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Immune response to influenza and pneumococcal vaccines in adults with inflammatory bowel disease: A systematic review and *meta*-analysis of 1429 patients

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ABSTRACT

Background: Patients with inflammatory bowel disease (IBD) have a high risk for infection. Pneumonia related to influenza and pneumococcal infection is one of the most common infection-related complications in IBD.
Aims: To evaluate the immunogenicity of pneumococcal and influenza vaccination in patients with IBD receiving different treatments.
Methods: We searched four databases for studies evaluating seroprotection and seroconversion rates after influenza or pneumococcal vaccination in IBD on 20th October 2020. In the *meta*-analysis, odds ratios (OR) were calculated with 95% confidence intervals (CI).
Results: We included twelve studies (1429 patients with IBD) in this *meta*-analysis. The seroconversion rate after pneumococcal vaccination and the seroprotection rate after influenza vaccination were not significantly lower in patients receiving conventional immunosuppressive treatment compared to the non-immunosuppressed patients. Meanwhile, the seroconversion rate following pneumococcal vaccine was significantly lower in patients with anti-TNF mono- or combination therapy (OR = 0.28, CI: 0.15–0.53, and OR = 0.27, CI: 0.15–0.49, respectively). In the analysis of patients with IBD on conventional immunosuppressive monotherapy versus anti-TNF therapy, the seroprotection rate after influenza immunization did not differ between patients receiving either anti-TNF mono-or combination therapy (OR = 1.45, CI: 0.62–3.38 and OR = 0.91, CI: 0.37–2.22, respectively).
Conclusion: Our data suggest that the immunization against Pneumococcus and influenza is safe and immunogenic despite immunosuppression.

1. Introduction

Prevention of infection is a major issue in the era of the SARS-CoV-2 pandemic, especially in immunocompromised patients. Inflammatory bowel disease (IBD) is a chronic gastrointestinal disease characterized by chronic inflammation triggered by internal and external environmental factors in a genetically susceptible individual. Patients with IBD have an increased risk for several infections, including vaccine-preventable influenza and *Pneumococcus*, especially under immunosuppressive treatment [1]. Moreover, one of the leading causes of mortality in IBD is infection-related complications. Patients with IBD hospitalized for infection have a significantly higher risk for mortality than those hospitalized for other reasons. Higher infection-related mortality has been reported in Crohn's disease and ulcerative colitis (Hazard ratio (HR) = 3.23, CI: 2.64–3.94 and HR = 2.21, CI: 1.93–2.53, respectively) [2,3].

One of the most common infection-related complications resulting in the hospitalization of patients with IBD is pneumonia

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Table 1
Characteristics of the studies included.

Author, year, country	Study type (number of centres)	Number of patients (CD/ UC/ IBD-U)	Number of HC	Treatment groups (n)	Age at vaccination, years (mean, SD)	Female n (%)	Disease duration (mean, SD)	Type of vaccine	Schedule	Evaluating time after vaccination	Definition of immune response
Pneumococcal vaccine											
Fiorino *et al.*, 2012, Italy	prospective (1)	96 (54/42/0)	–	NIS (35) AZA mono (19) IFX mono (26) Combo (16)	42 (19–70)[a]	41 (43%)	> 6 mo	PSV23, Pneumovax	Single	21–180 days	2-fold increase in antipneumococcal antibodies
Lee *et al.*, 2014, Republic of Korea	prospective (15)	197 (197/0/0)	–	5-ASA (37) AZA/6-MP mono (70) Anti-TNF mono (40) Combo (50)	36 (19–65) 26.5 (24–48) 32 (18–48) 30.5 (16–57)	16 (43%) 22 (31%) 14 (35%) 14 (28%)	23 mo (9-68) 30 mo (11-69) 87.5 mo (14-228) 59.5 mo (29.7-98.7)	PPSV23, Prodiax-23	Single	4 weeks	2-fold increase in IgG antibody titer
Melmed *et al.*, 2010, USA	prospective (1)	45 (30/14/1)	19	5-ASA (25) Combo (20) HC (19)	40 (22–68)[b] 36.5 (24–65)[b] 37 (23–64)[b]	4 (14%) 3 (25%) 3 (47%)	10 yrs (1-40)[b] 10 yrs (1-38)[b]	PSV- 23, Pneumovax	Single	4 weeks	2-fold increase in GMT and 1μg/ ml post-vaccination GMT in the majority (≥ 3)of antibodies
Pittet *et al.*, 2019, Switzerland	prospective (N/A)	306 (213/93/0)	–	NIS (66)[c] IS (240)[c]	46.3 (34.1–54.3)[d] 41.8 (28.6–52.2)[d]	121 (50%) 37 (56%)	NA	PCV13, Prevenar 13	Single	2 mo	OPA titre >8
van Aalst *et al.*, 2019, Netherland	prospective (2)	141 (97/44/0)	–	AZA/6-MP/ MTX mono (35) Anti-TNF mono (40) Combo (29) NIS (37)	49 (30–60)[d] 41 (25–56)[d] 38 (30–51)[d] 46 (31–56)[d]	22 (63%) 22 (55%) 18 (62%) 24 (65%)	NA	PCV13+PPV23	Serial (2 mo)	4–8 weeks	Antibody concentration of ≥1.3 μg/mL for ≥70% of all measured serotypes
Influenza vaccine											
Andrisani *et al.*, 2012, Italy	prospective (1)	62 (36/26/0)	31	Anti-TNF mono (47) Combo (15) HC (31)	40 (18–69)[b] 47 (20–75)[b] 31.5 (20–55)b	23 (49%) 4 (27%) 21 (68%)	8 yrs (1–32)[b] 7 yrs (1–21)[b]	Monovalent (Focetria): A/California/7/2009 (H1N1)	Single	4–6 weeks	Seroprotection: postvaccination HI titer ≥1:40 Seroconversion:HI titer ≥4 fold increase
Caldera *et al.* 2019, USA	RCT (1)	59 (41/18/0)	20	Anti-TNF mono (15) (standard vaccine dose) HC (20) VDZ (mono or combo)(19)	43 (32–52)[d] 40 (32–47)[d] 29 (26–52)[d] 29 (25–45)[d]	5 (33%) 10 (50%) 12 (63%) 9 (36%)	111 mo (62–276)[d] 140 mo (83–267)[d] 113 mo (55–162)[d]	Quadrivalent (Fluzone) A/California/7/2009 (H1N1) pdm09-like virus or A/Michigan/ 45/2015 (H1N1)pdm09-like virus; A/Hong Kong/4801/2014 (H3N2)-like virus; B/Brisbane/60/2008-like virus; B/Phuket/3073/2013-like	Single	2–4 weeks, 6 mo	Seroprotection: HI titer ≥1:40; Seroconversion: HI titer 4-fold rise
Cullen *et al.*, 2011, USA	prospective (1)	105 (57/48/0)	–	NIS (28) IS (77)	47.8 (20.5–63.2)[b] 40.1 (22.7–67.9)[b]	12 (43%) 38 (49%)	10.5 yrs (0–49)[b] 10 yrs (0–40)[b]	Monovalent: A/California/07/2009 (H1N1)	Single	2–4 weeks	Seroprotection: HI ≥40
Doornekamp *et al.*, 2020, Netherland	prospective (1)	27 (27/0/0)	20	Adalimumab (12)[e] HC (20) Ustekinumab (15)[e]	45 (28–59)[d] 36 (29–49)[d] 36 (26–56)[d]	5 (42%) 11 (55%) 11 (73%)	14 yrs (8–35)[d] 15 yrs (9–25)[d]	Trivalent (Influvac): A/Michigan/45/2015 (H1N1) pdm09; A/Singapore/INFIMH-16-0019/ 2016 (H3N2); B/Colorado/06/2017	Single	1,3 mo	Seroprotection: HI ≥40; Seroconversion: ≥ 4-fold rise

(*continued on next page*)

Table 1 (*continued*)

Author, year, country	Study type (number of centres)	Number of patients (CD/ UC/ IBD-U)	Number of HC	Treatment groups (n)	Age at vaccination, years (mean, SD)	Female n (%)	Disease duration (mean, SD)	Type of vaccine	Schedule	Evaluating time after vaccination	Definition of immune response
Hagihara *et al*., 2014, Japan	prospective (1)	88 43/45/0	0	NIS (30) IS (58)	44(14.4)	37 (42%)	NA	Trivalent: A/California/7/2009 (H1N1), A/Victoria/210/ 2009 (H3N2), B/ Brisbane/60/2008	Single	3 weeks, after flu season	Seroprotection: postvaccination HI titer $\geq$ 1:40; Seroconversion: HI titer $\geq$ 4-fold rise
Launay *et al*., 2015, France, A	prospective (16)	225 (172/53/0)	–	NIS (31) IS mono (77) Anti-TNF mono or combo (117)	44 (±13) 38 (±12) 38 (±11)	19 (61%) 46 (60%) 78 (67%)	14 yrs (±11) 10 yrs (±8) 10 yrs (±8)	Trivalent (Vaxigrip): A/Brisbane/ 59/2007 (H1N1), A/Brisbane/10/ 2007 (H3N2), B/Florida/4/2006 or A/California/7/2009 (H1N1), A/ Perth/16/2009 (H3N2), B/Brisbane/ 60/2008	Single	21–28 days, 6 mo	Seroprotection: postvaccination HI titer $\geq$ 1:40 and GMT fold rise; Seroconversion: HI titer $\geq$ 1:40 and $\geq$ 4-fold rise
Matsumoto *et al*., 2015, Japan, A	RCT (1)	39 (20/15/0/4[f])	7	AZA/6-MP mono (14) Anti-TNF mono (10) Combo (15) HC (7)	45.3 (26–73)	21 (46%)	8.8 yrs (1–30)	Trivalent: A/California/7/2009 (H1N1) pdm09, A/Victoria/361/2011 (H3N2), B/ Wisconsin/01/2010	Single	3 weeks, after flu season	Seroresponse: HI titer $\geq$4-fold rise; Seroprotection: HI titer $\geq$1:40
Matsumoto *et al*., 2015, Japan, B	RCT (1)	39 (18/18/0/3[f])	4	AZA/6-MP mono (15) Anti-TNF mono (11) Combo (13) HC (4)	42.4 (21–72)	17 (40%)	10 yrs (1–27)	Trivalent: A/California/7/2009 (H1N1) pdm09, A/Victoria/361/2011 (H3N2), B/ Wisconsin/01/2010	Booster (0,3 weeks)	3 weeks, after flu season	Seroresponse: HI titer $\geq$4-fold rise; Seroprotection: HI titer $\geq$1:40)

HC: healthy controls; SD: standard deviation; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: inflammatory bowel disease-unclassified; NIS: No immunosuppressive treatment; mono: monotherapy; IFX: infliximab; combo: combination therapy; mo: months; 5-ASA: 5-aminosalicylate; AZA/6-MP: azathioprine/6-mercaptopurine; Anti-TNF: anti-tumor necrosis factor; IgG: immunglobulin G; yrs: years; GMT: geometric mean titer; IS: immunosuppressive treatment; NA: not available; OPA: opsonophagocytic assay; MTX: methotrexate; HI: haemagglutinin inhibition; VDZ: vedolizumab.

[a] mean, range.

[b] median, range.

[c] NIS: treatment free (n = 27); VDZ (n = 13); 5-ASA (n = 27); topical steroid (n = 2).

[d] median, interquartile range.

[e] Adalimumab patients were on low dose corticosteroid (n = 3); immunomodulator (n = 3); Ustekinumab patients were on low dose corticosteroid (n = 2); high dose corticosteroid (n = 1); immunomodulator (n = 3).

[f] intestinal Behcet disease.

[4]. The most prevalent etiological pathogens of pneumonia in patients with IBD are *Streptococcus pneumoniae* and influenza virus [5]. It should be noted that morbidity and mortality associated with influenza infection arise partially from complications such as secondary bacterial or viral pneumonia, and exacerbation of underlying chronic conditions [6].

Current guidelines from the European Crohn's and Colitis Organization (ECCO) recommend vaccination against *Pneumococcus* and influenza [7]. However, some studies have spotlighted the impaired response to immunization in patients with IBD [8]. The negative effect of immunosuppressive treatment on the immune response to pneumococcal and influenza vaccines has already been shown in some immune-mediated diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus) [9]. Disease-related immune disorders and the applied immunosuppressive treatment probably compromise response rates to vaccines [8]. Although, some studies have described adequate response rates despite concomitant immunosuppression in IBD patients [10,11].

In a recent *meta*-analysis, the response rate of vaccines was not significantly lower in children with IBD than healthy controls and immunosuppressive treatment did not significantly reduce the response rate to vaccination [12]. Similarly, the authors of a recent systematic review reported that the administration of viral vaccines are immunogenic and safe in children with autoimmune diseases treated with systemic immunosuppressive drugs [13]. However, a previous *meta*-analysis found that adults with IBD on immunosuppressive therapy have a significantly lower response rate to vaccinations. The response rates to vaccines against hepatitis A and B, influenza, and *Pneumococcus* were pooled in this *meta*-analysis [14]. Consequently, that conclusion may not be valid for each vaccine. To date, no *meta*-analysis focused on the immune response of patients with IBD, specifically to vaccine-preventable common airborne diseases, like influenza and pneumococcal infection.

Therefore, we aimed to evaluate the immunogenicity and safety of pneumococcal and influenza vaccination in patients with IBD using *meta*-analysis.

2. Material and methods

We performed this systematic review and *meta*-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [15]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42021224123). There were no deviations from the protocol. For data synthesis, we used the methods recommended by the working group of the Cochrane Collaboration [16].

2.1. Search strategy and information source

We formulated two research questions regarding immunization against pneumococcal or influenza disease in patients with IBD: (1) Is the immune response to vaccination decreased in patients with IBD compared to healthy controls? (2) Is there any difference in the immune response to vaccination in patients with IBD with or without immunosuppressive therapy?

Search strategy: A search query based on the Patient-Intervention-Comparator-Outcome formula (PICO) was built and the following free text terms were searched: (Inflammatory Bowel Disease) AND (immunization) AND (methotrexate OR azathioprine OR certolizumab OR infliximab OR adalimumab OR Vedolizumab OR Ustekinumab OR golimumab OR tofacitinib OR immunomodulator OR "anti tnfalpha" OR "monoclonal antibodies" OR cyclosporin) AND (*Pneumococcus* OR influenza). See Supplementary Data 1 for the full-length search key and PICO frames.

We conducted a systematic search until 20 October 2020 in four electronic databases: MEDLINE (via PubMed), Embase, the Central Cochrane Register of Controlled Trials (CENTRAL), and Scopus. No restrictions were applied. In Scopus, "Article title, Abstract, Keywords" fields were used, and all fields were used in the other databases. We manually searched for additional studies in the reference lists of the included studies.

Patients and comparators: Studies involving adult IBD patients ($\geq$18 years) regardless of age, sex, type of IBD, treatment, and disease activity were searched. Healthy controls vaccinated against *Pneumococcus* or influenza were selected, as well. Any kind of pneumococcal (pneumococcal conjugate vaccine (PCV13) or pneumococcal polysaccharide vaccine (PPSV23) and influenza vaccination (inactivated influenza vaccine, recombinant influenza vaccine, or live attenuated influenza vaccine; monovalent, trivalent or quadrivalent) and any vaccination schedule (single or serial or booster, standard or high dose) were eligible.

Immunosuppressive treatment was defined as anti-TNF, azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, cyclosporine and ustekinumab used alone or in combination. Treatment-free patients and those treated with 5-aminosalicylates or antibiotics or vedolizumab or topical corticosteroids or topical 5-aminosalicylates formed the non-immunosuppressive group. Systemic corticosteroid alone or in combination with other medications was regarded as immunosuppressive treatment, except for one study where low dose corticosteroid (prednisolone $\leq$ 10 mg daily) was classified as non-immunosuppressive therapy. Patients receiving vedolizumab were considered as non-immunosuppressed as its immunomodulating effect is confined to the gastrointestinal mucosa, without affecting vaccine responses [17,18]. Immunosuppressive treatment was further classified as anti-TNF monotherapy, conventional immunosuppressive monotherapy without anti-TNF (azathioprine, 6-mercaptopurine, methotrexate monotherapy, tacrolimus, cyclosporine) and combination therapy.

Outcome: The primary outcomes were seroprotection rates (SPR) and seroconversion rates (SCR). Seroprotection indicates the amount of antibody that has been determined to be required to elicit protection. Seroconversion is an increase in the antibody titer chosen to indicate an immune response. Although seroconversion may be the more stringent value, both values indicate antibody response to vaccination. SPR and SCR rates were defined as the proportion of patients whose antibody concentration reached the specified seroprotection or seroconversion. We applied the SCR and SPR values for the analyses as reported in the particular studies based on their definition of seroprotection and/or seroconversion (see Table 1). The secondary outcomes were the incidence of local or systemic adverse events (AE) and exacerbations of IBD after the vaccination.

2.2. Study selection and eligibility

After the systematic search, all references were imported into a reference management software (EndNote X9.2. Clarivate Analytics), where duplicates were automatically and manually removed. Two investigators (DD, KEM) assessed the eligibility independently based on title, abstract, and full-text. At each step of selection, disagreements were resolved by consensus. A third author (PS) resolved discrepancies when necessary.

Based on the pre-defined research question and PICO, randomized controlled trials (RCT) and observational cohort studies were eligible. Studies in children and studies without a control group or a reported immune response rate were excluded. Furthermore,

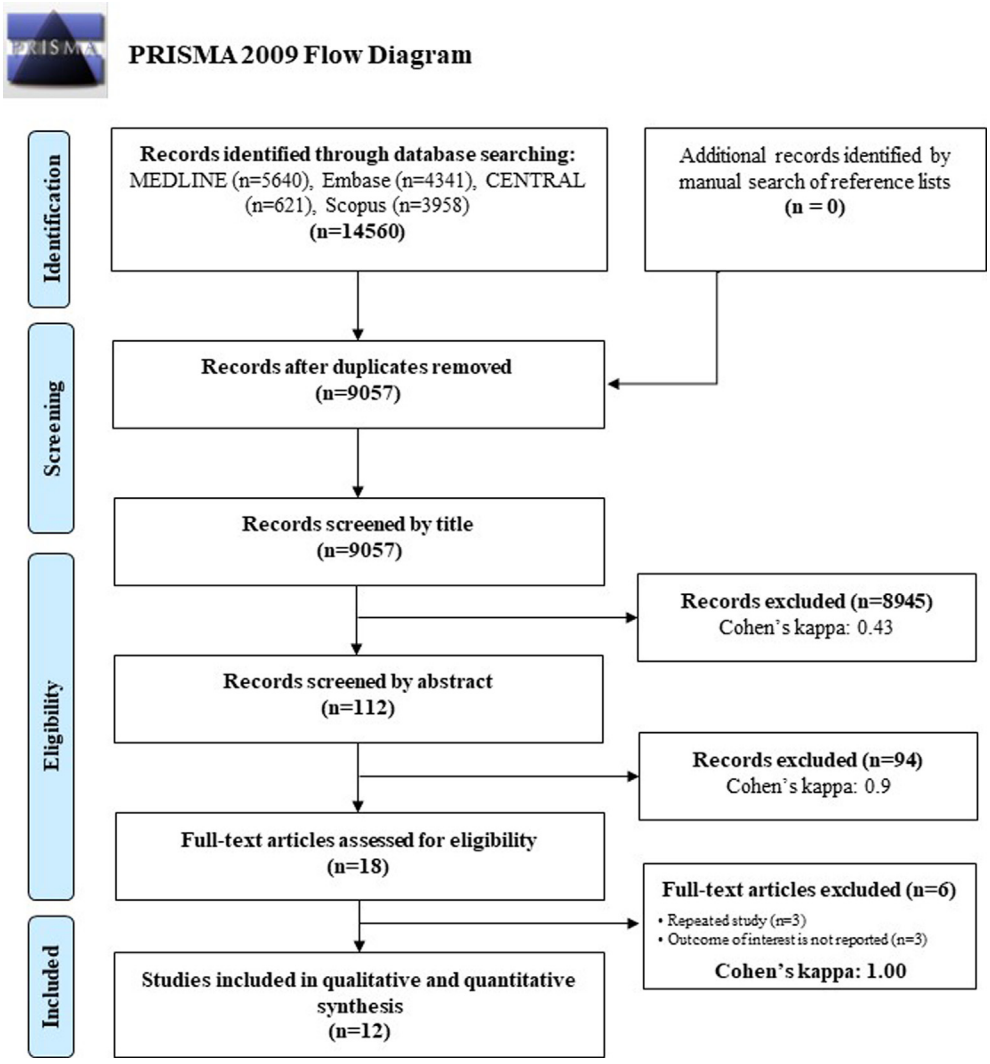

Fig. 1. PRISMA flowchart of study selection.

reviews, letters, research protocols, case reports were also excluded.

2.3. Data collection and analysis

Data were extracted separately into a standardized data collection form by two independent investigators (DD and KEM). Any disagreements were resolved by consensus or by a third author (PS) when necessary. The following data were extracted from each study: (1) first author, year of publication, country, study design, and the number of participating centers; (2) patient characteristics (sample size, type of IBD, age and gender distribution, treatment groups); (3) information of vaccination (type of vaccine, vaccination schedule); (4) type and definition of outcomes (evaluating time after vaccination, the definition of SPR and SCR, AEs, recurrence of disease activity); (5) number of patients achieving SPR and SCR and number of AEs and rate of disease exacerbation.

To compare the effect of different immunosuppressive therapy, the following classification was applied in the subgroup analysis: 1. Conventional immunosuppressive monotherapy without anti-TNF: azathioprine, 6-mercaptopurine, methotrexate monotherapy, tacrolimus, cyclosporine; 2. Anti-TNF monotherapy; 3. Combination therapy: a combination of a conventional immunosuppressant and anti-TNF; 4. Non-immunosuppressive therapy: 5-aminosalicylate, antibiotics, treatment-free, topical corticosteroids, vedolizumab, low-dose corticosteroid, no treatment.

2.4. Risk of bias assessment in the included studies

The quality of the included studies was independently assessed by two authors (DD and KEM) to ascertain their validity. Any disagreements were resolved by a third investigator (SzK). The revised Cochrane risk-of-bias tool for randomized trials (ROB2) was planned for the RCTs [19]. The Risk of Bias In Non-Randomized Studies–of Interventions (ROBINS-I) tool was used for observational studies [20]. Different items of bias were assessed: (1) confounding; (2) selection of participants; (3) classifications of interventions; (4) deviations from intended interventions; (5) missing data; (6) measurement of outcomes and (7) selection of the reported outcome. In the end, an overall bias assessment was performed.

2.5. Certainty of evidence: GRADE

We applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for evaluating the certainty of the evidence for the primary outcomes of the *meta*-analysis [21]. Outcomes were assessed based on five criteria: risk of bias,

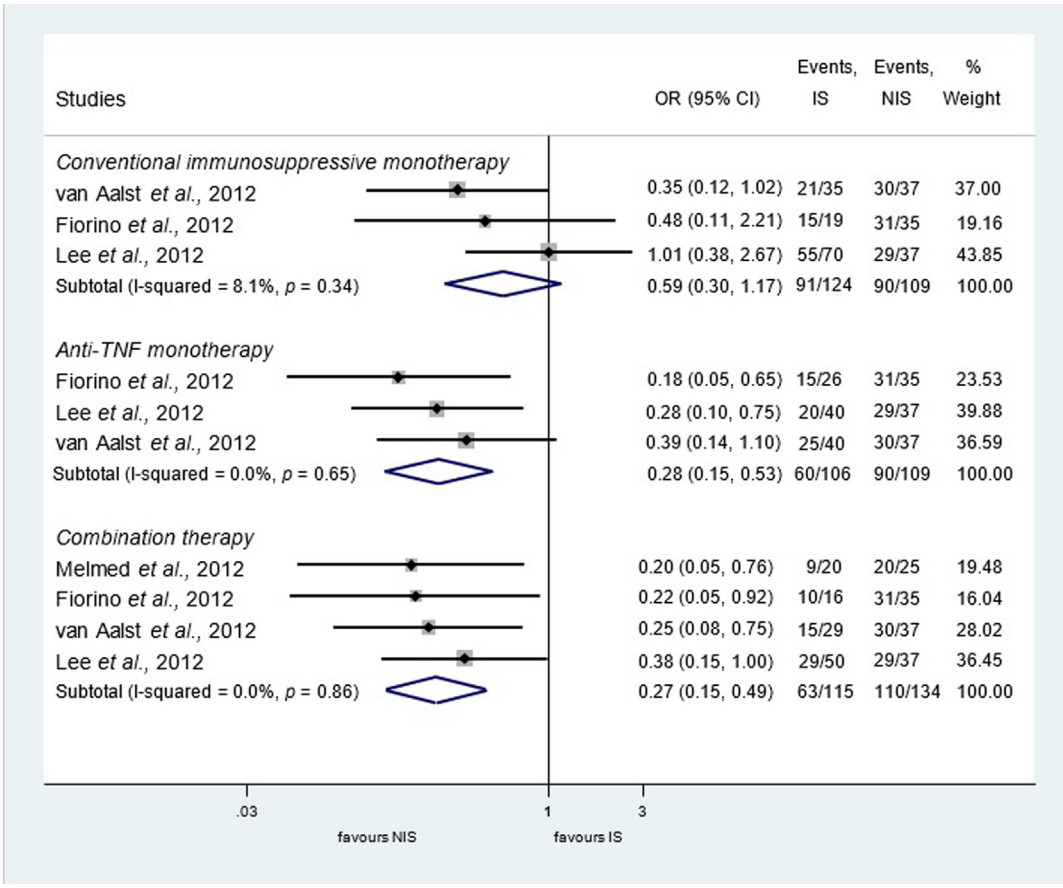

Fig. 2. Subgroup analysis of seroconversion rate after pneumococcal immunization in patients with inflammatory bowel disease treated with different immunosuppressive treatment vs. patients without immunosuppressive therapy. IS: immunosuppressive treatment; NIS: non-immunosuppressive treatment.

inconsistency, indirectness, imprecision, and publication bias. The overall quality of the evidence for each outcome was classified as high, moderate, low, or very low. The analysis was performed independently by two authors (DD, KEM), and any disagreements were resolved by consensus or a third author (SzK) if necessary.

2.6. Statistical analysis

Data analysis was based on the per-protocol principle. The odds ratio (OR) of seroprotection and seroconversion was the primary measure of treatment effect. OR and 95% confidence intervals (CI) per immunization (influenza or *Pneumococcus*) were analyzed from the original raw data of the articles. The *meta*-analyses were performed by computing pooled ORs using the random-effect model with DerSimonian-Laird estimation [22]. Statistical heterogeneity was tested using Cochrane's Q and the I^2 statistics. According to the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity was interpreted as moderate between 30% and 60%, substantial between 50% and 90%, and considerable above 75% [16]. The results were visualized in forest plots.

Sensitivity analysis was performed to assess the impact of each study on the overall effect size using the 'leave-one-out method.'

We planned to assess the publication bias by Egger's test and the visual inspection of funnel plots. Subgroup analyses were conducted for the primary outcome based on different types of immunosuppressive treatment. We also planned to calculate the ORs for secondary outcomes. Statistical analyses were performed with Stata 16 (StataCorp LLC, College Station, Texas, USA).

3. Results

3.1. Study selection

The initial search yielded 14,560 records, of which 9057 remained after removal of duplicates. After screening titles and abstracts, 18 articles were eligible for inclusion. From the data analysis six studies were excluded; three did not report the outcome of our interest [23-25], two publications (one conference abstract and one article) included follow-up data of two already included studies [26,27], and a conference abstract [28] reported on the same sample population as an eligible study [29] after a booster dose of influenza vaccine. We did not identify any additional studies in the references of primarily eligible studies. Finally, twelve articles met the eligibility criteria for quantitative analysis, five with pneumococcal [30-34] and seven with influenza vaccine [29,35-40]. The study selection flow diagram is shown in Fig. 1.

3.2. Study characteristics

After the selection ten prospective observational cohort studies [29-36,39,40] and two RCTs [37,38] were appropriate for this systematic review and *meta*-analysis. The allocation of the randomization patients in the two RCTs did not match our PICO; therefore, we handled them as observational studies. The studies were published between 2010 and 2020 reporting data from Europe [30,32,33,35,39,40], North America [34,36,37] and Asia

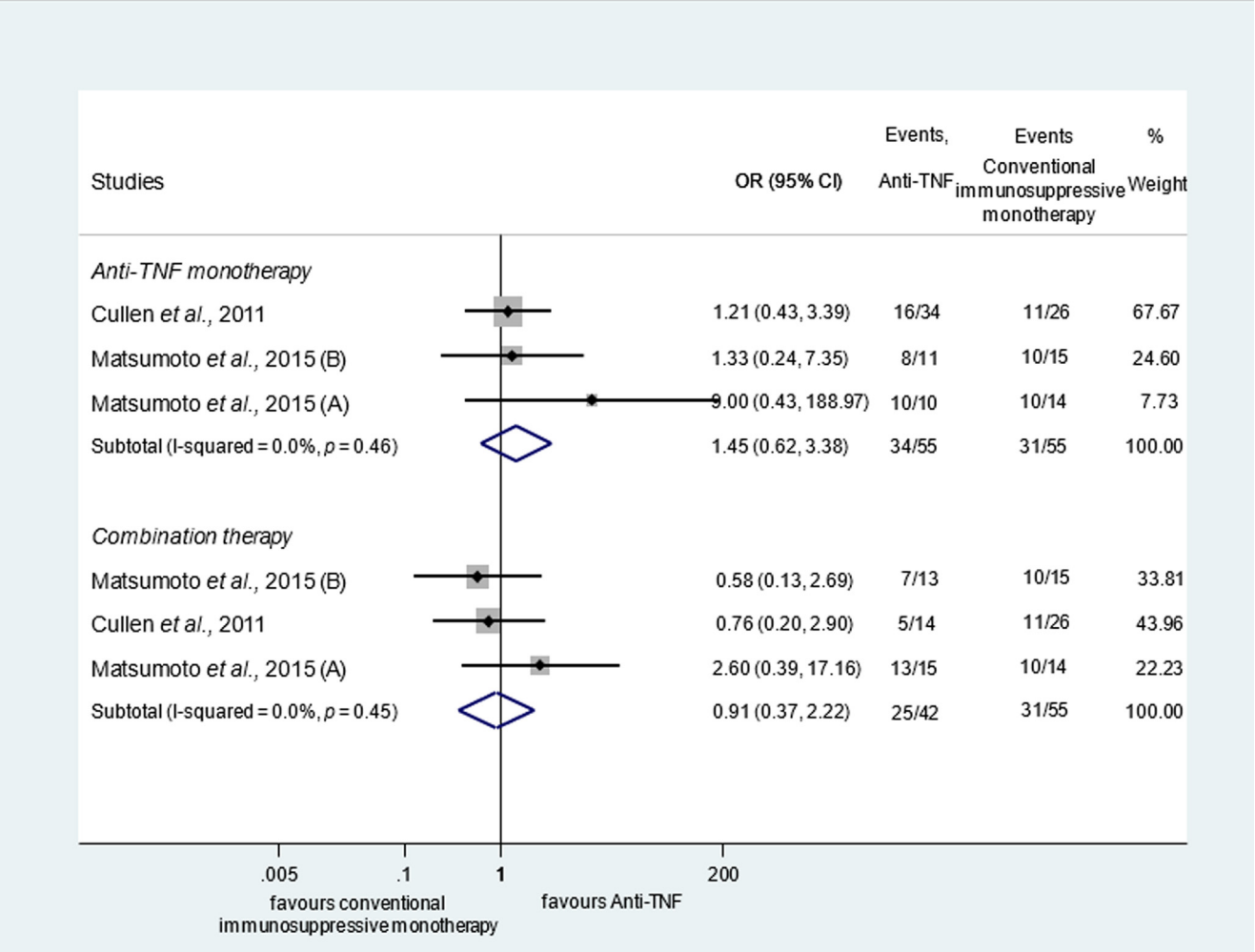

Fig. 3. Forest plot of seroprotection rate to influenza H1N1 strain in patients with inflammatory bowel disease with conventional immunosuppression or anti-TNF therapy.

[29,31,38]. The detailed characteristics of the included studies are described in Table 1.

3.2.1. Characteristics of studies reporting pneumococcal immunization

The number of patients with IBD ranged from 45 to 306 among the five studies [30-34]. The PSV23 vaccine was applied in three studies [30,31,34], PCV13 was used in one study [33], and finally, a serial immunization regimen (PCV13, three weeks later PSV23) was administered in one study [32]. The definition of seroconversion was identical in two of the five studies [30,31] (Table 1). Melmed *et al.* and van Aalst *et al.* used stricter criteria for seroconversion [33,34]. Pittet *et al.* administered an opsonophagocytic functional antibody assay, and they used the WHO recommended cut-off, that correlated at best with the range of 0.20–0.35 μg/ml antibody concentrations [32,41]. As these studies reflect, there is a lack of consensus on the correlates of protection after pneumococcal vaccination. The reported values of seroconversion rates from each study were used for the analyses. The time interval for evaluation of post-immunization immunogenicity ranged from 4 to 8 weeks in four studies [31-34], but in one study, the time interval was 21–180 days [30].

3.2.2. Characteristics of studies reporting influenza vaccination

The number of participants ranged between 47 and 225 in the seven studies [29,35-40]. Monovalent influenza vaccine (H1N1) was applied in two studies [35,36], and trivalent (H1N1, H3N2, B strains) vaccine was used in four studies [29,38-40]. Only one study compared the immune response rate with a high dose trivalent or standard dose quadrivalent influenza vaccine [37]. Only patients immunized with the standard dose quadrivalent vaccine were included from this study. Matsumoto *et al.* examined the immune response after a single or booster dose of trivalent influenza vaccine, so this study was divided into two groups in our analysis (Matsumoto A and Matsumoto B) [38]. The same definition of seroprotection was used in all studies. Seroconversion was similarly reported in five studies [29,35,37-39], and one study used a stricter definition [40]. (Table 1) Post-immunization immune response was assessed at two to four weeks in six studies [29,36-40], and four to six weeks in one study [35].

3.3. Qualitative and quantitative synthesis: Pneumococcal vaccination in IBD patients

3.3.1. Patients with IBD versus healthy controls

We did not find any study reporting the SPR in IBD and healthy controls after pneumococcal vaccination. Only one study, Melmed *et al.* investigated SCR in healthy controls (n = 19) and IBD patients with or without immunosuppressive treatment (n = 20 or n = 25, respectively) [34]. The SCR was significantly reduced in patients with immunosuppressive treatment in combination (45%) compared to healthy controls (84%) ($p = 0.01$), but the SCR in patients

without immunosuppressive therapy was similar (80%) to healthy controls (84%).

3.3.2. Patients with IBD receiving immunosuppressive therapy versus patients without immunosuppressive treatment

We were not able to analyse the SPR after pneumococcal immunization due to the lack of studies. The SCR for pneumococcal immunization was analyzed in three studies with 124 patients on conventional immunosuppressive therapy and 109 patients without immunosuppressive treatment [30,31,33]. The SCR was not significantly different in patients with conventional immunosuppressive therapy compared to patients without immunosuppressive treatment (OR = 0.59, CI: 0.3–1.17). Furthermore, a significantly lower SCR was observed in a subgroup of patients with an anti-TNF mono- or combination therapy compared to the group treated without immunosuppressive agents (OR = 0.28, CI: 0.15–0.53, and OR = 0.27, CI: 0.15–0.49, respectively) (Fig. 2).

We analyzed three further studies to determine whether anti-TNF mono- or combination therapy affects SCR compared to conventional immunosuppressive monotherapy [30,31,33]. Patients receiving anti-TNF monotherapy did not differ in their response rate compared to conventional immunosuppressive monotherapy, while significantly lower SCR was observed during combination therapy (OR = 0.49, CI: 0.19–1.23, and OR = 0.48, CI: 0.27–0.85, respectively).

3.4. Systematic review and meta-analysis: IBD patients after immunization with influenza

3.4.1. Patients with IBD versus healthy controls

3.4.1.1. Seroprotection rate. The SPR after influenza immunization was reported in four studies gathering 201 IBD patients and 82 healthy controls [35,37-39]. The response rate to H1N1, H3N2 or B strains of IBD patients and healthy controls was similar (OR = 1.25, CI: 0.48–3.29; OR = 1.3, CI: 0.29–5.86; OR = 0.92, CI: 0.38–2.20, respectively). The leave-one-out sensitivity analysis of SPR to H1N1 strain did not show any significant alteration in the results. (Supplementary Data 2).

3.4.1.2. Seroconversion rate. A total of 123 patients with IBD and 71 healthy controls were pooled from three studies to assess SCR for the H1N1strain [35,37,39]. The SCR was not decreased in patients with IBD (OR = 0.63, CI: 0.23–1.74). Due to the low number of studies, analyses for the H3N2 and B strains could not be performed [37,39]. In the study of Caldera *et al.* the SCR to H3N2 strain was comparable in patients with IBD and healthy controls (38% vs. 30%, $p = 0.23$) [37]. Doornekamp *et al.* found no significant differences in SCR between patients receiving ustekinumab or adalimumab and healthy controls (69% vs. 27% vs. 30%, $p = 0.23$ respectively) [39]. SCR for influenza B was analyzed in two studies without significant differences between patients with IBD and healthy controls [37,39].

3.4.2. Patients with IBD receiving immunosuppressive therapy

3.4.2.1. Seroprotection rate. In the analysis of conventional immunosuppressive monotherapy (excluding anti-TNF monotherapy) and non-immunosuppressive treatment, no differences in SPR to H1N1 strain were found in two studies [36,40]. Only one study reported the SPR to H1N1 strain significantly lower in patients with anti-TNF combination therapy compared to patients without immunosuppressive therapy (36% vs. 64%, $p = 0.02$) [36]. In contrast, Launay *et al.* found no significant difference in SPR in patients with anti-TNF mono- or combination therapy and in patients without immunosuppressive therapy (66% vs. 77%, $p = 0.38$) [40]. In the same study, the SPR to H3N2 strain was significantly higher in non-immunosuppressed patients than in patients with anti-TNF mono- or combination therapy (77% vs. 52%, $p = 0.022$) [40]. Finally, for influenza strain B, there was no significant difference between the two groups (97% vs. 95%, $p = 0.99$) [40].

In the subgroup analysis of patients with IBD on conventional immunosuppressive monotherapy versus anti-TNF therapy, the SPR to H1N1 strain did not differ neither in patients with anti-TNF monotherapy nor with combination therapy (OR = 1.45, CI: 0.62–3.38 and OR = 0.91, CI: 0.37–2.22, respectively) (Fig. 3). In the analysis of SPR to H3N2 and B strains after single and booster vaccination, there was no significant difference among patients receiving anti-TNF monotherapy, conventional immunosuppressive monotherapy, or combination therapy [38]. Furthermore, Launay *et al.* reported significantly reduced SPR to H3N2 strain in the anti-TNF group (mono- or combination therapy) compared to the conventional immunosuppressive monotherapy group (52% vs. 68%; $p = 0.03$) [40].

Data on SPR to H1N1 strain was provided in three studies including 57 patients treated with combination therapy and 102 with anti-TNF monotherapy [35,38,40]. The SPR was not significantly lower in patients with combination therapy (OR = 0.47, CI: 0.2–1.09). In the study by Matsumoto *et al.* there was no significant difference in SPR to H3N2 and B strains between the two groups even after single or booster immunization [38].

3.4.2.2. Seroconversion rate. The SCR to all three strains in patients with or without immunosuppressive treatment was presented in only one study [40]. In the study of Launay *et al.* the SCR to H1N1 strain did not differ significantly among groups without immunosuppressive treatment, with conventional immunosuppressive monotherapy, and with anti-TNF group (mono- or combination therapy) (67%, 64%, vs. 54%, respectively, $p = 0.26$) [40]. Compared to the group without immunosuppressive treatment, the SCR to H3N2 strain was significantly decreased in the anti-TNF group (mono- or combination therapy), but not in the conventional immunosuppressive monotherapy group (63% vs. 45%, $p = 0.038$ and 63% vs. 50%, $p = 0.23$, respectively). In case of strain B, the SCR was similar in anti-TNF group and in conventional immunosuppressive monotherapy compared to group without immunosuppressive treatment (60% vs. 63%, $p = 0.84$; 76% vs. 63%, $p = 0.23$, respectively).

Launay *et al.* evaluated SCR for H1N1 and H3N2 strains with similar results in patients with anti-TNF mono- or combination therapy versus conventional immunosuppressive monotherapy (H1N1: 64% vs. 54%; $p = 0.17$; H3N2: 50% vs. 41%; $p = 0.23$). Meanwhile, the SCR to strain B was significantly increased in the conventional immunosuppressive monotherapy group compared to the anti-TNF group (76% vs. 60%; $p = 0.037$) [40].

Only one study analyzed the SCR to H1N1 strain of patients with anti-TNF mono- and combination therapy (49% vs. 33%) without performing a pairwise statistical analysis [35]. For strains H3N2 and B, there were insufficient data for analysis.

3.5. Adverse events and occurrence of disease exacerbation

AEs are listed as the number of local and systemic side effects. AEs were reported in ten studies using different reporting methods, such as diary or phone calls or recalls at schedules visits. [29-33,35-38,40]. The time interval between immunization and data collection was also very variable, ranging from 7 days to 8 weeks. Systemic reactions occurred less frequently than local AEs after immunization either against influenza or pneumococcus. The frequency of local AEs did not differ among different treatment groups [29,31,36,38,40]. Due to variable data collection and lack of exact numbers, a *meta*-analysis could not be performed. See detailed information in Supplementary Data 3.

Clinical flare-ups after immunization were reported in five of twelve studies [31-33]. Due to the different definitions of flare-ups used in the studies, it was impossible to harmonize the results, so these data were analyzed as a systematic review. Pittet *et al.* reported a patient in the combination group who had a significant change in the clinical disease activity index; however, the C-reactive protein level was within normal range, and follow-up colonoscopy showed endoscopic remission of Crohn's disease [32]. Cullen *et al.* found no significant difference in the rate of clinical flare-ups between patients with or without immunosuppressive treatment [36]. Change in medication was also assessed in two studies [32,36] and one study claimed the number of hospitalizations after vaccination [32]. Pittet *et al.* reported seven patients who had to change their treatment after pneumococcal immunization [32]. Furthermore, three patients after influenza vaccination in the group of any type of immunosuppressive therapy had to modify their usual treatment [36]. Finally, only Pittet *et al.* reported one patient who was hospitalized for intestinal symptoms after immunization (Supplementary Data 4) [32].

3.6. Risk of bias assessment in the included studies

A detailed quality assessment of each study included in both systematic review and *meta*-analysis can be found in Supplementary Data 5.

We assessed the bias in five studies dealing with *Pneumococcus* vaccination with the ROBINS-I tool [30-34]. In the pre-intervention domains confounding bias was assessed as a serious risk in all studies. Selection bias was assessed as low risk in the included studies. Intervention domains were considered to carry a low risk of bias. In three studies, deviations of intended interventions were not reported [32-34], and two other studies were judged as having a moderate risk of bias due to significant drop out of patients [30,31]. Except for the study of Van Aalst *et al.* [33], all studies were judged to have a low risk for missing outcome data [30-32,34]. The rest of the post-intervention domains were classified as low risk of bias for all studies. Regarding the overall risk of bias, two studies were rated as carrying a serious risk of bias [30,31], and three studies were regarded as carrying a critical risk of bias [32-34]. Detailed information of bias assessment is presented in Supplementary Data 5.

Serious risk of confounding factors was found in four studies [29,35,38,40], the intervention and selection bias were assessed as low in all studies. Postintervention domains were mostly considered low risk of bias except for bias due to deviations from intended interventions because most studies did not report co-interventions and non-adherence to immunosuppressive treatment. Furthermore, missing data was also judged as a serious risk in the study of Doornekamp *et al.* [39]. The overall risk of bias was rated as serious in four studies [29,35,38,40], critical in one study [39] and moderate in two studies [36,37]. Detailed information of bias assessment is presented in Supplementary Data 5.

3.7. Certainty of evidence

Based on the GRADE analysis, the certainty of the evidence for SCR after pneumococcal immunization in patients with IBD compared to healthy controls was rated as very low. Assessment of SCR among patients with or without immunosuppressive treatment showed a low level of evidence.

The GRADE assessment of the SPR and SCR to each strain of influenza in IBD patients compared to healthy controls showed very low to low levels of evidence. SPR and SCR after influenza vaccination in patients with or without immunosuppressive treatment showed a very low level of evidence. The GRADE evidence profile is shown in Supplementary Data 6.

3.8. Publication bias

Due to the low number of included studies, we could not investigate publication bias by means of the Egger's test or the visual inspection of the funnel plots.

4. Discussion

Immunization is crucial in preventing airborne infections and their complications. In this systematic review and *meta*-analysis, the humoral immunogenicity and safety of pneumococcal and influenza vaccine in patients with IBD and healthy controls were compared. Overall, our analyses indicate that pneumococcal and influenza vaccines are generally immunogenic and safe in IBD patients, regardless of the treatment regimen. There was no significant difference in the SCR after pneumococcal and in the SPR after influenza vaccination between patients with conventional immunosuppressive monotherapy or without immunosuppressive treatment. In contrast, anti-TNF therapy was associated with a lower SCR to pneumococcal vaccination compared to patients without immunosuppressive treatment. Immunization has also been shown to be safe in patients on any type of immunosuppressive treatment, based on the low frequency of adverse events and disease exacerbation.

This is the first *meta*-analysis that focused on the serological response to Pneumococcal and influenza immunization in adults with IBD. Previous *meta*-analyses investigated pooled serological response after different vaccines in adults or children with IBD [12,14]. A previous *meta*-analysis evaluated the immune response of adult IBD patients after routine vaccination and described a lower response in patients receiving immunosuppressive therapy compared to those without immunosuppressive treatment [14]. However, the immunogenicity of different vaccines appears to be variable [8], and pooling data may not precisely reflect the effect of immunosuppressive treatment [12].

The SPR after influenza vaccination did not differ between IBD patients and healthy controls, in accordance to a previous *meta*-analysis reporting on pediatric IBD patients [12]. The SCR to pneumococcal vaccination was reduced in patients receiving immunosuppressive therapy compared with healthy controls based on the results of one study [34], however, the SCR was not lower in patients without immunosuppressive treatment similarly to the data of the *meta*-analysis reporting on pediatric IBD patients after PCV13 vaccination [12].

Previous studies have described high variability in the immune response to immunization in patients with IBD treated with various immunosuppressive medication [42,43]. Nguyen *et al.* found that patients with immunomodulator monotherapy (thiopurine or methotrexate) and anti-TNF mono- or combination therapy were less likely to develop adequate response than patients without immunosuppressive treatment. Moreover, anti-TNF agents mitigated the immune response to a greater extent than thiopurines and methotrexate [14]. Consequently, we compared the immune response in patients receiving different immunosuppressive medications to patients without immunosuppressive treatment. Our data suggest that anti-TNF treatment compromise the response to the pneumococcal vaccination but conventional immunosuppressive monotherapy does not. These results are consistent with the pediatric IBD study of Banaszkiewicz *et al.* [44]. Similarly, the existing studies did not report lower SPR after influenza immunization in patients treated with conventional immunosuppressive treatment compared to patients without immunosuppresseive treatment. This has not been analyzed in IBD, however, data on the association of conventional immunosuppressive treatment and serological response after influenza

immunization are conflicting in immunmediated diseases [45,46]. Regarding the anti-TNF mono-and combination therapy data on the seroprotection rate of patients with IBD following influenza immunization are scarce and contradicting to conclude any clinical implication.

There were only a few data available on the frequency of AEs and disease exacerbation following immunization, and therefore we were unable to perform an analysis. However, the low number of reported AEs seems to support that risk of AEs and disease flare-ups is low, and consequently, patients should not be restrained from immunization because of immunosuppressive treatment.

Some potential confounding factors were not presented in detail in the studies included, which increased the risk of bias in our analysis. One of these factors was disease activity, which potentially influences the response to immunization. Furthermore, no other chronic diseases or medications have been reported that may also affect the response to vaccination. In addition, the duration and the extension of the disease, the type of disease (CD or UC) may be potential confounding factors. Finally, the previously known infection or pre-vaccination rates were not precisely described for the analysis of the change in response rates after vaccination.

Our study has certain strengths and limitations. This is the first systematic review and *meta*-analysis focusing on response rates after pneumococcal and influenza vaccination in IBD patients and assessing the effect of different immunosuppressive treatments on the immunogenicity of these vaccines. Our *meta*-analysis has some limitations that suggest caution in interpreting the results. Firstly, all twelve studies were observational studies with small sample sizes. Secondly, most studies carried serious or critical risk of bias. Thirdly, SCR has been studied in limited studies in IBD patients and healthy controls after pneumococcal immunization, and for influenza strains H3N2 and B. Fourthly, despite the different mechanism of immunization, we pooled data from studies using PCV13 and PSV23. Fifthly, the correlates of protection are difficult to analyse for pneumococcal vaccination. Data from the studies included were pooled, however, the definition of response was different. Furthermore, there were insufficient data on serotype-specific response for separate analysis.

Our data raise some questions for further investigation. Most studies evaluated the humoral response after a relatively short time, so the long-term persistence of antibody levels remains questionable, especially in light of immunosuppressive treatment. The impact of new biologicals and small molecules on immunogenicity should be analyzed in the future. Finally, it is also a question of whether a booster or a higher dose of vaccine may increase the seroconversion rate.

In summary, our *meta*-analysis shows that patients with IBD can achieve adequate immune response to pneumococcal and influenza vaccination without safety considerations. Based on our data, conventional immunosuppressive monotherapy (without anti-TNF) is not associated with an impaired immune response to pneumococcal and influenza immunization. Anti-TNF therapy is associated with a mitigated response to pneumococcal but this is not established in case of influenza vaccination. However, more studies are needed to gather further evidence.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.02.027.

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