

A COMPREHENSIVE STUDY TO INVESTIGATE THE IMMUNE RESPONSE OF VACCINATION IN CHILDREN AND YOUNG PEOPLE DIAGNOSED WITH INFLAMMATORY BOWEL DISEASE

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Abstract

Objectives: *The objective of this study was to evaluate the immune response to vaccination in children and young individuals diagnosed with inflammatory bowel disease (IBD). The vaccine response may be influenced by both the underlying disease and its treatment in patients with IBDs.*

Methods: *The review compares the immune response of IBD patients to healthy controls and explores differences between those receiving immunosuppressive therapy (IS) and non-immunosuppressive therapy (NIS). The review aims to assess immune response adequacy, adverse events, and IBD exacerbations.*

Results: *Patients with IBD exhibited diverse immune responses, with influenza B showing the lowest response rate. Immunosuppressive therapy (IS) did not significantly affect response rates compared to non-IS treatment. Lower vaccine responses were associated with IS therapy, steroid use, and certain medications. In general, there were no significant differences in immune response between IBD patients and healthy individuals, except for lower responses to influenza B and hepatitis B vaccines. Adverse events following vaccination were well tolerated, with similar rates in IBD patients and healthy controls. Vaccination had limited impact on disease activity, with only a few isolated cases of IBD exacerbation reported.*

Conclusions: *The immunogenicity of vaccinations in children and young individuals with inflammatory bowel disease (IBD) is comparable to that of healthy individuals, and there is no significant difference in immune response between patients with IBD receiving immunosuppressive (IS) therapy and those without it. However, more research is required to thoroughly investigate this topic, as there are limited well-designed studies available.*

BACKGROUND

Autoimmune conditions such as Crohn's disease and ulcerative colitis fall under the category of inflammatory bowel diseases (IBDs), with their etiology involving genetic, immunological, and environmental factors, among others. The increasing prevalence of IBD in the 20th century can be attributed to a Western-style lifestyle, which acts as a significant contributing factor to the development of IBD. Additionally, there is also a noticeable rise in the incidence of IBD among children.¹

Children and young individuals diagnosed with inflammatory bowel disease (IBD) face an elevated susceptibility to various infections, including those preventable through vaccination. This increased risk primarily stems from the utilization of immunosuppressive (IS) therapy, which encompasses the use of steroids, antimetabolites, and biologics. Their immune status may also be compromised by factors such as malnutrition, surgeries, and prolonged hospital stays. Additionally, the risk of infection is further heightened by the fact that children with inflammatory bowel disease (IBD), much like their healthy peers, spend extensive hours in schools and daycare centers, exposing them to numerous microbes. Consequently, patients with inflammatory bowel disease (IBD) may frequently experience various types of infections that could manifest with more severe symptoms. It is worth noting that infection is a well-established factor that can trigger flare-ups in individuals with inflammatory bowel disease (IBD).^{1,2}

It is crucial to prioritize the protection of children and young individuals with inflammatory bowel disease (IBD) against infections for the aforementioned reasons. As a result, a committee established by the European Crohn's and Colitis Organization (ECCO) has emphasized the significance of immunizing patients with inflammatory bowel disease (IBD) against vaccine-preventable diseases. According to European Crohn's and Colitis Organization (ECCO), it is recommended that all patients with IBD adhere to the routine childhood immunization schedule for inactivated vaccines, while refraining from administering live vaccines to those with compromised immune systems. It is strongly advised to obtain a complete immunization history upon inflammatory bowel disease (IBD) diagnosis.¹ However, the immunosuppressive nature of IBD treatment may potentially affect the natural immune response following vaccination and impact its efficacy. ECCO underscores the need for further research to assess the immune response to various vaccine types in patients with inflammatory bowel disease (IBD). To date, only a limited number of studies have investigated the immunogenicity, or post-vaccination immune response, in pediatric patients with inflammatory bowel disease (IBD).² The objective of this study was to conduct a comprehensive analysis of available data regarding the immunogenicity of vaccines in children and young individuals with inflammatory bowel disease (IBD). Furthermore, we examined the impact of immunosuppressive (IS) therapy on the immunogenicity within this specific patient population.

Material

This study comprises review of published data on the immune response to vaccination in children and young individuals with inflammatory bowel disease (IBD). The inclusion criteria considered all relevant studies, letters, and abstracts that provided adequate data, irrespective of randomization and control types. However, the review excluded *in vitro* and animal models, vaccinations administered to individuals without inflammatory bowel disease (IBD), studies focusing on immunological status and patient awareness, as well as guidelines and opinions.

The participants included in this study were children and young individuals who had received a diagnosis of inflammatory bowel disease (IBD) at the time of their enrollment. In the context of this review, the term "young people" encompassed both adolescents and youth aged 10 to 24, as defined by the World Health Organization. The participants could be undergoing any form of treatment, including immunosuppressive (IS) therapy or non-immunosuppressive (NIS) therapy. Studies exclusively involving adults were not considered for analysis in this study.

The assessment focused on evaluating the immune response to primary or booster vaccinations, as well as vaccination series. However, experimental and therapeutic vaccine trials were excluded from the analysis. The control groups were healthy children and young people, and/or patients without immunosuppressive (IS) therapy.

The main objective of this study was to determine the attainment of a sufficient immune response following vaccination, which was defined as surpassing the specified antibody concentration for each specific vaccine. The study compared outcomes between individuals with inflammatory bowel disease (IBD) and healthy controls, as well as between patients with inflammatory bowel disease (IBD) undergoing immunosuppressive (IS) therapy and those receiving non-immunosuppressive (NIS) therapy. Additionally, the study evaluated the occurrence of adverse events and inflammatory bowel disease (IBD) exacerbations following vaccination, if such data were available.

Results

The included studies spanned from 2007 to 2020 and were predominantly conducted in North America (11 in the United States and 1 in Canada) or Europe (5 in Poland, and 1 each in Germany, the United Kingdom, and Turkey). More than half of the studies were full-text publications, while the remaining studies comprised abstracts, letters, and one instance of a series of varicella vaccinations. The studies exhibited notable heterogeneity in terms of interventions, which was expected due to the diverse range of vaccines examined. The majority of studies focused on the hepatitis B virus (HBV, 6 out of 20), hepatitis A virus (HAV, 3 out of 20), and influenza vaccines (4 out of 20), while the remaining vaccines were assessed in individual trials. Inactivated vaccines were predominantly used, with the exception of three studies that

employed attenuated varicella vaccines. The studies demonstrated relative homogeneity in terms of population characteristics, with median ages of patients ranging from 9 to 19 years old and diagnoses including Crohn's disease, ulcerative colitis, or indeterminate inflammatory bowel disease (IBD).² One study included children (2 out of 15) with autoimmune hepatitis, but it was excluded from the study. More than half of the studies (11 out of 20) were conducted without a control group, assessing post vaccination immune response within the entire group of inflammatory bowel disease (IBD) patients, sometimes by referencing vaccine historical or registration data for the general population. In 5 studies, immune response was compared between patients receiving immunosuppressive (IS) treatment and those without IS treatment, while 8 studies incorporated a control group of healthy children.²

The immune response to vaccination varied among patients with inflammatory bowel disease (IBD), ranging from 39% to 100% exhibiting an adequate response. The lowest rate of immune response was observed for influenza B. Comparatively, healthy controls demonstrated higher immune response rates, ranging from 53% to 100%. A similar pattern was observed when comparing patients with and without immunosuppressive (IS) therapy, with 29% to 100% of those receiving immunosuppressive (IS) therapy exhibiting adequate immunogenicity, compared to 42% to 100% of those without immunosuppressive (IS) therapy. The publications also highlighted various factors that were associated with lower vaccine immune response, including IS therapy, steroid treatment, infliximab treatment with higher frequency, biological and combination treatment, as well as the presence of inflammatory bowel disease (IBD) alone, as reported by the authors. Eight studies were included in the analysis to evaluate the impact of inflammatory bowel disease (IBD) on post-vaccination immune response. Among these studies, half of them specifically focused on influenza vaccines. The study was conducted by categorizing this studies into subgroups based on the vaccine type, comparing IBD patients with healthy subjects. The findings revealed that except for a lower immune response observed in IBD patients against the influenza B serotype (OR = 0.45, 95% CI = 0.29–0.70) and a single study on the hepatitis B vaccine, which also showed reduced immunogenicity in this group (OR = 0.32, 95% CI = 0.12–0.86), there were no significant differences in immune response between healthy children and those with IBD. The overall analysis indicated a slightly better post-vaccination immune response in healthy subjects compared to IBD patients, although the difference did not reach statistical significance (OR = 0.73, 95% CI = 0.45–1.17).

The analysis included six studies, with four of them specifically examining influenza vaccines, to evaluate the post-vaccination immune response in patients receiving immunosuppressive (IS) therapy. Similar to the comparison between patients with inflammatory bowel disease (IBD) and healthy subjects, the only significant difference observed was a weaker immune response to the influenza B serotype in the immunosuppressive (IS) therapy group (OR = 0.34, 95% CI = 0.13–0.95). Likewise, when analyzing the effect of immunosuppressive (IS) treatment on vaccine response, there was a statistically non-significant trend indicating better immunogenicity in patients not receiving immunosuppressive (IS) therapy (OR = 0.65, 95% CI = 0.41–1.03).

Out of the total studies reviewed, only nine of them examined adverse events following vaccination. Overall, the administration of vaccines was well tolerated. Local adverse events, such as soreness, redness, and tenderness at the injection site, were observed in up to 43% of vaccinated patients. Minor systemic effects, including headaches, fever, and flu-like symptoms, were reported in less than 6% of cases. The incidence of adverse events in healthy controls was similar to that in patients with inflammatory bowel disease (IBD), regardless of the type of treatment utilized.

The impact of vaccination on disease activity was assessed in five studies. However, no statistically significant differences were observed between pre- and post-vaccination disease activity scores. Throughout the follow-up period, there were five isolated cases of inflammatory bowel disease (IBD) exacerbation. It is challenging to determine the exact effect of the vaccine on these exacerbations. In two cases, the patients had already shown signs of disease activity before vaccination, and in another case, the patient was in the process of tapering off steroids. The researchers and monitoring authorities concluded that it is unlikely that the vaccines were the cause of these inflammatory bowel disease (IBD) exacerbations.

Discussion

In this review, we assessed the immunogenicity of vaccination in pediatric patients with inflammatory bowel disease (IBD). Interestingly, this findings revealed that there was no notable disparity in post vaccination immunogenicity between healthy children and patients with inflammatory bowel disease (IBD), irrespective of the type of therapy they had received. This study provides valuable insights into the immunogenicity of vaccination in this specific population for the first time. Contrary to the findings of the previous review and analysis conducted by Nguyen et al, which focused on the impact of immunosuppressive (IS) medications on post vaccination immune response in adults with inflammatory bowel disease (IBD), this results present a different perspective.⁵ Nguyen et al included 9 studies that evaluated the effectiveness of 4 different vaccines (HAV, HBV, influenza, and Streptococcus pneumoniae) in their analysis. They concluded that individuals receiving any form of immunosuppressive (IS) therapy had a 59% lower likelihood of achieving adequate seroprotection.⁵ Moreover, the groups on anti-tumour necrosis factor (anti-TNF) agents, immunomodulators, or combination therapy (anti-TNF and immunomodulatory) exhibited a 68%, 37%, or 65% lower probability, respectively, of achieving an adequate immune response compared to those not receiving immunosuppressive (IS) therapy. This findings diverge from these results.^{3,5}

The different outcomes observed in this study can be attributed to several factors. Firstly, there seems to be a higher immunogenicity of vaccines in children compared to adults, although the exact reasons for this remain unclear. Children and young individuals are constantly exposed to infections, which may contribute to their more responsive immune systems.² A study by Gisbert et al, examining the effectiveness of HBV vaccination in inflammatory bowel disease (IBD) patients, identified patient age as a significant factor influencing the response rate. Secondly, the disparity in post-vaccination immunogenicity between children and adults could be due to the longer duration of disease in adults, often associated with a higher incidence of surgeries that can compromise the patients' immune status.⁷ Additionally, the prolonged use of immunosuppressive (IS) therapy in adults, known to impact immune response to vaccines in inflammatory bowel disease (IBD) patients, might contribute to the variations in immunogenicity. However, the exact mechanisms behind this impairment are not yet fully understood, and most studies evaluating vaccine immunogenicity in inflammatory bowel disease (IBD) patients do not report the duration of therapy. Further research is needed to assess the influence of therapy duration on vaccine response. Lastly, the type of vaccine administered may also play a role in post-vaccination immunogenicity.^{7,8} For instance, vaccines against HAV have shown high seroconversion rates, reaching up to 97.6% in adults (Park et al) and 97% in children (Radzikowski et al). In contrast, the immunogenicity of influenza vaccines can be lower, ranging from 44% to 64%.^{8,9} The varying immune responses to different vaccines have prompted international committees on inflammatory bowel disease (IBD) to recommend evaluating vaccine response in this patient population. Moreover, Nguyen et al, who focused on adult inflammatory bowel disease (IBD) patients, used stricter inclusion and quality assessment criteria due to the availability of more studies in adults. They also employed a slightly different statistical method assuming less heterogeneity in their analysis.⁵

The influenza vaccination studies were the most extensive and well-designed in this analysis. The quantitative analysis clearly highlighted their significance and demonstrated a stronger impact compared to the overall analysis. These studies revealed comparable immunogenicity for influenza A, but a notably weaker response for influenza B in both patients receiving IS treatment and patients with IBD in general.⁴ This finding aligns with observations in healthy children, where lower immunogenicity to the B serotype has been observed. On the other hand, studies involving adults with IBD showed a reduction in immunogenicity among patients receiving IS therapy, but without specific emphasis on serotype B. Additionally, studies involving children receiving IS treatment for reasons unrelated to IBD showed similar or non-significantly different immunogenicity across all serotypes.⁴ Ogimi et al. demonstrated higher type-B antibody titers in patients with rheumatic diseases receiving IS treatment compared to healthy controls. Similarly, in studies involving adults, three analyses on influenza vaccine immunogenicity in patients with systemic lupus erythematosus and rheumatoid arthritis undergoing IS therapy reported comparable seroprotection rates.¹⁰ The immunogenicity of influenza vaccines in patients with IBD or receiving IS therapy varied across serotypes. Studies indicated that immunogenicity was either significantly decreased for H1N1 and H3N2 vaccination, or not significantly different for influenza B, compared to healthy controls. These inconsistencies could be attributed to the nature of the influenza vaccine itself, as it incorporates different strains each year, making direct comparisons between studies challenging. Additionally, factors such as reduced immunogenicity of the B antigen component or lower sensitivity of hemagglutination inhibition in assessing serologic responses to the influenza B virus may also contribute to the observed variations.^{6,10}

Conclusions

There is no significant difference in the immunogenicity of vaccinations between children and young people with IBD compared to healthy individuals. Similarly, the immune response to vaccination in patients with IBD receiving IS therapy is not significantly lower than those without IS therapy. However, due to the limited number of well-designed studies available, further investigation is needed to explore this issue in more depth.

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