## **ORIGINAL ARTICLE**



# Interventions Increase Vaccination Rates in Inflammatory Bowel Disease and Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Received: 27 June 2022 / Accepted: 24 February 2023 / Published online: 6 April 2023 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

## Abstract

**Background** Patients with immune-mediated conditions such as IBD and RA are at risk for vaccine-preventable infections. Despite guideline recommendations, prior studies have shown suboptimal vaccination rates.

Aim We conducted a systematic review and meta-analysis to compare the different interventions intended to increase vaccination rates.

**Methods** A systematic search was conducted of MEDLINE/PubMed, Embase, CINAHL, and Cochrane Library up to 2020 for studies with interventions intended to increase vaccination rates. We performed a random-effects meta-analysis to generate pooled odds ratios (ORs) to assess all interventions against no interventions. Our primary outcome was pneumococcal vaccination (PCV) rate.

**Results** Our review found 8580 articles, for which 15 IBD and 8 RA articles met the inclusion criteria; 21 articles were included in the analysis. PCV was the predominant vaccination (91%). In our analysis of patients with IBD, almost all interventions (patient-oriented, physician-oriented, or barrier-oriented) increased PCV uptake [OR, 4.74; 95% CI, 2.44–6.56,

**Conference Presentation** The preliminary results of our study (systematic review) were presented in oral form at the American College of Gastroenterology Conference virtually in October 2020. The final results of our study (systematic review + meta-analysis) were presented at Digestive Disease Week international gastroenterology conference virtually in May 2021. At Digestive Disease Week 2021, this poster received Poster of Distinction.

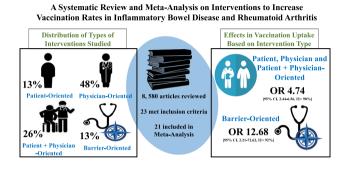
An editorial commenting on this article is available at https://doi. org/10.1007/s10620-023-07905-5.

Extended author information available on the last page of the article

I2 = 90%] compared to no intervention. The greatest effect was seen in barrier-oriented studies [OR, 12.68; 95% CI, 2.21–72.62, I2 = 92%]. For RA data, all interventions had increased PCV uptake compared to no interventions (OR 2.74; 95% CI, 1.80–4.17, I2 = 95%).

**Conclusion** Our data suggest that many different interventions can increase PCV rates. It appears that barrier-oriented interventions may have the greatest positive effect on increasing PCV uptake. However, clinicians should be encouraged to implement measures best suited to their practice. Future high-quality randomized controlled trials are needed to determine the best approach to optimize vaccination rates.

#### **Graphical Abstract**



Keywords Inflammatory bowel disease · Vaccinations · Preventative care

## Introduction

Patients with immune-mediated conditions such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) are at risk for vaccine-preventable infections [1], with rates of serious life-threatening infection ranging from 8.4 to 22.4 per 1000 person years [2]. In the USA, it is estimated that between 9 and 45 million illnesses can be prevented by vaccinations [3]. Additionally, vaccinations are extremely important cost-saving interventions, as the cost of vaccinepreventable illness in the USA is approximately \$27 billion [3].

Unfortunately, vaccination rates in patients with IBD and RA are suboptimal for a multitude of reasons. Only about 50% of gastroenterologists routinely collected vaccination status information, despite most perceiving vaccinations as "extremely important" [4, 5]. Forty-five percent of gastroenterologists felt that primary care physicians should administer vaccinations; however, some primary care physicians felt that gastroenterologists should be responsible [6, 7]. When surveyed, 28% of patients received an annual flu shot and only 9% were up-to-date on pneumococcal vaccination (PCV) [8]. When asked for reasons for low vaccination rates, 49% stated they lacked awareness and 18% had concerns about side-effects [8, 9]. Other limitations were linked to concern for safety of vaccination in the immunosuppressed and the possibility of exacerbation of underlying IBD [10]. Over the years, there have been many studies that have assessed interventions attempting to increase vaccination rates in both IBD and RA patients. These interventions ranged from reminders and education for patients to education and electronic medical record interventions for physicians. Lastly, in the recent years, there has been implementation interventions to address barriers to patient adherence in the form of patient navigators. The sole responsibility of patient navigators is to provide patients with personalized guidance to navigate the health system. Therefore, we conducted a systematic review and meta-analysis of the different modalities currently studied to increase vaccination rates in these patients.

## Methods

## **Literature Search**

This study was reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [11]. We searched MEDLINE (PubMed-New), Embase (Elsevier), Cumulative Index to Nursing and Allied Health Literature (EBSCO), and Cochrane Library (Wiley). The search was created and conducted by a librarian (IKG) in consultation with the study authors. Strategies consisted of free text keywords and database-specific controlled vocabulary terms for IBD, RA, vaccines, and the concept of uptake. The search was built to be highly sensitive due to the heterogeneous nature of terms used to describe vaccines and vaccination uptake rates. The decision to use patients with either IBD or RA was because they are both immune-mediated conditions that are treated with the same or similar immunosuppressive medications, which in theory will increase the risk of vaccine-preventable diseases. All databases were searched from database inception PubMed 1966; Embase 1947; CINAHL 1937; and Cochrane Library 1993 through July 2020 (for IBD) or August 2020 (for RA) for studies in patients with these diseases. Separate searches were done for each patient population but the terms for vaccines and uptake remained the same in each. Full search strategies, including applied limits, for each database are available in supplementary data (see Supplementary data). Vaccinations that were included in the systematic review were based on and consistent with the recommendations from American College of Gastroenterology and European Crohn's and Colitis Organization in collaboration of Canadian IBD society vaccination and preventive care guidelines [12, 13]. Manual searches of bibliographies and the journals Crohn's and Colitis 360 were performed to identify any further studies that met inclusion criteria. Potentially relevant articles were obtained in full text and reviewed independently. Study review and selection were done by two independent reviewers [DF and JP], using Covidence systematic review software [14].

## **Selection Criteria**

Our inclusion criteria consisted of patients  $\geq$  18 years old, patients with either IBD or RA, full-length peer-reviewed publications, and articles in English. We excluded conference proceedings, abstract-only articles, and review articles.

We classified interventions into four groups: (1) patientoriented (i.e., reminders and education), (2) physicianoriented (i.e., education and electronic medical record), (3) combined patient- + physician-oriented and (4) barrieroriented (i.e., navigator systems, which are defined as persons whose primary responsibility is to provide personalized guidance to patients as they navigate through the health system). Disagreements between the two independents reviewers were discussed with a third party reviewer [MP].

## **Data Extraction**

The PRIMSA flow diagrams for IBD (Fig. 1) and RA (Fig. 2) show the number of studies included at each stage of the screening. A data extraction sheet was designed in Microsoft Excel for the following items: year published, country, dates of study, type of study, setting (i.e., academic vs private practice), office type (general gastroenterology)

vs IBD clinic vs rheumatology clinic), number of gastroenterologists/rheumatologists, number of patients, IBD phenotype, classification of intervention, specific vaccination studies with pre- and post-intervention vaccination rates, and confirmation of vaccination (see supplemental documents).

#### **Statistical Analysis**

We performed the analysis in two different steps. First, we described pre- and post-intervention outcomes of the included studies. Second, based on the descriptive review of the studies, PCV rates were the most studied; therefore, PCV rate became our primary outcome for the meta-analysis.

The meta-analysis was performed by 2 of us [MN, AW]; we calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) using Mantel–Haenszel random-effects model to assess all interventions against no interventions. Statistical heterogeneity was assessed using the I-square statistic (<25% was indicative of low heterogeneity and >75%was indicative of high heterogeneity not due to chance). We performed direct comparisons using RevMan (Cochrane Collaboration, Copenhagen, Denmark, version 5.4). Due to the small number of included studies, we were not able to assess for publication bias [15].

## Results

## Literature Search/Demographics

## IBD

As shown in Fig. 1, our IBD literature search identified 5625 citations. After removal of duplicate studies, screening, and full-text review, 15 studies met the inclusion criteria for the systematic review (Table 1) [16–30]. The studies were published between 2013 and 2019 in the USA (n = 10), Europe (n=4), or Australia/United Kingdom (n=1). A total of 6959 patients and at least 284 gastroenterologists were studied (33.0% of the studies did not include number of gastroenterologists). Practice settings varied, with the majority being academic centers (n = 10); the remaining centers were community-based (n=2), Veteran Affairs system (n=1), private practice (n = 1), and a combination of academic and private practice (n=1). Most of the studies (13/15) were pre-posttest interventions and the remaining were randomized controlled trials. Many of the studies were physician-oriented (8/15), and the remaining were patient-oriented (3/15), combined patient and physician-oriented (2/15), and barrier-oriented (2/15). Barrier-oriented was implemented with either an infectious disease physician or an IBD nurse acting as a navigator. Vaccinations included in these studies were pneumococcal (15/15), influenza (14/15), hepatitis A/B (5/15),

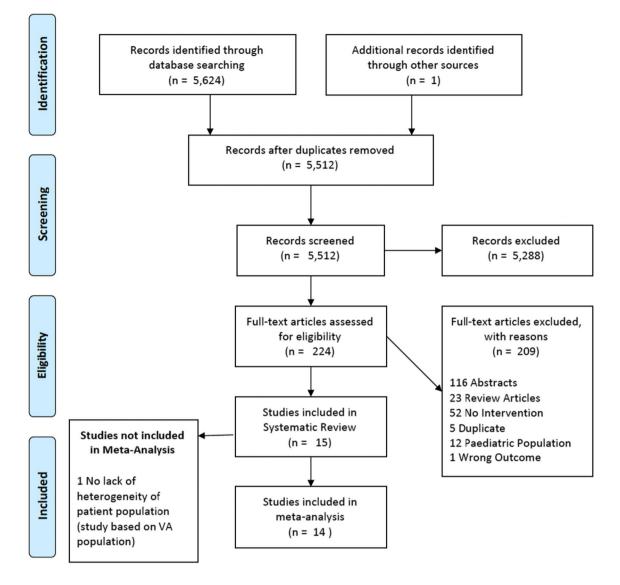


Fig. 1 PRISMA flow diagram of search strategies for inflammatory bowel disease articles

Human Papilloma (3/15), tetanus (2/15), and Herpes Zoster (1/15). For PCV rates, 9/15 study endpoints were based on chart audits and 6/15 were patient reported (see supplemental Documents). Regardless of the intervention, there was an increase in PCV rates in 14/15 interventions compared to no intervention (Fig. 3).

## RA

As shown in Fig. 2, our RA literature search identified 2955 citations. After removal of duplicate studies, screening, and full-text review, 8 studies met the inclusion criteria for the systematic review (Table 2) [31-38]. The studies were published

between 2009 and 2020 in the USA (n=8) or Europe (n=2). A total of 12,950 patients and at least 52 rheumatologists were studied (63.0% of the studies did not document the number of rheumatologists). Practice settings varied among academic centers (n=4), a combination of academic and community practices (n=3), and a tertiary care center (n=1). All studies were pre-post-test interventions (8/8). Half of the studies were combined patient- and physician-oriented (4/8) and the remaining were physician-oriented (3/8) and barrier-oriented with a nurse navigator (1/8). Vaccinations included in these studies were pneumococcal (6/8), influenza (5/8), and Herpes Zoster (2/8). For PCV rates, 4/6 study endpoints were based on chart audits, 1/6 was patient reported and 1/6 was both chart audit and patient reported (see supplemental Documents). There was an increase in PCV rates for all interventions compared to no intervention (Fig. 4).

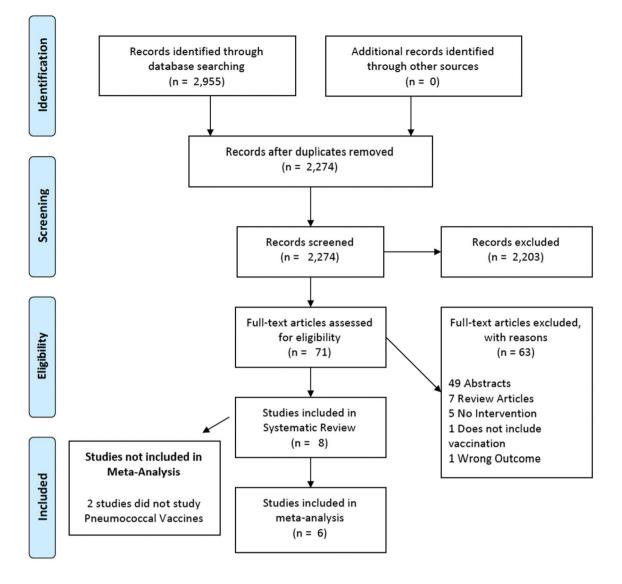


Fig. 2 PRISMA flow diagram of search strategies for rheumatoid arthritis articles

## **Meta-Analysis**

## **IBD Meta-Analysis**

Of the 15 studies in the IBD literature search, 14 studies were included in the meta-analysis. One study was entered as two separate entries because study participants were divided between academic and private practice setting [25]. For the 14 studies, there were 508 patients in the pre-intervention arm (440 in the patient and/or physician-oriented and 68 in the navigator-oriented) and 1224 patients in the post-intervention arm (1111 in the patient- and/or physician-oriented and 113 in the navigator-oriented). As shown in Fig. 5, all interventions had increased PCV uptake compared with no intervention (OR, 4.74; 95%)

CI, 2.94–7.64, I2 = 90%). The greatest effect was seen in barrier-oriented studies (OR, 12.68; 95% CI, 2.21–72.62, I2 = 92%).

#### **RA Meta-Analysis**

Of the 8 studies in the RA literature search, 6 studies were included in the meta-analysis. One study was entered as two separate entries because there were two different sites at which patients were studied [34]. For the 6 studies, there were 3,215 patients in the pre-intervention arm and 4,399 patients in the post-intervention arm. As shown in Fig. 6, all interventions had increased PCV uptake compared to no intervention (OR, 2.74; 95% CI, 1.80–4.17, I2=95%).

Table 1 Inflam	Table 1 Inflammatory bowel disease studies used for systematic review	sase studies used f	for systematic revi-	ew						
Author	Year published	Location	Dates of study	Type of study	Setting	Intervention	Classification of Pneumococcal vaccination	Pneumococcal va	ccination	Confirmation of
							intervention	Pre-intervention	Post-interven- tion	vaccination
Parker S et al	2013	United States		Pretest Posttest	Academic	Patient educa- tion with a questionnaire	Patient-oriented	31%	54%	Chart audit
Reich JS et al	2015	United States	2012 -2014	Pretest Posttest	Academic	Vaccination form. Educa- tional info on PCV	Patient-oriented	21%	32%	Patient reported
Reich JS et al	2019	United States	2017 -2018	RCT	Academic	EHR: Portal messages, Educational information about IBD every 2 weeks. Reminders to get vaccinated	Patient-oriented	73%	93%	Chart audit
Christensen K et al	2015	Denmark	2013 –2014	Pretest Posttest	Academic	Physician education with oral and writ- ten reminders	Physician- oriented	12%	36%	Patient reported
Ewelukwa O et al	2018	United States	2015 -2016	Pretest Posttest	Academic	Physician centered with incorporation of a scribe	Physician- oriented	13%	63%	Chart audit
Feuerstein J et al 2017	ıl 2017	United States		Pretest Posttest	Academic Private practice	Providers emailed AGA quality meas- ures. Handout in each clinic room. Screen in EHR summarizing IBD history and quality measures Private Pratice: Online template summarizing measures	Physician- oriented	21%	<b>35</b> % 75%	Chart audit

Table 1 (continued)	(pənu									
Author	Year published	Location	Dates of study	Type of study	Setting	Intervention	Classification of	Classification of Pneumococcal vaccination	ccination	Confirmation of
							intervention	Pre-intervention	Post-interven- tion	vaccination
Greene L et al	2015	United States	2011 -2013	Pretest Posttest	Community based	Provider educa- tion with one hour private audit feedback session, online and mobile monorraphs	Physician- oriented	0.3%	6%	Chart audit
Greene L et al	2015	United States	2012 -2014	Pretest Posttest	Community based	Provider educa- tion with one hour private audit feedback session. Online and mobile mono- grabhs	Physician- oriented	3%	2%	Patient reported
Lee A et al	2016	United States	2014	Pretest Posttest	Academic	Educational ses- sion to review core quality measures	Physician- oriented	80%	%06	Chart audit
Sapir T et al	2016	United States	2013 -2015	Pretest Posttest	Private practice	CME on Quality Improvement, audit feedback session and webinar. Online tool- kit included monographs	Physician- oriented	8%	28%	Chart audit
Valluru N et al	2018	United States	1999 –2016	Pretest Posttest	Veterans affair	EHR, IBD Health Maintenance Template	Physician- oriented	3%	85%	Chart audit
Bensinger A et al	2019	United States	2015 -2017	Pretest Posttest	Academic	EHR, IBD note template, order set, and patient educa- tion handout	Combined patient + phy- sician- ori- ented	2%	38%	Chart audit

	(non)									
Author	Year published Location	Location	Dates of study	Type of study	Setting	Intervention	Classification of Pneumococcal vaccination	Pneumococcal v	accination	Confirmation of
							intervention	Pre-intervention	Pre-intervention Post-interven- tion	vaccination
Walsh A et al	2013	Australia and UK	2010	Pretest Posttest Academic	Academic	Patient and Physician education with informational form	Combined patient + phy- sician- ori- ented	7%	49%	Patient reported
Coenen S et al	2017	Belgium	20142015	RCT	Academic	Patient educa- tion with navigation tool (IBD nurse) and vaccina- tion cards	Barrier-oriented	23%	62%	Patient reported
Sitte J et al	2019	France	2016 - 2017	Pretest Posttest	Academic	Patient educa- tion with questionnaire and Infec- tious Disease consult	Barrier-oriented	16%	86%	Patient reported

Table 1 (acc

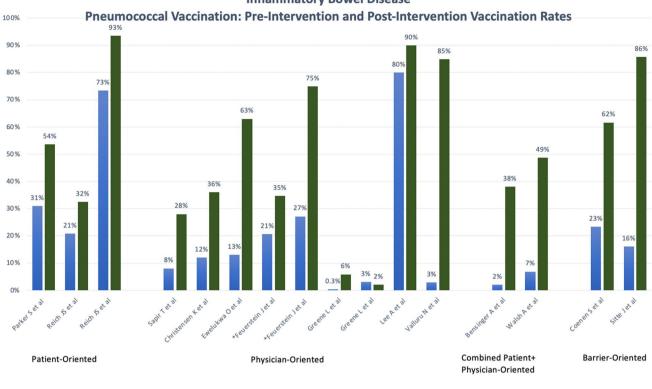
## Influenza Vaccination

Influenza vaccination was the second most studied vaccination. In the IBD studies 14 out of 15 studies and in the RA studies 5 out of 7 studies included influenza vaccination [16–38]. Pre-intervention vaccination rates for the annual influenza vaccination was higher than the baseline pre-intervention rates for pneumococcal vaccination in 14 out of the 19 studies (11 out of the 14 IBD studies and 3 out of 5 RA studies) as depicted in Tables 3 and 4 [16-38]. In the IBD studies, all intervention types (Patient-Oriented, Physician-Oriented, Combined Patient-+Physician-Oriented, and Barrier-Oriented) increased in vaccination rates in IBD. Of the 3 RA studies, only one study showed an increased in vaccination rate post-intervention for influenza vaccination [34]. Of the remaining two studies, one study the pre- and postintervention vaccination rates remained exactly the same [31] and the other actually had a drop in post-intervention vaccination rate by 4% [32].

## Discussion

From our knowledge, this is the first systematic review and meta-analysis to assess interventions to increase PCV rates in both IBD and RA patients. After an extensive review of over 8,580 studies, a detailed analysis of 23 articles was completed. Our study suggests that any intervention intended to increase PCV rates may be beneficial. Additionally, our data may provide more emphasis on the need for barrieroriented interventions, such as healthcare navigators.

Patients with IBD are noted to be at an increased risk of vaccine-preventable illnesses, such as influenza, pneumococcal pneumonia, and even Herpes Zoster infections [5, 28, 39, 40]. Studies have suggested that many factors may cause vaccination rates to be low, such as lack of both patient and physician awareness of guidelines and both institutional and societal barriers that may all lead to decrease vaccination rates [8, 9]. Furthermore, a primary hurdle in optimal vaccination rates is patient perceptions of vaccinations. Over the years many models, such as Health Beliefs Model and Theory of Planned Behavior, have been used to study psychosocial predictors of vaccine behaviors [41, 42]. The Health Belief Model looked at social and behavioral determinants for patients' behaviors to see how they affected how they affected a patient's willingness to adopt disease prevention strategies or take screening tests [41]. Overcoming these barriers for our IBD and RA populations is of upmost importance, as vaccine-preventable diseases accounted for \$27 billion dollars in treatment [1]. For example, pneumococcal pneumonia results in an estimated 150,000 hospitalizations each year in the USA with approximately 3000 to 4000 deaths from invasive forms of pneumococcal meningitis



# **Inflammatory Bowel Disease**

Post-Intervention Pre-Intervention

Fig. 3 Pre- and Post-intervention pneumococcal vaccination rates in inflammatory bowel disease studies. There was an increase in vaccination rates noted with all interventions except one. \*Feuerstein J

et al. was divided into two as there were two different groups: one that was an academic practice and the other a private practice

and bacteremia [43]. In the era of COVID-19, it is especially important to understand the interventions that may best increase vaccination rates.

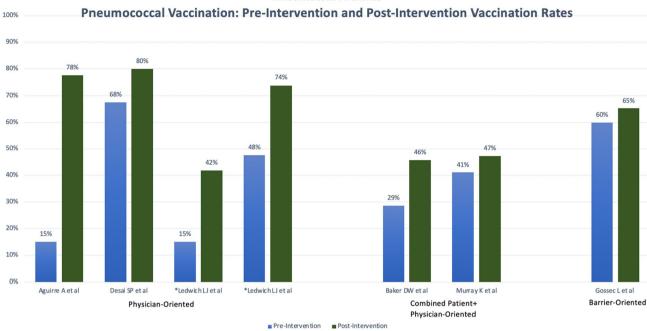
Similar to previous studies, our data suggest that vaccination rates remain suboptimal in these patient populations. By performing a meta-analysis, we were able to highlight the importance of using multiple varying interventions to increase PCV rates in our patients. Specifically, pooling data from both IBD and RA patients allowed us to identify a possible trend that increasing intervention intensity (i.e., progressing from patient-oriented interventions, to physician-oriented interventions, to combined patient-physician interventions, and finally barrier-oriented interventions [such as navigators]) resulted in increased PCV uptake. Additionally, a recently published systematic review was consistent with our conclusion that interventions can increase adherence to preventative care in patients with IBD [44].

Barrier-oriented interventions, including healthcare navigation (i.e., designated nursing/medical assistant), outreach programs, and patient and physician education, have been implemented in many diseases and preventative strategies [45, 46]. For example, navigation systems have been suggested to be one of the most impactful interventions in colorectal cancer screening [47] and is the main component of multitarget stool DNA testing [48]. Additionally, other systems have used navigation to improve varying outcomes, such as treatment adherence for cancer patients and controlling hemoglobin A1c [46]. While our study highlights that barrier-oriented strategies can greatly improve PCV rates, we do not want to underemphasize that other modalities such as physician and patient education and systematic interventions can also be very effective and resources should best be evaluated by each institution.

Our study has many strengths. Our reproducible and comprehensive search strategy across multiple biomedical databases identified over potential 8000 articles. This highly sensitivity/low specificity search in combination with hand searching relevant journals led to a small but robust evidentiary foundation for our study. Furthermore, this study incorporated two similar immune-mediated disease states, IBD and RA, which to our knowledge has not been previously done to answer these questions.

Despite, the similarity in IBD and RA as being immunemedicated disease states, both the populations are different. In general, patients with RA are older females and likely have other comorbidities that would recommend

Author	Year published	Location	Dates of study	Type of study	Setting	Intervention	Classification of intervention	Pneumococcal vac- cination	ccal vac-	Confirmation of vaccination
								Pre-inter- vention	Post- interven- tion	
Aguirre A et al	2020	NSA	2015-2017	Pretest-post-test	Academic	Clinic nurses reviewed lists of unvac- cinated patients on a weekly bases to flag patients in need of PCV Medical assistants integrated review of vaccination history into their routine clinical duties	Physician-oriented	15%	78%	Chart audit
Desai SP et al	2013	USA	2008–2011	Pretest-post-test	Community and academic practice	Point of Care paper reminder form All doctors reminded at staff meetings and via email reminders about impor- tance of documenting vaccination status in EHR	Physician-oriented 68%	68%	80%	Chart audit
Ledwich LJ et al	2009	NSA	2005-2007	Pretest-post-test	Academic practice Community practice	Best practice alerts for influenza and pneumococcal Site 1: Physician led Site 2: Nurse led	Physician-oriented	15% 48%	42% 74%	Chart audit
Baker DW et al	2016	USA	2013-2014	Pretest-post-test	Academic	Best Practices Alerts for vaccinations in HER Vaccinations administered in clinic (Except HZV) Individual physi- cian feedback Mail reminders and follow-up reminders sent to patients	Combined patient + physi- cian-oriented	29%	46%	Patient report + chart audit
Broderick R et al	2018	USA	2013-2015	Pretest-post-test	Academic	Pre-intervention period: provider edu- cation Intervention period: provider education again. EMR-based alerts and study notifications. Weekly emails with enrollment information. Follow-up with questionnaire to record vaccination in last 12 months	Combined patient + physi- cian-oriented	N/A	N/A	Chart audit
Murray K et al	2020	Ireland	2017-2018	Pretest-post-test	Academic	Worksheet with information on vac- cine recommendations. Educational session for rheum staff. Arthritis and Infection Worksheets General Practioners Letters	Combined patient + physi- cian-oriented	41%	47%	Patient reported
Sheth H et al	2016	USA	2012-2015	Pretest-post-test	Academic and community practice	Best Practices Alerts for HZV in EHR for MA and physicians. Patient education on importance of vaccines from staff and handouts. Physician education with formal presentations, and small group meetings	Combined patient + physi- cian-oriented	N/A	N/A	Chart audit
Gossec L et al	2019	France	2014–2015	Pretest-post-test	Tertiary care center	Nurses provided advice on screening and management during the trial and 3 years later. Nurse advised patient to visit PCP or rheumatologist for vaccination	Barrier-oriented	60%	65%	Chart audit



**Rheumatoid Arthritis** 

Fig.4 Pre- and Post-intervention pneumococcal vaccination rates in rheumatoid arthritis studies. There was an increase in vaccination rates.\*Ledwich LJ et al. was divided into two as there were two dif-

ferent groups: one that was an academic practice and the other a community practice

	Interver	tion	No Interve	ention		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
2.1.3 Patient and/or P	hysician (	Driented	1					
Walsh 2013	289	594	63	919	8.2%	12.87 [9.52, 17.42]	2013	-
Parker 2013	45	84	26	84	7.4%	2.57 [1.37, 4.84]	2013	_ <b>_</b>
Christensen 2015	36	99	16	130	7.3%	4.07 [2.10, 7.91]	2015	
Greene CD 2015	4	200	6	200	5.3%	0.66 [0.18, 2.37]	2015	
Greene UC 2015	17	290	1	300	3.4%	18.62 [2.46, 140.84]	2015	· · · · · · · · · · · · · · · · · · ·
Reich 2015	71	219	39	187	7.9%	1.82 [1.16, 2.86]	2015	
Sapir 2016	56	200	16	199	7.5%	4.45 [2.45, 8.08]	2016	
_ee 2016	45	50	40	50	5.7%	2.25 [0.71, 7.14]	2016	
euerstein AP 2017	197	569	76	367	8.2%	2.03 [1.49, 2.75]	2017	-
Feuerstein PP 2017	149	200	54	200	7.9%	7.90 [5.06, 12.33]	2017	
Ewelukwa 2018	140	401	55	423	8.1%	3.59 [2.53, 5.09]	2018	+
Reich 2019	43	46	47	64	5.2%	5.18 [1.42, 18.93]	2019	
Bensinger 2019	19	50	1	50	3.3%	30.03 [3.83, 235.77]	2019	
Subtotal (95% CI)		3002		3173	85.5%	4.00 [2.44, 6.56]		•
Total events	1111		440					
Heterogeneity: Tau <sup>2</sup> =	0.62; Chi2	= 113.5	0, df = 12 (	P < 0.00	001); I <sup>2</sup> =	89%		
Test for overall effect:	Z = 5.51 (F	P < 0.000	001)					
2.1.4 Barrier Oriente								
				407	7.40	5 07 10 00 0 00	0047	
Coenen 2017	53	86	25	107	7.4%	5.27 [2.82, 9.83]		
Sitte 2019 Subtotal (95% CI)	60	70 156	43	267 374	7.1% 14.5%	31.26 [14.84, 65.82] 12.68 [2.21, 72.62]	2019	
	440	150	~~	5/4	14.3%	12.00 [2.21, 72.02]		
Fotal events	113	40.04	68					
Heterogeneity: Tau² =				= 0.0003	); 1* = 929	lo lo		
Fest for overall effect:	∠ = 2.85 (F	r = 0.004	4)					
fotal (95% CI)		3158		3547	100.0%	4.74 [2.94, 7.64]		◆
Total events	1224		508					
Heterogeneity: Tau <sup>2</sup> =	0.70; Chi2	= 140.3	6, df = 14 (	P < 0.00	001); I <sup>2</sup> =	90%		0.001 0.1 1 10 10
Fest for overall effect:	Z = 6.38 (F	> < 0.000	001)					Favours no intervention Favours intervention
Fest for subaroup diff				2 22 2000				

Fig. 5 Pooled estimates of association between interventions and vaccination uptake in inflammatory bowel disease patients. Compared with no intervention, all interventions (patient-oriented, /physicianoriented, combined patient+physician-oriented, or barrier-oriented) increased vaccination uptake [Odds ratio 4.74; 95% confidence interval, 2.94-7.64, I2=90%]. The greatest effect was seen in barrieroriented studies [Odds ratio, 12.68; 95% confidence interval, 2.21-72.62, I2=92%]

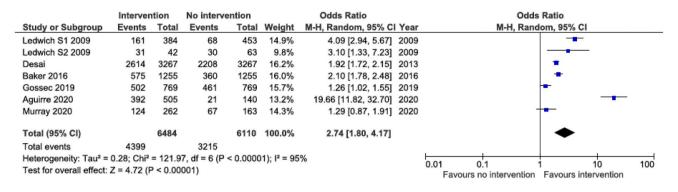


Fig. 6 Pooled estimates of association between interventions and vaccination uptake in rheumatoid arthritis patients. All interventions (patient-oriented, physician-oriented, combined patient+physician-

oriented, or barrier-oriented) increased vaccination uptake [Odds ratio, 2.74; 95% confidence interval, 1.80-4.17, I2=95%] compared to no intervention

Table 3 D	IBD studies Pre-	and Post-intervention	vaccination rates	for Pneumococcal	l and Influenza
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Author	Classification of intervention	Pneumococcal vacc	ination	Influenza	
		Pre-intervention	Post-inter- vention	Pre-intervention	Post- inter- vention
Parker S et al	Patient-oriented	31%	54%	54%	81%
Reich JS et al	Patient-oriented	21%	32%	23%	47%
Reich JS et al	Patient-oriented	73%	93%	69%	85%
Christensen K et al	Physician-oriented	12%	36%	42%	62%
Ewelukwa O et al	Physician-oriented	13%	63%	12%	35%
Feuerstein J et al	Physician-oriented	21%	35%	34%	58%
		27%	75%	46%	87%
Greene L et al	Physician-oriented	0.3%	6%	4%	25%
Greene L et al	Physician-oriented	3%	2%	21%	22%
Lee A et al	Physician-oriented	80%	90%	82%	90%
Sapir T et al	Physician-oriented	8%	28%	28%	43%
Valluru N et al	Physician-oriented	3%	85%	4%	90%
Bensinger A et al	Combined patient + physician- oriented	2%	38%	19%	59%
Walsh A et al	Combined patient + physician- oriented	7%	49%	46%	66%
Coenen S et al	Barrier-oriented	23%	62%	10%	36%
Sitte J et al	Barrier-oriented	16%	86%	N/A	N/A

Study names marked in Bold depict studies that had a higher baseline of Influenza vaccination

them to have a pneumococcal vaccination. Limitations of our study included incomplete reporting of vaccination status prior to and after intervention; in most of the studies the vaccination status was based on self-reporting or documentation in chart audits that were based on patient reporting. Not all the patients received vaccinations at the various practices. There is also publication bias that is present. Other aspects that added to the high heterogeneity included the following: variations in primary documentation and in intervention populations and a lack of randomized controlled trials as most of the studies were quasiexperimental. There were also a small number of studies included in each sub-classification (patient-oriented vs physician-oriented vs combined patient- and physicianoriented); however, we were able to increase the power in our analysis by grouping these sub-classifications together. Despite the high heterogeneity, this study is clinically relevant as it shows that any intervention resulted in an increased uptake in PCV rates. This high heterogeneity is reflective of the different types of interventions used in the underlying studies of the meta-analysis. The existence of heterogeneity suggests that there may not be a single intervention effect but a distribution of intervention effects. Lastly, as previously stated, there is a discrepancy between

Table 4	RA studies	Pre- and Post-intervent	tion vaccination rates f	or Pneumococcal and Influenza
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Author	Classification of intervention	Pneumococcal vacc	ination	Influenza vaccinatio	on
		Pre-intervention	Post-interven- tion	Pre-intervention	Post- inter- vention
Aguirre A et al	Physician-oriented	15%	78%	N/A	N/A
Desai SP et al	Physician-oriented	68%	80%	N/A	N/A
Ledwich LJ et al	Physician-oriented	15%	42%	43%	58%
		48%	74%	69%	82%
Baker DW et al	Combined patient + physician-oriented	29%	46%	90%	86%
Broderick R et al	Combined patient + physician-oriented	N/A	N/A	53%	77%
Murray K et al	Combined patient + physician-oriented	41%	47%	62%	62%
Sheth H et al	Combined patient + physician-oriented	N/A	N/A	N/A	N/A
Gossec L et al	Barrier-oriented	60%	65%	44%	55%

Study names marked in Bold depict studies that had a higher baseline of Influenza vaccination

internal medicine physicians and gastroenterologists on who's responsibility vaccination are [6, 7]. It is possible that gastroenterologist and the rheumatologist view on who is responsible for recommendations of vaccination can also affect the vaccination rates. A meta-analysis was not completed on influenza vaccination for both IBD and RA data due to the lack of studies. In the IBD studies only one study was barrier-oriented and in the RA studies of the 3 studies that included influenza vaccination only one studies showed increased in vaccination rates.

The results of this study demonstrate that all of the studied interventions demonstrate evidence for increasing vaccination rates in patients with IBD and RA. Each healthcare organization and provider should evaluate their resources and assess which intervention is best suited for their patients. Our study also suggests that using barrier-oriented interventions, such as navigators, may have a substantial effect in increasing vaccination rates; however, any substantial conclusion cannot be made as we are limited by only two studies that assessed navigators. Further randomized controlled trials, especially in the USA, need to be conducted to further evaluate navigation and its degree of efficacy in our healthcare system.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-023-07903-7.

**Acknowledgments** Jalpa Patel and Dina Fakhouri had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author's contribution JP, BW, AKW, FAF, and MP contributed to study concept and design. JP, DF, MN, AKW, FAF, and MP contributed to acquisition, analysis, or interpretation of data. JP, MN, MP, and JF contributed to drafting of the manuscript. Critical revision of the manuscript for important intellectual content: all authors. MN and AKW contributed to statistical analysis. JP, DF, and IK: administrative, technical, material support, and acquisition of data. MP contributed to study supervision.

Funding This work was not funded.

**Data availability** The data underlying this article are available in the article and in its online supplementary material. Data were obtained from prior publications which are cited in the references.

#### Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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