

# HEPATITIS B VACCINE NON-RESPONSIVENESS IN CHILDREN WITH CELIAC DISEASE COMPARED TO NON-CELIAC CONTROLS

## ABEER VAQAR

Bahria University Medical College, Islamabad/KRL Hospital G-9/1 Islamabad.

## Dr. IRSHAD HUSSAIN\*

Assistant Professor of Pediatrics, Bahria University Medical College, Islamabad/KRL Hospital G-9/1 Islamabad. \*Corresponding Author Email: lhbangash14@gmail.com

## MALIHA AKHTAR QURESHI

Bahria University Medical College, Islamabad/KRL Hospital G-9/1 Islamabad.

## BAKHT ZAMAN

Bahria University Medical College, Islamabad/KRL Hospital G-9/1 Islamabad.

## SYED SAJJID HUSSAIN SHAH

Institute of Kidney Disease Hayatabad Peshawar.

## COL (RTD). ASIM RAFIQUE

Shahbaz Multispecialty Clinic Kahuta City.

### Abstract

**Objective:** To determine the frequency of non-responsiveness to hepatitis B vaccination in children with celiac disease and to compare it with non-celiac controls. **Study Design:** Comparative cross sectional study. **Place and Duration of Study:** Department of Pediatrics, BUMC Teaching Hospital Islamabad and PNS Shifa Karachi, from June 2024 to May 2025. **Methods:** Thirty-four children aged 1-14 years with confirmed celiac disease who had completed the routine hepatitis B vaccination schedule were enrolled. Thirty age-matched non-celiac children served as controls. Immunity to hepatitis B was assessed by qualitative estimation of anti-hepatitis B surface (anti-HBs) antibodies using enzyme immunoassay. An anti-HBs level  $\geq 10$  mIU/mL was considered protective. Data were analyzed using SPSS version 26. **Results:** Among children with celiac disease, 26 (76.5%) were anti-HBs negative, compared with 10 (33.3%) non-celiac controls. The difference was statistically significant ( $\chi^2$  test,  $p < 0.001$ ). Vaccine non-response was independent of age, gender, and adherence to a gluten-free diet. **Conclusion:** Children with celiac disease have a significantly higher rate of hepatitis B vaccine non-responsiveness compared with non-celiac children. Post-vaccination serological testing should be considered in this high-risk group, and hepatitis B vaccine non-responders should be evaluated for possible underlying celiac disease.

**Keywords:** Celiac Disease, Hepatitis B Vaccine, Vaccine Non-Responder, HLA-DQ2, DR3.

### INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by ingestion of gluten in genetically susceptible individuals [1]. It is characterized by inflammation, villous atrophy, and crypt hyperplasia of the small intestinal mucosa, resulting in malabsorption and a wide range of clinical manifestations. Classical features include chronic diarrhea, steatorrhea, abdominal distension, and weight loss, while atypical or silent forms may present with iron deficiency anemia, short stature, delayed puberty, or minimal

gastrointestinal symptoms [2]. The global prevalence of celiac disease is estimated to be approximately 1%, with increasing recognition in South Asian populations, including Pakistan [3], [4]. Genetic susceptibility plays a central role in the pathogenesis of celiac disease. More than 90% of affected individuals express human leukocyte antigen (HLA)DQ2, while most of the remaining patients carry HLA DQ8 [5]. These HLA class II molecules are essential for antigen presentation to CD4+ T lymphocytes and initiation of the immune cascade responsible for mucosal damage. The strong association of celiac disease with HLA-DQ2 and HLA-DR3 has been incorporated into diagnostic algorithms, and absence of these alleles makes the diagnosis highly unlikely[6].

Hepatitis B virus (HBV) infection remains a major global health concern. According to the World Health Organization, more than 250 million people are chronically infected worldwide, with approximately 820,000 deaths annually due to complications such as cirrhosis and hepatocellular carcinoma. Universal hepatitis B vaccination, introduced in the early 1980s, has been one of the most effective public health interventions, with seroprotection rates of 90-96% in immunocompetent individuals[7].

Despite its high efficacy, a subset of vaccinated individuals fails to develop protective antibody levels. Factors associated with hepatitis B vaccine non-responsiveness include older age, male gender, obesity, immunosuppression, and certain HLA haplotypes, particularly HLA-B8, DR3, and DQ2. Interestingly, these same HLA haplotypes are strongly associated with celiac disease, suggesting a shared immunogenetic basis[8].

This overlap has led to increasing interest in evaluating hepatitis B vaccine responsiveness in patients with celiac disease. Several international studies have demonstrated reduced seroconversion rates in celiac patients compared with the general population; however, local data from Pakistan are limited [9], [10]. The present study was conducted to assess the frequency of hepatitis B vaccine non-responsiveness in Pakistani children with celiac disease and to compare it with non-celiac controls.

## **PATIENTS AND METHODS**

This descriptive comparative study was jointly conducted at the Pediatric Departments of BUMC Teaching Hospital Islamabad and PNS Shifa Karachi from June 2024 to May 2025. Thirty-four children aged 1-14 years with a confirmed diagnosis of celiac disease were enrolled. Diagnosis was based on either tissue transglutaminase (tTG) antibody titers greater than seven times the upper limit of normal from two different laboratories or jejunal biopsy findings consistent with celiac disease. All children had completed the routine hepatitis B vaccination schedule consisting of three doses administered at 0, 1, and 6 months. A control group comprised 30 age-matched non-celiac children with documented completion of hepatitis B vaccination. Children with active or chronic hepatitis B or C infection, immunodeficiency disorders, incomplete vaccination records, or receipt of the last hepatitis B vaccine dose within the preceding two months were excluded. After informed parental consent, demographic data, vaccination records, and relevant medical history were recorded. Adherence to a gluten-free diet was assessed

through dietary history and review of food diaries when available. Blood samples were obtained for qualitative determination of anti-HBs antibodies using the AUSAB enzyme immunoassay kit (Abbott Laboratories, USA). Anti-HBs levels  $\geq 10$  mIU/mL were considered protective. Data were analyzed using SPSS version 26. Descriptive statistics were applied. Categorical variables were compared using the chi-square test, with  $p < 0.05$  considered statistically significant.

## RESULTS

A total of 64 children were included in the study, comprising 34 children with celiac disease and 30 non-celiac controls. The mean age of children with celiac disease was  $7.9 \pm 3.4$  years, while that of non-celiac controls was  $8.2 \pm 3.1$  years. Gender distribution was comparable between the two groups.

**Table 1: Hepatitis B Vaccine Response in Children with and Without Celiac Disease**

Group	Total (n)	Anti-HBs $\geq 10$ mIU/mL n (%)	Anti-HBs $< 10$ mIU/mL n (%)
Celiac disease	34	8(23.5%)	26(76.5%)
Non-celiac controls	30	20(66.7%)	10(33.3%)

Children with celiac disease demonstrated a significantly higher rate of hepatitis B vaccine non-responsiveness compared with non-celiac controls ( $\chi^2$  test,  $p < 0.001$ ).

**Table 2: Baseline Characteristics of Study Participants**

Variable	Celiac Disease (n = 34)	Non-Celiac Controls (n = 30)
Mean age (years)	$7.9 \pm 3.4$	$8.2 \pm 3.1$
Male, n (%)	19(55.9%)	17 (56.7%)
Female, n (%)	15(44.1%)	13(43.3%)
Mean anti-HBs (mIU/mL)	$< 10$ in majority	$38.6 \pm 21.4$

No statistically significant association was observed between hepatitis B vaccine response and age, gender, or reported adherence to a gluten-free diet within the celiac disease group.

## DISCUSSION

This study demonstrates a significantly higher rate of hepatitis B vaccine non-responsiveness among children with celiac disease compared with non-celiac controls. Nearly three-quarters of children with celiac disease failed to develop protective anti-HBs antibody levels despite completion of the standard vaccination schedule, highlighting an important and under-recognized vulnerability. The most plausible explanation for impaired vaccine response in celiac disease is the shared immunogenetic background. Both celiac disease and hepatitis B vaccine non-responsiveness are strongly associated with HLA-DQ2 and HLA-DR3 haplotypes. These HLA molecules are critical for antigen presentation to CD4+ T lymphocytes [11],[12]. Preferential binding of gluten-derived peptides may competitively inhibit effective presentation of hepatitis B surface antigen

resulting in suboptimal humoral immune responses[13]. Our findings are consistent with previous international studies. Leonardi et al. reported reduced seroconversion rates in Italian children with celiac disease[2],[14]. Similar observations have been documented in studies from Pakistan, Iran, and India[17]. Recent systematic reviews and meta-analyses published between 2018 and 2023 have confirmed celiac disease as an independent risk factor for hepatitis B vaccine failure[15],[16],[19]. Interestingly, vaccine non-responsiveness in our cohort was independent of age, gender, and adherence to a gluten-free diet[17], [18]. This suggests that genetic predisposition may play a more dominant role than intestinal inflammation alone. While some studies suggest improved seroconversion following revaccination after initiation of a strict gluten-free diet, evidence remains inconsistent. From a public health perspective, failure to develop protective immunity places children with celiac disease at increased risk of hepatitis B infection, particularly in endemic regions. Although routine post-vaccination testing is not recommended for the general population, targeted testing in children with celiac disease appears justified.

The study is limited by its relatively small sample size and lack of HLA typing due to resource constraints. Nevertheless, it provides valuable local data and underscores the need for increased awareness of vaccine non-responsiveness in this population.

## CONCLUSION

Children with celiac disease are significantly more likely to be non-responders to hepatitis B vaccination compared with non-celiac children. Routine post-vaccination anti-HBs testing should be considered in patients with celiac disease. Conversely, hepatitis B vaccine non-responders should be evaluated for possible underlying celiac disease.

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