

IMMUNE RESPONSE TO VACCINATION IN CHILDREN AND YOUNG PEOPLE WITH INFLAMMATORY BOWEL DISEASE: A 10 YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *In the past decade, there is a notable uptrend in the incidence of IBD among the pediatric population. The immunosuppressive nature of IBD treatment may compromise the natural immune response, potentially impacting vaccination effectiveness. This study aims to provide a 10 year systematic review of post vaccination immune response in pediatric IBD patients.*

Methods: *This systematic review adhered to the PRISMA 2020 standards and included full-text English literature published between 2014 and 2024. Exclusion criteria involved editorials, review articles from the same journal, and submissions lacking a DOI. Literature was gathered from online sources such as PubMed and SagePub.*

Result: *Our search in PubMed yielded 156 articles, while SagePub produced 243 articles. Focusing on the year 2014, PubMed had 127 articles, and SagePub had 102. Ultimately we selected 6 papers that met our criteria, 3 from PubMed and 3 from SagePub.*

Conclusion: *This study concludes that the immunogenicity of certain vaccines such as PCV13, PPSV23, and rotavirus were not affected by the IBD, except for cholera. No adverse effect were found directly related to vaccination in pediatric IBD patients.*

Keyword: *Inflammatory bowel disease, vaccination, children*

INTRODUCTION

Inflammatory bowel diseases (IBD) are autoimmune disorders characterized by a complex etiopathogenesis influenced by genetic, immunologic, and environmental factors, among others. Inflammatory bowel disease is caused by a dysregulated mucosal immune response to the intestinal microflora in genetically predisposed hosts. It consists of such as Crohn's disease and ulcerative colitis. The susceptibility to IBD has been increased by the identification of over 100 genes through genome-wide association scans. However, genetic susceptibility can not completely explain the high incidence and prevalence of IBD.¹

IBD in adolescents and children accounts for approximately 30% of total IBD. In 1994, the incidence of pediatric IBD in Canada stood at 9.5 per 100,000, rising to 11.4 per 100,000 by 2005. Notably, the most significant escalation was observed among young children, with an annual increase of 5% in those under 4 years and a 7.6% rise in the 6-9 age group. North America and Europe have the highest incidence of pediatric IBD. In developing countries, its incidence is rising due to the popularization of westernized lifestyle.^{1,2}

IBD is generally diagnosed in adolescent or young adult. In the past decades, there is a notable uptrend in the incidence of IBD among the pediatric population. The classic symptoms of IBD amongst children are weight loss, abdominal pain, and bloody diarrhea. However, children may have nonclassic symptoms such as isolated poor growth, anemia, or other extraintestinal manifestations.^{2,3}

IBD among pediatric patients causes an increased risk of infection, even in cases that could be prevented with vaccines. Therapeutic goals of IBD include eradicating symptoms, normalizing the quality of life, promoting growth restoration, and preventing complications, all while minimizing the negative effects of medications. The treatment of IBD involves the use of steroids, antimetabolites, and even surgery. Children with IBD are frequently exposed to various microbes at school and in day-care centers. Malnutrition and prolonged hospital stays also contribute to the lowered immune status. Consequently, infections may occur frequently and manifest more severely in these patients.³

The European Crohn's and Colitis Organization (ECCO) recommends immunization against preventable diseases for individuals with IBD, specifically advocating adherence to the routine childhood immunization schedule with inactivated vaccines for all IBD patients. However, ECCO advises against using live vaccines in those who are immunosuppressed. ECCO strongly recommends to obtain an immunization history at the time of IBD diagnosis.⁴

The immunosuppressive nature of IBD treatment may compromise the natural immune response, potentially impacting vaccination effectiveness. In the last 10 years, only a limited number of studies have investigated immune response post vaccination (immunogenicity) in pediatric IBD patients.⁵ This study aims to provide a 10 year systematic review of post vaccination immune response in pediatric IBD patients.

METHODS

Protocol

The author followed the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 to ensure that this study adhered to the requirements. This method was chosen to guarantee the accuracy of the conclusions drawn from the inquiry.

Criteria for Eligibility

This systematic review was done by assessing evidence on post vaccination immune response in children with IBS. Evidence was compiled and analyzed thoroughly to provide an explanation and enhance the handling of patients' treatments. The primary objective of this paper is to demonstrate the relevance of the identified main points as a whole.

The inclusion criteria for this study are as follows: 1) The paper must be written in English, and 2) The studied papers include several that were published between 2014 and 2024. The exclusion criteria for this study are: 1) Editorials; 2) Submissions without a DOI; 3) Review articles that have already been published; and 4) Identical entries in published journals.

Search Strategy

We used "inflammatory bowel disease", "vaccination", "children", as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"inflammatory bowel diseases"[MeSH Terms] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "diseases"[All Fields]) OR "inflammatory bowel diseases"[All Fields] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "disease"[All Fields]) OR "inflammatory bowel disease"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR*

"vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ((ffft[Filter]) AND (fft[Filter]) AND (2014:2024[pdat])) used in searching the literature.

Data retrieval

The authors assessed studies by reviewing their abstracts and titles to determine their eligibility. We selected relevant studies based on their inclusion criteria, focusing on research that aligned with their article's objectives. A consistent trend across multiple studies led to a conclusive finding. The selected submissions were required to be in English and previously unpublished.

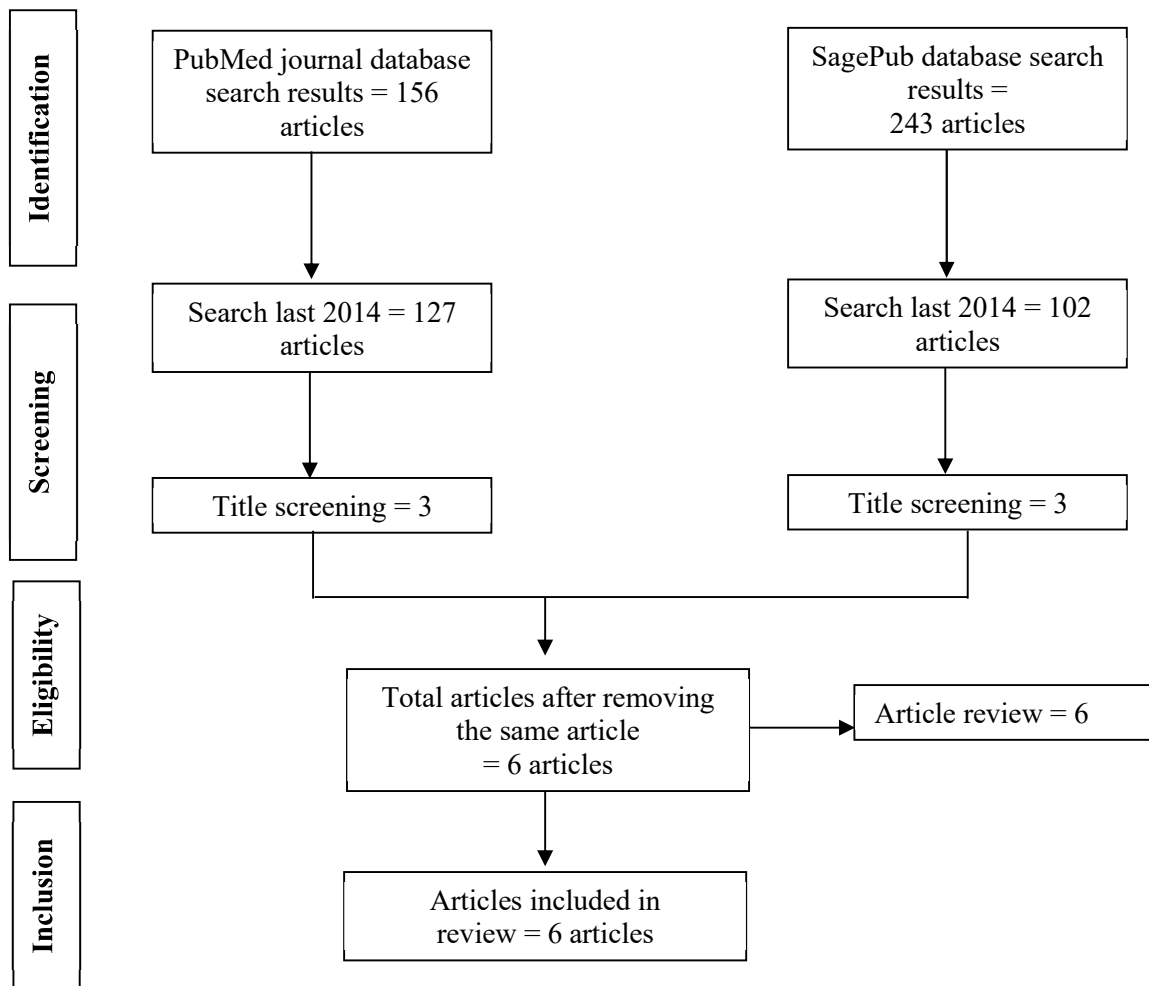


Figure 1. Article search flowchart

This systematic review only considered literatures that met all inclusion criteria and relevance to the topic. Studies not meeting these criteria were excluded, and their conclusions were not considered. The subsequent analysis delved into various details uncovered during the research inquiry, including names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author individually examined the research mentioned in the publication's title and abstract before deciding which publications to explore further. The next step involves evaluating all articles that meet the criteria set for inclusion in the review. Based on the uncovered findings, decisions will be made regarding which articles to include in the review. This criteria streamlines the process of selecting papers for further assessment, discussing the earlier investigations conducted and the elements that make them suitable for inclusion in the review.

RESULT

In our search on the PubMed database, we found 156 articles, while on SagePub, the search yielded 243 articles. Specifically, for the year 2014, PubMed produced 127 articles, and SagePub had 102. Ultimately, we selected a total of 5 papers, with 3 from PubMed and 3 from SagePub. The study includes six literatures that met the criteria, and Table 1 displays the literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Kowalska-Duplaga et al., 2018. ⁶	Multicenter	Prospective study	267 patients	A total of 267 participants, consisting of 214 children with IBD and 53 controls, were recruited for the study. None of the children had received the complete recommended routine childhood immunization schedule in Poland. Controls were found to be over four times more likely to be vaccinated compared to IBD patients, particularly with vaccines covered by insurance (OR 4.1, 95% CI 2.2–7.9).
Nguyen et al., 2017. ¹⁰	Korea	Retrospective cohort study	51 patients	A total of 51 pediatric patients diagnosed with IBD before the age of 10 and receiving antiTNF- α were identified. The age at diagnosis ranged from 15 months to 9 years. Out of these 51 patients, 67% (34/51) had documented completion of their primary vaccination series. The remaining patients either had no documentation or incomplete records of immunizations. Serological assessment specifically for Hepatitis B surface antibody revealed that 67% (27/44 patients with documented serology) did not respond

				adequately to their initial Hepatitis B vaccine series. Among the non-responders, six (6/27) had records of receiving a Hepatitis B vaccine booster and subsequent titers, with four of them achieving seroprotection. Eighteen of the non-responders (18/27) either did not receive a Hepatitis B vaccine booster or did not undergo repeat titers measurement.
Tentem et al., 2019. ⁹	Memphis, Tennessee	Retrospective study	190 patients	A retrospective review of the IBD database at Le Bonheur Children's Hospital was conducted to identify cases diagnosed between 2003 and 2015. The study included 106 out of 190 IBD patients who were on immunosuppressive drugs, and whose immunization records could be retrieved from the state database. Medical records were examined to identify infections in these patients from the time of diagnosis to the present. The age range of IBD patients in the study was 2 to 18 years. Only 4 out of 106 patients (3.7%) had received the PPSV23 vaccine, and only 1 patient (0.9%) had probable pneumococcal disease, with none having invasive pneumococcal disease. More commonly encountered infections included Clostridium difficile (11 patients) and Cytomegalovirus colitis (4 patients). All patients received the recommended PCV13 vaccine, but the majority of pediatric IBD patients did not receive the PPSV23 vaccine.
Flatt et al, 2023. ⁷	Multicenter	Cohort study	907,477 patients	Within a group of 907,477 children, 96 participants were

				<p>diagnosed with IBD, resulting in an incidence rate of 2.1 per 100,000 person-years at risk. The univariable analysis hazard ratio (HR) for rotavirus vaccination was 1.45 (95% confidence interval (CI) 0.93–2.28). After adjusting in the multivariable model, the HR decreased to 1.19 (95% CI 0.53–2.69). This study indicates that there is no statistically significant association between rotavirus vaccination and the development of IBD</p>
Liles et al., 2021. ⁸	Multi center	Cohort Study	333 patients	<p>Amongst a population of 2.4 million children aged under 10, 333 cases of IBD were identified with onset between 2007 and 2016. The crude incidence of IBD showed a slight increase over the study period (p-value for trend = 0.046). Out of the 333 cases, 227 (68%) were born before 2007. In the case-control study, 42 cases born in 2007 or later, with continuous enrollment since birth, were matched with 210 controls. The adjusted odds ratio for any rotavirus vaccination in IBD cases, when compared to the matched controls, was 0.72 (95% confidence interval 0.19–2.65).</p>
Dembinski et al., 2021. ¹¹	Multi center	Prospective study	70 patients	<p>The study assessed the seroconversion rates of anti-cholera toxin B subunit IgA and IgG in two groups: one receiving immunosuppressive (IS) treatment and the other without IS treatment (NIS). Immunogenicity was evaluated in 70 children, with 79% undergoing IS treatment. Post-vaccination seroconversion occurred in 33% of children for IgA and 70% for IgG. No</p>

				<p>statistically significant differences were observed in immune responses between the IS and NIS groups: 35% vs. 27% (p = .90) for IgA and 68% vs. 80.0% (p = .16) for IgG, respectively. There was one reported case of IBD exacerbation following vaccination.</p>
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Kowalska-Duplaga, et al.⁶ (2019) demonstrated poor vaccination status in the majority of immunocompromised children with inflammatory bowel disease, which is no different between the patients with Crohn’s disease and ulcerative colitis. There is an unmet need to implement educational vaccination strategies addressed to both physicians and patients’ families.

Nguyen, et al.¹⁰ (2018) showed that vaccinations are well-tolerated in patients with IBD. Protective immunity can be achieved in patients with IBD requiring immunosuppressive therapy. Booster vaccination can be administered to provide long-term protective immunity.

Temtem, et al.⁹ (2019) confirmed in their study that majority of pediatric IBD patients received PPSV23 vaccination. This vaccination may contribute to the low rate of invasive pneumococcal disease and nonpneumococcal infections were more common in the study population.

Flatt, et al.⁷ (2023) showed that there was no association between rotavirus vaccination and development of IBD. This study demonstrated the safety of rotavirus vaccination, even amongst the pediatric IBD population.

Liles, et al.⁸ (2021) showed an increase in IBD incidence amongst pediatric population during ten year period. This study also supports the findings that rotavirus vaccination is not associated with IBD development.

Dembinski, et al.¹¹ (2021) showed that immunogenicity of oral cholera vaccine in children with IBD was lower compared to the healthy controls. The oral cholera vaccine is safe to use in pediatric IBD patients. The treatment type does not affect the vaccine immunogenicity.

DISCUSSION

Patients with IBD have a low rate of immunization for vaccine-preventable diseases. Kowalska-Duplaga et al.⁶ (2019) found that IBD children received a lower vaccination completion compared to healthy controls. This study suggested that most important factor resulting in the extremely low immunization rate in IBD pediatric patients is the lack of reimbursement of vaccine costs. Common reasons patients have for not receiving influenza vaccination include fear of adverse effects or serious complications, belief that the vaccine is not effective, concern that the vaccine will induce an IBD flare, lack of awareness that the vaccine is indicated, belief that the vaccine is unnecessary, and, importantly, the medical care provider either did not offer the vaccine or advised against it.^{6,12}

The fear of an IBD flare as a post vaccination side effect was found amongst the population of this study. Immune response post vaccination or immunogenicity showed no significant difference between IBD patients or healthy control.⁵ Dembinski et al.⁵ (2020) found that there was no significant difference in immunogenicity between IBS pediatric patients and healthy controls. Only local adverse events such as soreness, redness, and tenderness were found near the injection sites and minor systematic symptoms such as headaches, fever, and flu-like symptoms were found. Nguyen et al.¹⁰ (2018) supported this claim and demonstrated that protective immunity can be achieved in pediatric IBD patients.^{5,10}

However, thorough examination needs to be considered in utilizing live vaccines on pediatric IBD patients receiving immunosuppression, particularly on those with severe immune defects. Immunosuppression agents such as anti-tumour necrosis factor (anti-TNF) agents, immunomodulators, or combination therapy (anti-TNF and immunomodulatory) may increase the risk of contracting infections prevented by these vaccines. Immunosuppressive therapy were usually done with prednisone >2 mg/kg or >20 mg/day, methotrexate >0.4 mg/kg/week, azathioprine >3 mg/kg/day, 6-mercaptopurine >1.5 mg/kg/day, or biologics such as tumor necrosis factor (TNF) antagonists.⁵

Pediatric IBD patients on immunosuppression may be at an increased risk of invasive pneumococcal infection. The guidelines from IDSA recommend administration of pneumococcal polysaccharide vaccine (PPSV23) to patients older

than 2 years of age with chronic inflammatory illnesses on immunosuppressive therapy, with an additional dose 5 years later. Study by Temtem, et al.⁹ (2019) showed there were no case of infectious pulmonary disease in IBD patients that received PCV13 vaccine. However, non-pneumococcal infections were frequently seen, probably because the majority of pediatric IBD patients in this study did not receive PPSV23 vaccine.⁹

Rotavirus causes acute gastroenteritis episodes (AGE) characterised by vomiting, diarrhoea, fever, and tiredness. Rotavirus is the most common cause of gastroenteritis in children under 2 years old, and remains the most common viral cause of gastroenteritis in paediatric cases globally in unvaccinated groups. Rotavirus vaccination with the live-attenuated rotavirus vaccine were given in two doses at 8 and 12 weeks of age.⁷

Live vaccination and pediatric IBD were previously suggested to incite an inflammatory trigger in the gut mucosa. However, Liles, et al.⁸ (2021) showed that rotavirus vaccination is not associated with IBD development. This statement is also supported by Flatt, et al.⁷ (2023) who demonstrated the safety of rotavirus vaccination, even amongst the pediatric IBD population. Various results regarding the correlation between IBD development and rotavirus vaccination were probably caused by disparities between the study populations where there is likely differing prevalence of infectious diseases and differences in the routine administration of the rotavirus vaccination.^{7,8}

The of traveler's diarrhea is higher among IBD patients than healthy population, particularly for those who receive immunosuppressive therapy. Travelers' diarrhea is primarily caused by enterotoxigenic *Escherichia coli* and severe infections such as cholera is caused by *Vibrio cholerae*. Effective cholera vaccines are available which targets cholera toxin subunit B (CTB). CTB shares structural and antigenic similarities with the heat-labile toxin produced by enterotoxigenic *E. coli*, which may allow the cholera vaccine to provide additional protection against travelers' diarrhea. Study by Dembinski et al., (2021) showed that oral cholera vaccine was safe to be used amongst pediatric IBD patients.¹¹

Post-vaccine anti-CTB seroconversions in healthy children have been estimated to reach as high as 81%–90% for IgA and 75%–81% for IgG. This study showed that seroconversion for pediatric patients with IBD in this study reached 33% for IgA and 70% for IgG. This demonstrated that the immunogenicity of the oral cholera vaccine in children with IBD was lower than previously observed in healthy controls. However, this study suggested that the cholera vaccine may allow IBD patients to travel more safely, hence still beneficial.¹¹

CONCLUSION

The development of IBD in children and young adult is affected by various factors. Immunosuppressive therapy of IBD may increase the risk of infections. ECCO recommended a series of vaccination to combat against preventable diseases in IBD patients. This study concludes that the immunogenicity of certain vaccines such as PCV13, PPSV23, and rotavirus were not affected by the IBD, with the exception of cholera vaccine. No serious adverse effects were directly related to vaccination in pediatric IBD patients.

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