.87)	-3.30 (-4.44, -2.15)	-6.05 (-6.84, -5.27)
Quintile 2	-3.73 (-4.24, -3.22)	-4.04 (-4.82, -3.25)	-3.40 (-4.52, -2.29)	-4.00 (-4.82, -3.17)
Quintile 3	-3.06 (-3.57, -2.54)	-3.35 (-4.14, -2.57)	-2.70 (-3.81, -1.58)	-3.37 (-4.20, -2.53)
Quintile 4	-2.24 (-2.75, -1.74)	-2.15 (-2.972, -1.38)	-2.16 (-3.52, -1.06)	-2.67 (-3.49, -1.84)
Quintile 5 (highest)	0	0	0	0
Comorbidity				
0	0	0	0	0
1	4.81 (4.36, 5.26)	3.46 (2.72, 4.20)	3.86 (2.76, 4.96)	5.68 (5.04, 6.33)
≥2	8.75 (7.68, 9.83)	8.68 (6.65, 10.7)	9.17 (6.31, 12.0)	8.40 (7.02, 9.79)
IMID-specific procedure	4.98 (4.26, 5.71)	6.91 (5.59, 8.23)	-	4.04 (3.17, 4.92)
Immune therapy				
None	0	0	0	0
Anti-inflammatory/immune-modulatory therapy	3.09 (2.72, 3.45)	2.97 (2.40, 3.53)	4.48 (2.58, 6.37)	3.06 (2.57, 3.55)

Any biologic	9.10 (7.95, 10.3)	9.17 (7.15, 11.2)	5.77 (2.31, 9.24)	9.46 (7.93, 11.0)

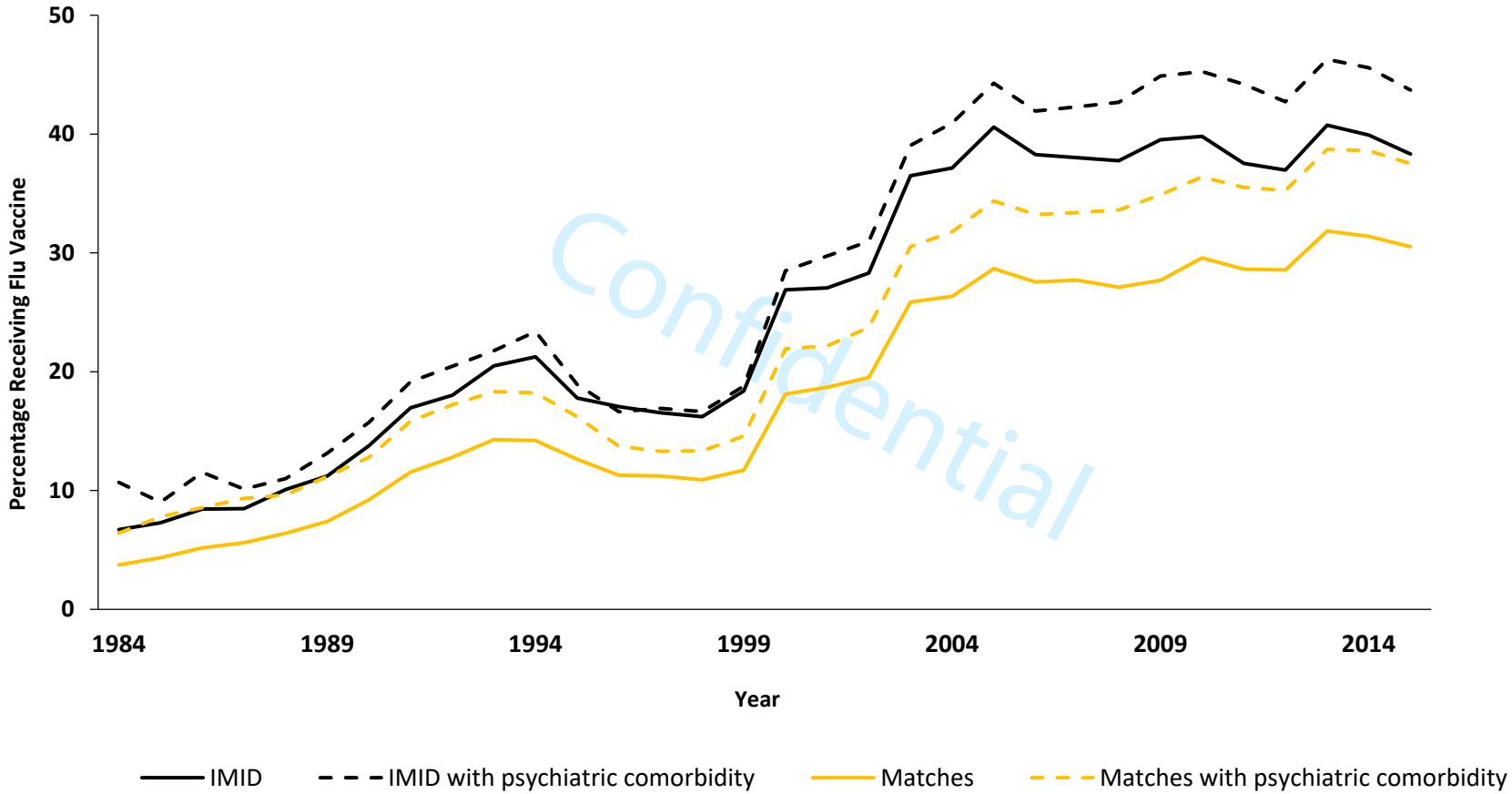
IMID = Immune-mediated inflammatory disease; IBD = inflammatory bowel disease; MS = multiple sclerosis; RA = rheumatoid arthritis; a-IMID*anxiety interaction -0.74 (-2.62, -0.86); b-IBD* anxiety interaction -0.78 (-2.27, 0.71); c-MS* anxiety interaction 2.43 (0.36, 4.49); d-RA*anxiety interaction -2.35 (-3.62, -1.07)

Figure 1. Percentage of persons in the immune-mediated inflammatory disease (IMID) and matched cohorts who received an influenza vaccination stratified by psychiatric comorbidity status, 1984-2015[a]

a-2016 not presented as data available for only first quarter

Figure 2. Age and sex-standardized percentage of persons in the immune-mediated inflammatory disease (IMID) and matched cohorts who received an influenza vaccination, 1984-2015[a]

Arrows indicate changes in groups eligible for provincial (public funding): 1999- age ≥65 years, chronic conditions, health care workers; 2004- children aged 6-23 months and their families; 2005- chronic respiratory diseases; 2007- pregnant women; 2009 – H1N1 epidemic; 2010- universal coverage; 2014- pharmacists able to administer influenza vaccine; a-2016 not presented as data available for only first quarter



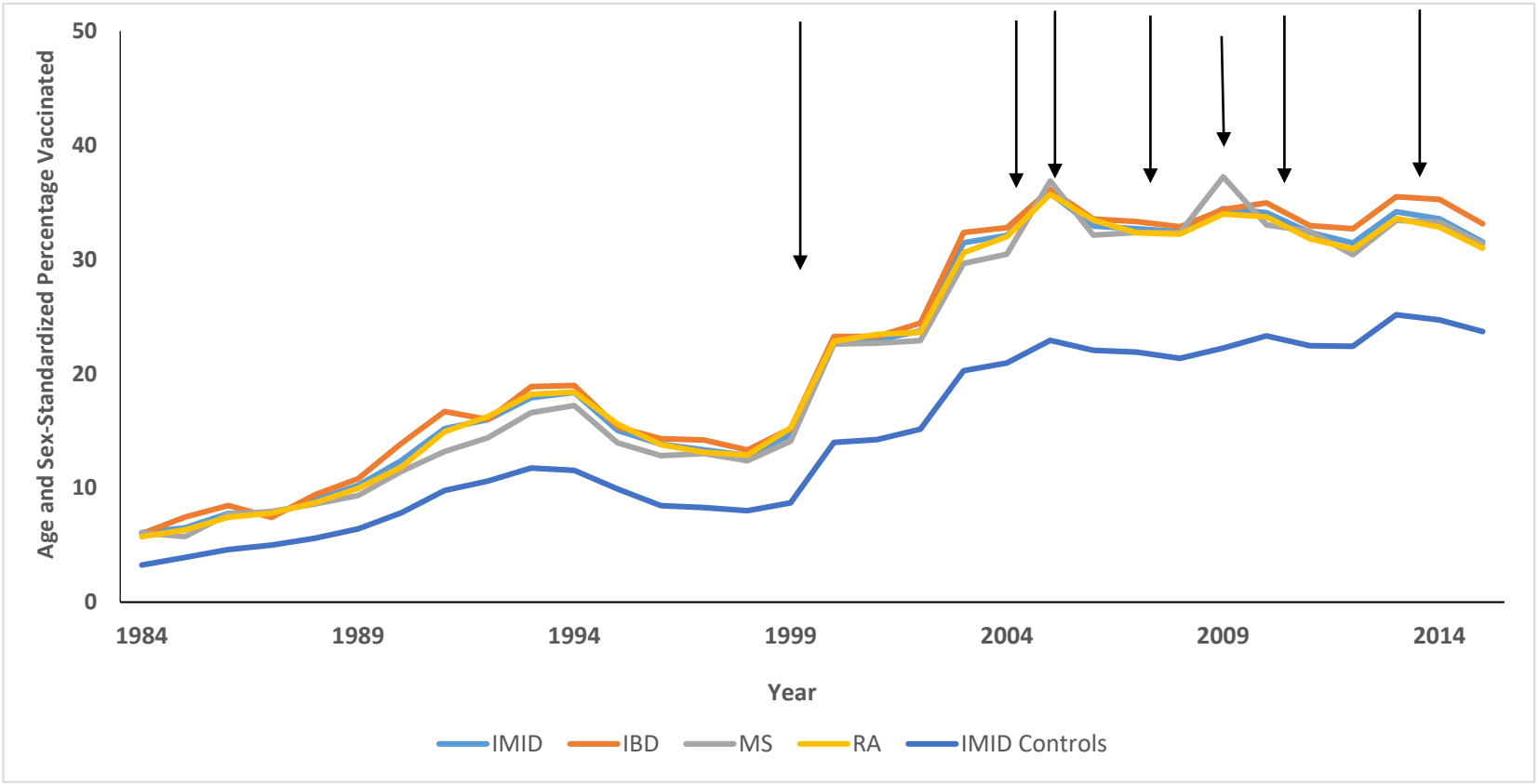


Table e-1 Tariff and procedure codes to identify surgeries for inflammatory bowel disease

Procedure	**Physician Claim Tariff Codes**
Intestinal suture	3221, 3223
Colostomy	3195
Colectomy	3179
Colectomy, proctectomy	3180, 3181, 3182, 3183, 3184
Proctosigmoidectomy	3286
Proctosigmoidectomy, protectomy	3288, 3289, 3290
Rectal surgery	3301
Small bowel resection	3201, 3174
Ileostomy	3193
	Hospital Procedures
Incision, excision & anastomosis of intestine	45, excluding 451 & 452 diagnostic procedures
	1NM – colon + 59, 87, 89, 92 excision

Table e-2 Diagnostic and procedure codes to identify joint-related procedures for rheumatoid arthritis

Procedure	ICD-9-CM code	CCI code
Hip replacement (incl. Partial, total, revisions)	81.50, 81.51, 81.53, 81.52	1.VA.53.LA-PN^^ or 1.VA.53.PN-PN^^ 1.VA.53.LA-PM^^ or 1.VA.53.PN-PM^^
Knee replacement	81.54, 81.55	1.VG.53.LA-PN or 1.VG.53.LA-PP
Elbow replacement	81.84	1.TM.80.^^
Shoulder replacement	81.80, 81.81, 81.83	1.TA.53.^^
Wrist fusion	81.25, 81.26	1.UB.75.^^, 1.UG.75.^^
Ankle fusion	81.1	1.WA.75.^^
Foot joint fusion	81.1	1.WE.75.^^
Foot joint replacement	81.57	1.WJ.53.^^
Cervical spine fusion	81.01, 81.02, 81.03	1.SA.75.^^
Hand joint replacement	81.7	1.UC.53.^^, 1.UC.55. ^^

ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification; CCI = Canadian Classification of Intervention code. ^ CCI codes are 10 characters long and broken into components. The first number in the code followed by 2 letters indicates anatomical location or development stage. Subsequent codes provide more specific information about the intervention. The ^ indicates that ll of the codes with more specific indicators were included.

Table e-3

Treatment / Disease	Inflammatory Bowel Disease	Multiple Sclerosis	Rheumatoid Arthritis
Corticosteroids[1]	Methylprednisolone (H02AB04)	Methylprednisolone (H02AB04)	Methylprednisolone (H02AB04)
	Prednisolone (H02AB06)	Prednisolone (H02AB06)	Prednisolone (H02AB06)
	Prednisone (H02AB07)	Prednisone (H02AB07)	Prednisone (H02AB07)
	Budesonide		Triamcinolone (H02AB08)
	Hydrocortisone (enema)		Cortisone (H02AB10))
Anti-inflammatory or Immunomodulatory therapies[2]	5-ASA (A07EC02, A07EC03)	Glatiramer acetate (L03AX13)	Sulfasalazine (A07EC01)
	Sulfasalazine (A07EC01)	Interferon-beta 1a (L03AB07)	Sodium aurothiomalate (M01CB01)
		Interferon-beta 1b (L03AB08)	Auranofin (M01CB03)
		Dimethyl fumarate (N07XX09)	Aurothioglucose (M01CB04)
		Teriflunomide (L04AA31)	Penicillamine (M01CC01)
		Peg interferon-beta (L03AB13)	Hydroxychloroquine (P01BA02)
Traditional immunosuppressive therapies[3]	Azathioprine (L04AX01)	Azathioprine (L04AX01)	Azathioprine (L04AX01)
	Methotrexate (L04AX03)	Methotrexate (L04AX03)	Methotrexate (L04AX03)
	6-mercaptopurine (L01BB02)	Mitoxantrone (L01DB07)	Cyclophosphamide (L01AA01)
	Cyclosporine (L04AA01)	Cyclophosphamide (L01AA01)	Cyclosporine (L04AA01)

	Tacrolimus (L04AD02)		Leflunomide (L04AA13)
Novel therapies/ Biologics[3]	Infliximab (L04AA12)	Natalizumab (L04AA23)	Infliximab (L04AA12)
	adalimumab (L04AA17)	Fingolimod (L04AA27)	adalimumab (L04AA17)
	Golimumab (L04AB06)	Alemtuzumab (L04AA34)	Etanercept (L04AA11)
	Ustekinumab (L04AC05)	Cladribine[4] (L04AA40)	Anakinra (L04AA14)
	Vedolizumab (L04AA33)	Ocrelizumab[4] (L04AA36)	Rituximab (L01XC02)
			Abatacept (L04AA24)
			Tocilizumab (L04AC07)
			Tofacitinib (L04AA29)
			Golimumab (L04AB06)
			Certolizumab (L04AB05)

1- Corticosteroids were not included as immune therapies for MS because they are not used as an chronic therapy, but exclusively for episodic treatment of relapses. 2- Therapies in this row in the MS column were considered first-line. 3- Therapies in this row in the MS column were considered second-line. 4- Not available during the study period.

Figure e1. Percentage of the IMID and matched cohorts immunized against influenza in 2015 stratified by age group