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# IMPACT OF HEPATITIS B GENOTYPES AND TIME OF VACCINE LAST DOSE ON VACCINE BREAKTHROUGH INFECTIONS AMONG VACCINATED SUBJECTS IN BAUCHI STATE, NIGERIA

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## ABSTRACT

Hepatitis B Virus (HBV) infection is a global public health concern. It contributes significantly to liver cirrhosis and hepatocellular carcinoma. The introduction of HBV vaccination into the national immunization program has reduced its incidence. However, breakthrough infections have been reported among vaccinated individuals. This study explored the pattern of HBV genotypes associated with vaccine breakthrough infections in Bauchi metropolis emphasizing on waning down of immunity with time. A cross-sectional study of one hundred and ninety six vaccinated males and females within the ages of 1 year to 50 years that had received at least 2 doses of HB vaccine was investigated. The study aimed at investigating pattern of HB vaccine breakthrough infections focusing on the relationship between immunogenicity and time of last dose of vaccine. Vaccine immunogenicity titre was determined by ELISA. Seromarkers were determined, the HBV DNA genotypes of those positive for HBsAg were tested and characterized by polymerase chain reaction. Result indicated that individuals within the ages of 1-10 years had 61% vaccine optimal response, while subjects above 10 years had lower rate of vaccine response. Subjects who received vaccine last dose 1 year to 5 years ago had 64.9% immunogenicity, while those with over five years vaccine last dose showed low rate. Similarly, 3.5% vaccine breakthrough infection was detected, and all had mixed genotypes B and E. This infers that exposure to HBV genotypes B and E may cause breakthrough infection among vaccinated subjects. There is a need for diagnosing hepatitis B infection to genotype level.

**Keywords**: Hepatitis B virus, Breakthrough infection, Hepatitis B genotypes, Vaccine.

## INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health challenge, despite the widespread implementation of vaccination programs (Gong *et al*., 2024). The HBV vaccine, based on recombinant hepatitis B surface antigen (HBsAg), has significantly reduced the incidence of infection worldwide. However, breakthrough infections cases where vaccinated individuals still acquire HBV pose a growing concern. Vaccine breakthrough infection has been defined as detection of HBV DNA or HBsAg in an individual who previously completed the recommended hepatitis B vaccine series (Qiu *et al*., 2024). This infection is often associated with viral genetic diversity, particularly the distribution of HBV genotypes and the emergence of vaccine escape mutants (Wong *et al*., 2021). HBV is classified into at least ten genotypes (A–J), each with distinct geographic distributions and clinical implications. Genotype A predominates in Africa and Europe, genotype B and C in Asia, genotype D in the Mediterranean region, and genotype E in West Africa. These genotypes influence disease progression, treatment response, and the likelihood of vaccine breakthrough infections (Inoue and Tanaka, 2020).

Vaccine Breakthrough Infection (VBI) has been referred to a phenomenon where HB Virus evades vaccine-induced immunity and establishes infection Zadeh (*et al*., 2025). However, other mechanisms have been implicated in contributing to the breakthrough infections scenario such as Waning immunity, where Anti-HBs antibody levels decline over time, especially in individuals vaccinated during infancy (CDC, 2022; Mironova and Ghany, 2024). Some studies suggest that protective immunity may wane after 15-20 years without booster doses (Zadeh *et al*., 2025). Vaccine escape mutations: Mutations in the "a" determinant region of the HBsAg (amino acids 124-147). Mutation within this region, particularly G145R and D144A, alter antigenicity and reduce neutralization by vaccine-induced antibodies (Usman *et al.*, 2024). Also, Genotype variation: HBV genotypes vary in their ability to develop escape mutations. Genotypes C and D, prevalent in Asia and the Middle East are more frequently connected with breakthrough infections. Besides, host factors has been accused as another predisposing factors where Immunocompromised individuals, such as those with HIV or undergoing chemotherapy, are more susceptible to breakthrough infections despite vaccination (El-Mowafy *et al*., 2024).

Epidemiologically, recent studies suggest that HBV genotypes influence the frequency and nature of vaccine escape mutations. Genotype D has been frequently associated with breakthrough infections in Europe and the Middle East. Genotype C shows higher mutation rates in Asia, contributing to vaccine escape. While Genotype E has been reported to be prevalent in West Africa, and has been linked to unique mutations that may compromise vaccine efficacy (Inoue & Tanaka, 2020). These genotype-specific differences highlight the importance of monitoring HBV genetic diversity in vaccinated populations.

Clinical manifestations of breakthrough infections may involve: occult, low-level viremia (HBV DNA positive with negative HBsAg) to acute symptomatic hepatitis and, in some cases, progression to chronic infection (Wong *et al.*, 2021). The clinical course depends on age at infection, immune status, viral genotype, and presence of escape mutations. For

breakthrough infections can be occult, reliance on HBsAg testing alone may miss cases; combined testing (anti-HBs, HBsAg, and HBV DNA) is recommended when breakthrough is suspected, particularly in high-risk or immunocompromised individuals (Abegas, 2021). The emergence of vaccine escape mutants underscores the need for continuous surveillance of HBV genotypes. Breakthrough infections can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma, undermining vaccination efforts (Gong *et al*., 2024). Therefore, understanding genotype-specific patterns involved in breakthrough infection with focus on vaccine wane down is critical for refining vaccine strategies, developing next-generation vaccines, and ensuring global HBV control.

## MATERIALS AND METHODS

Cross-sectional design was used in this study. The prevalence of hepatitis B vaccine breakthrough was used in determining the sample size which is between 1-10% and 196 subjects were recruited with 5% α level and 99% strength were considered as confidence levels. In collecting the samples, random sampling technique was employed. A structured questionnaire, assent form for minors and consent forms were used for demographic information. Ethical approval was obtained from the Bauchi ministry of health. Study population included vaccinated subjects of both sexes within the ages of 1 year to 60 years who resident in Bauchi metropolis at the time of this investigation and have been vaccinated with at least 2 doses of HB vaccine.

### Sample Collection and Analysis

Five milliliters (5ml) of venous blood was collected from 196 vaccinated subjects selected through randomized sampling technique. The blood samples collected were transferred into a plain tube and lightly centrifuged for 2 minutes at 1500 rpm. The serum was separated and used first to detect all the 5 seromarkers of hepatitis B as indicated in Table 1. Those found positive for hepatitis B surface antigen were further subjected to molecular assay for the detection and characterization of HB genotypes using multiplex polymerase chain reaction.

### Detection of Hepatitis B Sero-markers using 5-Panel Kit

Serum specimens were tested for HB five seromarkers using 5 in One (Combo) Test Panel obtained from GIMA Laboratories, No. 30, Area 9, Douda Avenue, Fangshan Distric Beijing, 102433 China with Lot No. 20201125. The specimens were mixed well prior to assay. The pouches were opened at the notch and the device removed. Each test device was appropriately labeled with the samples' identification numbers and placed on a clean, flat surface. A 100 microliter serum was applied on the sample hole using pipette. A drop of 0.9% normal saline was added to the sample well for easy migration, and results were read within 15 minutes. Interpretation of result: negative result: Any sample that developed pink band only in the control (C), it was considered negative, while any sample that developed band on both the control (C) and test (T) path was considered positive. Whereas, sample that did not develop band in the control (C) path but only in the test (T), was considered invalid and the test was repeated.

### Determining HBsAb Level by ELISA Method

This was carried out by ELISA technique. Well One of the micro titre plate was assigned for blank control, well two was reserved for positive control, while well 3 was for negative control according to the manufacturer's instruction. Fifty microliter (50*uL)* of each the controls were added to the appropriate well, and Fifty microliter (50*u*L) of HBsAg Peroxidase was pipetted into each well save for the blank. The titer plate was tapped gently for about 3 minute for homogeneity. The plate was incubated in water bath for 1 hour at 37ºC. After the one hour, the plate was washed 3 times. Equal volume of solution A and B (TMB) were mixed in a clean tube and a 100uL was added to each well including the blank. The preparation was covered with a dark cover and incubated for 30 minutes at room temperature. A 100 *u*L of $2NH_2SO_4$ to each well including the blank to stop the reaction, and within 30 minutes, the absorbance of both the controls and the test samples were determined with photocholorimeter at 450*nm* reading wavelength with 620-690nm reference wavelength. The blank sample was used to blank the photometer. Then results were determined by calculating it based on the manufacturer's instructions. According to the WHO, HBsAb ≥ 10mIU/mL is considered optimal vaccine response; ≤10mIU/mL is suboptimal vaccine response, while non-detectable antibody (0IU/mL) is considered vaccine non response.

### Detection and Characterization of Hepatitis B Genotypes

The Genotyping principle was based on multiplex nested PCR assay. This PCR technique characterizes HB genotypes following a previous technique described by Naito *et al.,* (2001) for the detection of HB genotypes forward primer: GAGTCTAGACTCGTGGTGGACT-3', and reverse primer: 5'CGTGTGCACTTCGCTTGTC-3', were used. The volume of PCR reactions was 20 µl. Round one of the PCR reaction consisted of; 2 µl of 1st Round universal Primers, 2 µl of DNA extracted and 16 µl of $DH_2O$ which made the volume of 20µl. Thermal cycler PTC 100, MJ Research PCR machine was used.. The conditions of the reaction were: Pre-denaturation at 95$^O$C for 5minutes, Denaturation at 94$^O$C for 40 seconds, Annealing at 54$^O$C for 49 seconds, Extension at 72$^O$C for 40 seconds at 35 cycles and the final extension was 5 minutes at 72$^O$C. Also, the PCR second reactions were; pre-denaturation at 94$^O$C 5 minutes, denaturation at 94$^O$C 20 seconds, annealing at 59$^O$C 20 seconds and extension at 72$^O$C 30 seconds for 15 cycles. The PCR reaction products were conducted on 1.5 percent agarose gel electrophoresis tat provides genotype-specific base pair (bp). Standard Genotype-specific base pair ladder was used to interpret the results. For each genotype has a specific mobility distance. The PCR bands were then visualized using UV trans-illuminator box, (Biorad). The sizes of PCR products were estimated according to the migration pattern of a 100bp DNA ladder. The HBV genotypes were determined according to the amplified size of PCR product.

### Statistical Analysis

The statistical package of social science version 23 was used to analyze the generated data. Both the qualitative and quantitative data were analyzed using Chi-Square, ANOVA and Correlations analysis (frequency and proportion). The correlations between antibody levels and ages were carried out and the $P \leq 0.05$ was considered significant. In the analysis of the data as stated below under the statistical analysis, Percentages and frequency distributions were used to describe the baseline characteristics.

## RESULTS AND DISCUSSION

The sero-prevalence of hepatitis B infection among the vaccinated indicated 3.5% (HBsAg). Because hepatitis B surface antigen positive rate is used as index in determining prevalence of hepatitis B infection. Hepatitis B core antibody (BcAb) was 14%, which is a marker for exposure to hepatitis

B virus, although not necessarily infection. Only 2% was found to be positive for HBeAb. All these low rates could be attributed to HB vaccine efficacy in the vaccinated population, which implies that the vaccine reduces the rate of exposure to HBV. Similar, 82% of the vaccinated subjects had evidence of vaccine response in circulation. This high rate of antibody evidence against HB infers the efficacy of the vaccine to stimulate immunogenicity against HB infection to some certain level as shown in Table 1.

**Table 1: Rates of Hepatitis B Sero-markers among the Vaccinated Subjects in Bauchi**

| | STUDY GROUPS | | | |
|---|---|---|---|---|
| **HBV Markers** | **No. Tested** | **No. Positive (%)** | **No. Negative (%)** | **P ≤ 0.05** |
| HBsAg | 196 | 7(3.5) | 189(95) | 0.001 |
| HBsAb | 196 | 161(82) | 37(18.9) | 0.02 |
| HBeAg | 196 | 7(3.5) | 189(196) | 0.04 |
| HBeAb | 196 | 4(2) | 188(95) | 0.06 |
| HBcAb | 196 | 27(14) | 169(88) | 0.03 |

HBsAg-Hepatitis B surface Antigen, HBsAb-Hepatitis B surface Antibody, HBeAg-Hepatitis B envelope Antigen, HBeAb-Hepatitis B envelope Antibody, HBcAb-Hepatits B core Antibody.

On the analysis of the relationship between vaccine immunogenicity and ages/time of last dose of vaccine received, the result indicated that vaccinated individuals within the ages of 1-10 years had the highest rate of 61% vaccine optimal response. While vaccinated subjects above 10 years had the lowest rate of vaccine optimal response. The presence of active and robust immune system among the subjects within the age of 1 year to 10 years might be the reason for their highest rate vaccine optimal response. It is believed that younger adults respond actively to vaccine inoculum than those who have advanced in age. There was significant relationship between age and vaccine immunogenicity as P≤ 0.05. Also, on the relationship between the time of vaccine last dose received, and vaccine response, the result revealed that subjects who received their vaccine last dose about 1 year to 5 years ago had the highest rate of 64.9% vaccine optimal response compared to those who received vaccine last dose over 5 years ago. This implies that vaccine efficacy can wane down with time as indicated in Table 2.

**Table 2: Relationships between HepB Vaccine Immunogenicity and Ages and Time of Vaccine Last Dose in Bauchi**

| **HB VS** | **HepB Vaccine Immunogenicity (HBsAb Titres)** | | | | |
|---|---|---|---|---|---|
| | **≥10mIU/mL** | **<10mIU/mL** | **≤ 0mIU/mL** | | |
| **Age group (yrs)** | **No. Tested** | **Optimal (%)** | **Suboptimal (%)** | **No respond (%)** | **p< 0.05** |
| ` | 107 | 65(61) | 32(30) | 1(11) | 0.001 |
| 31-40 | 16 | 3(19) | 9(56) | 4(25) | |
| 11-20 | 44 | 17(39) | 15(34) | 12(27) | |
| 21-30 | 9 | 4(44) | 4(44) | 10(9) | |
| 41-50 | 11 | 3(27) | 3(27) | 5(46) | |
| > 50 | 9 | 4(44) | 2(22) | 3(33) | |
| Total | 196 | 96(49) | 65(33) | 35(18) | |
| **TVLD**(in years) | | | | | |
| 1-5 | 57 | 37(64.9) | 15(26.3) | 5(8.8) | 0.001 |
| 6-10 | 91 | 43(47.3) | 34(37.4) | 14(15.4) | |
| 11-15 | 37 | 12(32.4) | 4(37.8) | 11(29.7) | |
| 16-20 | 11 | 4(36.4) | 2 (18.2) | 5(45.5) | |

HB VS= hepatitis B vaccinated subjects, TVLD= Time of vaccine last dose received

The breakthrough cases were person(s) with validated history/record of hepatitis B primary vaccination who have been pre-screened and found negative for HBsAg yet come down with HB infection when exposed to HBV. The rate of vaccine breakthrough infection was 3.5%. And all hepatitis B genotypes detected in all the breakthrough infections cases were mixed genotype B and E. Plate 1 shows mixed A reaction tested on five known negative samples against DNA standard Ladder, positive and negative control to ascertain the sensitivity of the assay. Plate 2 indicates Mix B containing five samples, DNA Ladder, positive and negative control where mixed genotypes B and E are detected. This result infers a high chance of breakthrough infection when exposed to HBV mixed genotype B and E.

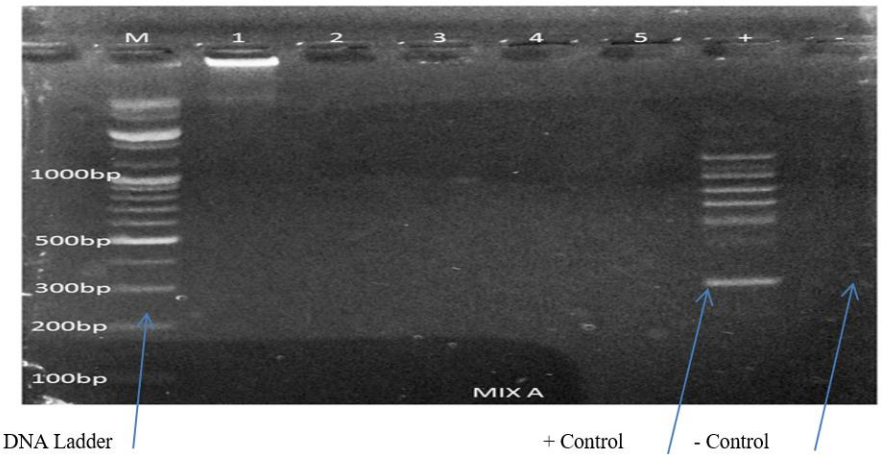


Figure 1: Mix A Agarose Gel Electrophoretogram

Aga gel Mix A of Polymerase Chain Reaction: containing five negative samples tested against the DNA Ladder labeled M, positive and negative control labeled + and – carried out on 1.5% agarose to ascertains the sensitivity and specificity of the assay gel electrophoresis using HBV genotypes outer primers.

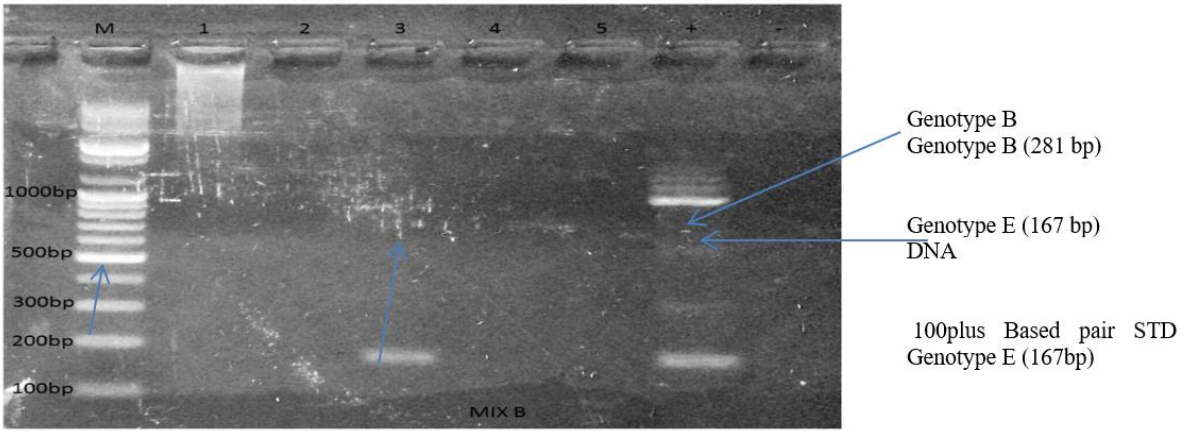


Figure 2: Agarose Gel Electrophoretogram

Aga gel Mix B of Polymerase Chain Reaction: containing five negative samples, DNA Ladder labeled M, and positive and negative control labeled (+) and (–) arried out on 1.5% agarose gel electrophoresis using HBV genotypes outer primers. Sample 1 indicated Primer dimmer reaction while 3 shows genotype E and sample 6 shows mixed genotypes B and E infection from breakthrough infection case.

**Discussion**

The prevention of vaccine-preventable infections such as hepatitis B virus infection has been achieved primarily by vaccination. Following the discovery of HBV vaccine in the 1980s, there has been a significant decrease in both the acute and chronic forms of hepatitis B infection in many countries across the globe. However, this success is now being threatened with the emergence of a scenario called HBV vaccine breakthrough infection (Yang *et al.,* 2016). The World Health Organization (WHO, 2021) has recommended that vaccine immune response greater than ten mill-international unit/milliliter (≥10mIU/mL) to be the global vaccine optimal response or protective antibody level for HBV vaccine immunogenicity. But Following the titration of anti-hepatitis B surface (Anti-HBs) by ELISA technique, only 49% had optimal response level (≥10mIU/mL) which was similar to the 50% rate earlier reported among the vaccinated in Sabo, Niger State (Olumuyiwa *et al.*, 2011).

On the relationship between the time of vaccine last dose received, and vaccine response, the result indicated that subjects who received their vaccine last dose about 1 year to 5 years ago had the highest rate of 64.9% vaccine optimal response compared to those who received vaccine last dose over 5 years ago. This agrees with the report of Abegaz (2021), and Oyinloye *et al.* (2019) who argued that: vaccine optimal response level thrives during the first few years of vaccine last dose. This implies that vaccine efficacy can wane down with time.

Similarly, on the relationship between vaccine response and ages of the vaccinated, it was obvious that individuals who received their vaccine dose(s) within the ages of 1-5 years and 6-10 years demonstrated the highest rate of 64.9% and 47.3% vaccine optimal response respectively. But other vaccinated subjects that advanced in age demonstrated lover rates of vaccine optimal response. This finding is consistent with the report of Cooling (2015) who reported that vaccinated individuals are more definitely protected within the ten years of their last dose of vaccine than beyond. However, individuals who were vaccinated more than 10 years ago had lower rate of vaccine optimal response. This implies that their immunity is gradually waning down with time because had been vaccinated long ago. This scenario agrees with the suggestion of Chitnis, and Wong, (2024) and Konopleva *el*

*al.,* (2022) who in separate studies reported that vaccine immune wanes down with time.

The reason for younger age producing highest rate of protective antibody response may be connected with the fact that they have robust natural immunity to fight infectious agent than aged (Esteve *et al*., 2019; Ye *et al*., 2023) Reports have it that elderly people have decreased antibody immunogenicity to Hep B and hepatitis A vaccine (Oyinloye and Bukbuk, 2021; Gong *et al*., 2024).

In recent years, the risks related to hepatitis B infection resulting from varying genotypes have become a public health concern globally. Vaccine breakthrough infections have proven to be an emerging scenario with a global scale, although with varying rate and causes in different regions (Wong *et al*., 2021). The finding in this study indicated 3.5% vaccine breakthrough infection rate. Consequently, it was mixed genotypes B and E that were implicated (detected) in all the breakthrough infection. Although genotype E has been reported to be dominant in west Africa and has also been reported in some cases of breakthrough infections (Ahmad *et al*., 2019). However, reports on HB vaccine breakthrough infections with mixed genotypes B and E are very scarce. Besides, it has been postulated that HBV vaccine breakthrough infection is mainly caused by the wild-type genotype E strain and that immune escape mutants are uncommon (Mamood *et al*., 2016). Global travels may be connected to the introduction of genotype B in a mixed infection. This infers that exposure to HB genotype B and E has the propensity for vaccine breakthrough infections.

## CONCLUSION

Hepatitis B vaccination remains a cornerstone of global HBV prevention. However, breakthrough infections highlight the complex interplay between waning immunity, and viral genotypes. The predominance of HBV mixed genotypes B and E in vaccine breakthrough infections in Bauchi underscores the need of continuous molecular surveillance and potential genotype-targeted vaccine strategies. Enhancing monitoring systems and integrating genotype data into public health planning could strengthen vaccine effectiveness to reduce HBV-related morbidity. Molecular surveillance and genotype-focused research are essential to sustain the success of HBV vaccination programs worldwide.

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