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Valerio-Fabros, MP, Padua, JRO. Seropositivity of Anti-HBs Titer Among College Students Several Years After Completion of the Primary Hepatitis B Vaccination Series
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ORIGINAL ARTICLE

SEROPOSITIVITY OF ANTI-HBS TITER AMONG COLLEGE STUDENTS SEVERAL YEARS AFTER COMPLETION OF THE PRIMARY HEPATITIS B VACCINATION SERIES

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ABSTRACT

Background: The Philippines is hyperendemic for hepatitis B infection. Vaccination is crucial for protection. Local data on the antibody response after completion of the primary vaccination series is limited.

Objective: This study aimed to measure the anti-HBs levels among college students who completed primary hepatitis B vaccination series, compare seropositivity across stratified groups and correlate anti-HBs levels with the time elapsed since the last vaccine dose.

Methods: This cross-sectional study included 111 college students in health-related courses with immunization record showing the complete primary Hepatitis B vaccination series. Participants were stratified based on the following vaccination schedules: 0-1-6-month group; 0-1-2-month group; and booster group. Anti-HBs titers were determined.

Data Analysis: Statistical analyses included One-way ANOVA, Kruskal-Wallis test, Fisher's Exact test and Shapiro-Wilk normality test. Kaplan-Meier Survival Estimate assessed the probability of anti-HBs seropositivity over time. Data were analyzed using STATA 13.1.

Results: The baseline characteristics of the study population were homogenous. The median anti-HBs titer several years after primary vaccination was low at 2.9 mIU/mL. Participants in the booster group had the highest seropositivity rate (57.14%) with a median titer of 30.16 mIU/mL. There was an inverse relationship between anti-HBs titer and elapsed time since the last vaccine dose. Kaplan-Meier Survival Estimate showed that the seropositivity decreases to 90.56% after 15.8 years, 51.3% after 17.5 years, and 2.97% at 18 years.

Conclusion: This study revealed low anti-HBs titers among students who previously completed primary vaccination series, with no significant difference between two schedules. Booster doses resulted in the highest seropositivity. Over-all, seropositivity declines over time.

KEYWORDS: *Hepatitis B, Hepatitis B Antibodies, Primary Hepatitis B Vaccination*

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INTRODUCTION

Hepatitis B infection is a major global health problem, infecting 257 million people and causing 686,000 deaths annually, according to the WHO Global Hepatitis 2017 Report.[1] The Western Pacific region bears the greatest burden, with infection rates of 6.2%. The Philippines is hyperendemic for Hepatitis B affecting 16.7% or 7.3 million Filipinos, especially among those aged 20-39 years.[2] This rate is double the average prevalence in the Western Pacific region.[3] Approximately 10% of Filipino mothers are chronic carriers of hepatitis B virus, with in utero transmission occurring in less than 2% of cases. Without post-exposure prophylaxis, infants born to HBsAg- and HBeAg-positive mothers face a 70-90% risk of acquiring the virus, while those born to HBsAg-positive but HBeAg-negative mothers have a 5-20% risk. [4] Without the birth dose, even with three doses, 3-5% of infants will develop chronic liver infection. Twenty to thirty percent will develop chronic liver infection between 30-50 years of age. As a result, 9,000 people die yearly from chronic liver disease.[5,6]

Vaccination is crucial for protection against hepatitis B infection. In the Philippines, strategies include routine Hepatitis B vaccination through the Expanded Program on Immunization since 1992, the introduction of a birth dose in 2007, and administering this dose within 24 hours in 2011.[7] Despite these measures, the country remains hyperendemic for the disease. Contributing factors may include vaccine failure, waning immunity, and loss of immune response over time.[8] There is limited data in the country on the persistence of anti-HBs and immune memory after vaccination despite the vaccine's high immunogenicity. A local prospective cross-sectional study by Lu in 2018, found that 52% of subjects aged 3 months to 18 years were seroprotected after completing the primary Hepatitis B vaccination series. Seroprotection rates varied by age: 82% for 3 months to 2 years old, 41% for 3-9 years old, and only 26% for those 10-18 years old.[9] The College of Public Health of the University of the Philippines-Manila & University of the Philippines-Los Baños in 2007 determined that 71.5% of pediatric hepatitis B vaccine recipients were seropositive for anti-HBs 5-11 years post-immunization.[10] This raises concerns that protection from primary vaccination may not be lifelong, and booster doses might be necessary to maintain long-term protection into adulthood. A booster dose refers to an additional Hepatitis B vaccine administered after a primary vaccination series to provide rapid protective immunity against a significant infection.[11] Nevertheless, anti-HBs determination post-vaccination is not routinely recommended because Hepatitis B vaccine is highly immunogenic.[11,12,13]

Despite the established long-term immune memory following primary Hepatitis B vaccination, certain population subgroups, such as college students in health-related fields, may still warrant attention due to potential gaps in the understanding of their immune response. The Centers for Disease Control and Prevention (CDC) does not routinely recommend booster doses for individuals with normal immune status, as long-term protection is thought to persist even in the absence of detectable antibodies.[11] However, in populations frequently exposed to health risks, understanding seropositivity levels could be key in identifying any factors that influence the maintenance of protective immunity. Given the high prevalence of hepatitis B in the Philippines, there is a need to assess the long-term effectiveness of the vaccination program. This study aimed to contribute to the broader understanding of how long-term immune responses manifest in this specific subgroup, potentially addressing gaps in the data regarding the persistence of seroprotection. Additionally, by exploring the association between anti-HBs levels and the time since vaccination, this research could help refine current recommendations for monitoring Hepatitis B immunity in specific high-risk populations.

This study aimed to determine the anti-HBs levels among college students in health-related courses several years after the completion of the

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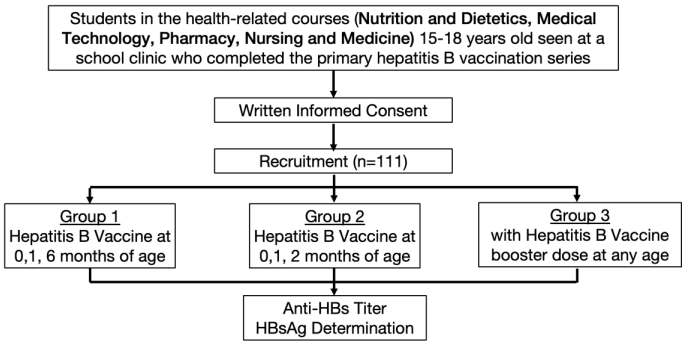
primary Hepatitis B vaccination series, identify which of the stratified groups (recipients of the 0-1-2 month schedule, the 0-1-6 month schedule, or those with a booster dose) had the highest antibody seropositivity, and establish a correlation between the anti-HBs titer and the time elapsed since the last dose of the Hepatitis B vaccine.

MATERIALS AND METHODS

Study Design

Students in the health care field are at risk for acquiring hepatitis B infection when they do their on-the-job training in the hospital, hence, the need to assess their protection against the infection. This cross-sectional study assessed the immune status of adolescents who completed the Primary Hepatitis B vaccination series.

Flowchart



Study Sample and Statistical Analysis

This study included college students enrolled in health-related courses (nutrition and dietetics, medical technology, pharmacy, nursing, and medicine) 15 to 18 years old seen at a school clinic with immunization record showing the complete Primary Hepatitis B vaccination series. The subjects were assigned into three groups based on the dosing schedule of the hepatitis B vaccine series: Group 1 (0-1-6 months), Group 2 (0-1-2 months), and Group 3 (with booster dose/s). The booster group consists of participants who received an additional dose of Hepatitis B vaccine at any point following the completion of the primary vaccination series. Subjects with previous infection with hepatitis, symptoms of clinically overt hepatitis, positive HBsAg, chronic renal failure, malignancy, and on immunosuppressive therapy were excluded.[15]

The sample size was computed as follows:[16]

$$n \geq \frac{Z^2{}_{\alpha} \times 4 \times P \times (1-P)}{d^2}$$

$$n \geq \frac{1.96^2 \times 4 \times 0.7153 \times (1-0.7153)}{0.18^2}$$

$$n \geq 96.58 \approx 97$$

The sample size computed for this research was a minimum of 97 patients, based on 71.53% prevalence of Anti-HBs seropositivity among pediatric vaccinees years after primary hepatitis B immunization.[10] This computation accounts for 5% level of significance and desired 18% total width of the confidence interval.

A total of 111 subjects were recruited. Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables, mean and SD for normally distributed continuous variables. One-way ANOVA, Kruskal-Wallis test, and Fisher's Exact test were used to determine the difference of mean, rank, and frequency, respectively, within the three groups. Shapiro-Wilk was used to evaluate the normality of the continuous variables. Kaplan-Meier survival estimate was used to determine the probability of anti-HBs seropositivity at a given time. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

Data Collection

College students enrolled in health-related courses aged 15 to 18 years who had their routine physical examination seen at a school clinic were screened and recruited by the principal investigator. The principal investigator coordinated with the director and physicians of the school clinic. The

researcher acted as the investigator only, not as the attending physician. The investigator explained the study to the participant, secured informed consent and administered the data collection forms. The immunization record was reviewed. All students under the above-mentioned health-related courses undergo routine screening for hepatitis B as part of their medical care, including the Anti-HBs titer and HBsAg determination. In line with this, the participants shouldered the expenses for the blood tests. At least 5 mL of whole blood was extracted for the anti-HBs titer and HBsAg determination using a chemiluminescent microparticle immunoassay method (Abbott Architect i1000SR) with >99.5% and 99.7% specificity; 100.0% and 97.5% sensitivity, respectively. Anti-HBs concentration ≥10.0 mIU/mL were considered reactive by the Architect Anti-HBs assay.

The attending physician at the school clinic recorded the quantitative test results upon the students' follow up. The investigators had access to these results with the permission of the school clinic. A subgroup analysis was performed as to those who received the vaccines at ages 0-1-2 months or 0-1-6 months. Those who received booster doses were also noted. The number of booster doses received, timing, and interval were recorded and analyzed. For patients with low and negative titers, the attending physician determined the intervention. The intervention was not part of the study.

This study is in accordance with the Declaration of Helsinki 2015. This study was done in compliance with the ethical principles set by the World Health Organization Operational Guidelines in Biomedical Studies 2011, International Conference on Harmonization on Good Clinical Practice, Council for International Organizations for Medical Sciences 2016, Good Research Practice, Philippine National Ethical Guidelines for Health and Health-Related Research of 2017 and the Philippine Data Privacy Act of 2012 and its Implementing Rules and Regulations of 2016.

The data collected in this research is confidential. The researchers protected the personal data of all participants in compliance with the Data Privacy Act of 2012 and its 2016 IRR. The Research Ethics Committee had access to the data for checking, without making the information public. The identity of all participants will remain confidential in the event of any publication of this study. This study was conducted upon review and approval of the Research Ethics Committee on July 13, 2019, and the investigator was compliant to Good Clinical Practice.

For participants 15-17 years old, a written informed consent form, fully explained and understood by the parents and the student, was signed. For those not accompanied by their parent/guardian, the informed consent form was brought home for signing of the parent/guardian. For participants 18 years old, a regular consent form was secured.

The participants did not receive any monetary compensation for participating in this study. Routine screening for hepatitis B was done in the school clinic. This included anti-HBs titer and HBsAg determinations. The principal investigator was responsible for the monetary compensation and/or treatment in a study-related injury and adverse events (e.g., compartment syndrome secondary to severe bleeding). Complications such as pain, hematoma, minimal bleeding, inflammation, and infection may develop on the site of extraction, were explained in detail. These were easily avoided by following the standard blood extraction procedure. Asepsis and proper infection control method were done. The laboratory released the test results to the subjects. The subjects shouldered the diagnostic tests expenses and the necessary booster doses of the hepatitis B vaccine.

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RESULTS

A total of 111 subjects were enrolled in the study. Table 1 shows the demographic and clinical profile of the subjects. There is no significant difference among the groups in terms of age, sex, place of vaccination and HBsAg levels. The mean age is 17.86 ± 0.34 years and 78% are males. Forty-three (43) subjects were given the primary hepatitis B vaccine series at 0-1-6-months schedule, twenty-six (26) received the three doses at 0-1-2 months schedule. Forty-three (43) subjects received booster doses. Of which, 38 received one dose, four had two doses and one had three doses.

Table 1 Demographic and clinical profile of the patients

	Total (n=111)	0-1-6 months (n=43)	0-1-2 months (n=26)	With booster dose (n=42)	p-value
Age in years (Mean ± SD)	17.86 ± 0.34	17.88 ± 0.32	17.81 ± 0.40	17.88 ± 0.33	0.628
Sex					
Male (%)	33 (29.73)	14 (32.56)	9 (34.62)	10 (23.81)	0.558
Female (%)	78 (70.27)	29 (67.44)	17 (65.38)	32 (76.19)	
Place of vaccination					
Local health center (%)	7 (6.31)	1 (2.33)	4 (15.38)	2 (4.76)	0.084
Private clinic (%)	104 (94.69)	42 (97.67)	22 (84.62)	40 (95.24)	
HBsAg, S/CO* (Median IQR)	0.28 (0.25–0.33)	0.2 (0.25–0.31)	0.28 (0.25–0.41)	0.3 (0.25–0.35)	0.741
Anti-HBs Titer, mIU/mL** (Median IQR)	2.9 (0.77–34.76)	1.24 (0.26–7.03)	2 (0.91–4.57)	30.16 (2.36–147)	**<0.001**
Anti-HBs seropositivity	37 (33.33%)	8 (18.60%)	5 (19.23%)	24 (57.14%)	**<0.001**
Interval of booster in months (Median IQR)	205 (177–213)	210 (201–215)	215 (209–217)	168 (123–210)	**<0.001**

*Laboratory's reference value for HBsAg is <1.00 S/CO, which means non-reactive.
**Laboratory's reference value for Anti-HBs titer is ≥10.00 mIU/ml, which means reactive.

The normality of continuous variables was first assessed using the Shapiro-Wilk test. For normally distributed continuous variables such as age, the one-way ANOVA test was used to compare means across different groups, yielding a p-value of 0.628, which indicated no significant difference in age among the groups. Descriptive statistics for age were reported using mean and standard deviation. For non-normally distributed continuous variables, such as HBsAg levels, Anti-HBs titer, and the interval of booster doses, the Kruskal-Wallis test was employed. This revealed no significant differences in HBsAg levels (p=0.741), but significant differences in Anti-HBs titers (p<0.001) and booster intervals (p<0.001). Categorical variables such as sex, place of vaccination, and Anti-HBs seropositivity were analyzed using Fisher's Exact test, which showed no significant differences in sex distribution (p=0.558) and place of vaccination (p=0.084), but significant differences in Anti-HBs seropositivity rates (p<0.001).

Majority of the vaccines were given in private clinics (94.69%). Of which, 40.38% received the primary series at 0-1-6-months schedule, and 21.15% were given at 0-1-2-month schedule. Only seven participants received their hepatitis B immunization from local health centers. Of which, one followed the 0-1-6-month schedule; four followed the 0-1-2-month schedule; and two received booster doses from private clinics. Based on the dosing schedule, 18.60% remained seropositive for anti-HBs in the 0-1-6-month group and 19.23% were seropositive in the 0-1-2-month group. Among those who received booster doses, 57.14% remained seropositive for anti-HBs.

Table 2 Anti-HBs titers of 0-1-6 month group and 0-1-2 month group

	Total (n=69)	0-1-6 months (n=43)	0-1-2 months (n=26)	p-value
Anti-HBs Titer, mIU/mL (Median IQR)	2.9 (0.77–34.76)	1.24 (0.26–7.03)	2(0.91–4.57)	0.620
Anti-HBs seropositivity (%)	13 (18.84)	8 (18.60)	5 (19.23)	1.000

Fischer's Exact test compared the seropositivity between the two vaccination schedules. There is no significant difference between the two groups without booster in terms of seropositivity (p-value 1.000).

Patients who received a booster dose had the highest median anti-HBs titer (30.16 mIU/mL) compared to patients with no booster from the 0-1-6-month (1.24 mIU/mL) and 0-1-2-month (2 mIU/mL) groups. The median elapsed time after the last vaccine dose and the antibody level determination are: 210 months (17.5 years) in the 0-1-6-month group; 215 months (17.9 years) in the 0-1-2-month group; and 168 months (14 years) in the booster group. Among all groups, there is a moderate inverse correlation between the elapsed months and anti-HBs titer (r=-0.4057). There is a very weak direct correlation between the last dose of the 0-1-6-month schedule and the antibody titer (r=0.0194). A strong

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inverse correlation is seen in the 0-1-2-month schedule and anti-HBs titer (r=-0.0546) while there is a moderate inverse correlation between the time from last booster dose and the anti-HBs titer (r=-0.4253). The longer the time elapsed from the last dose, the lower is the anti-HBs titer (Figures 1-4).

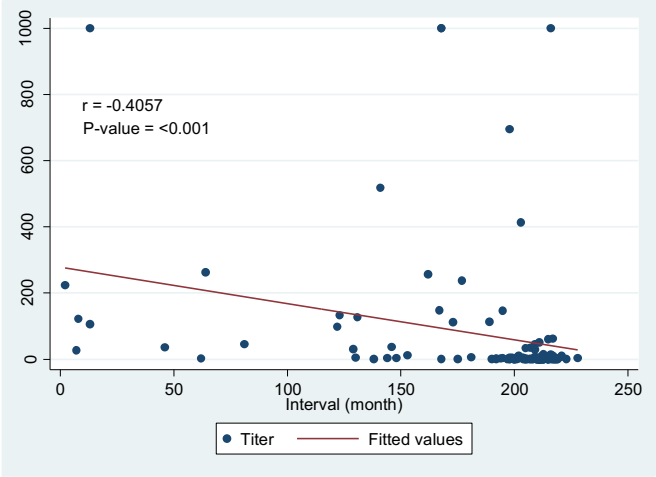

Figure 1. Scatter plot of time elapsed from the last hepatitis B vaccine dose of all groups (in months) to anti-HBs titer determination

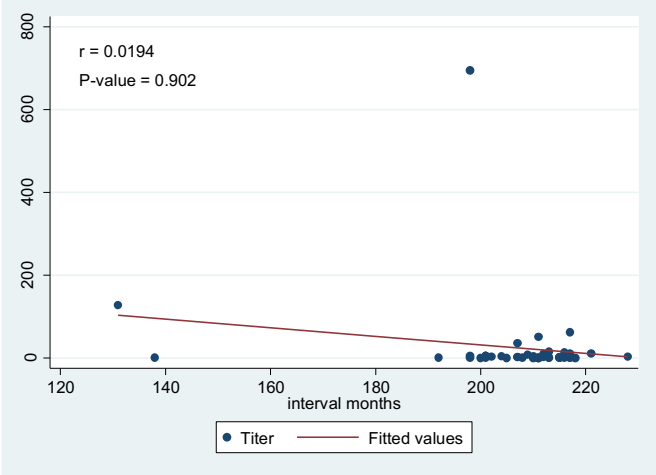

Figure 2. Scatter plot of time elapsed from the last hepatitis B vaccination dose (in months) and anti-HBs titer among those who received the vaccines in a 0-1-6-month dosing interval

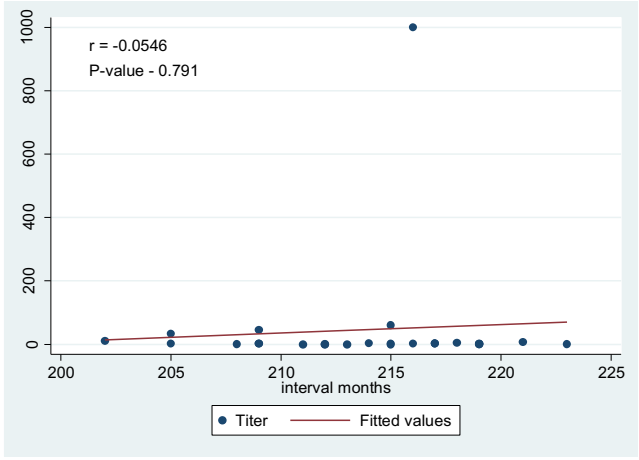

Figure 3. Scatter plot of time elapsed from the last hepatitis B vaccination dose (in months) and anti-HBs titer among those who received the vaccines in a 0-1-2-month dosing interval

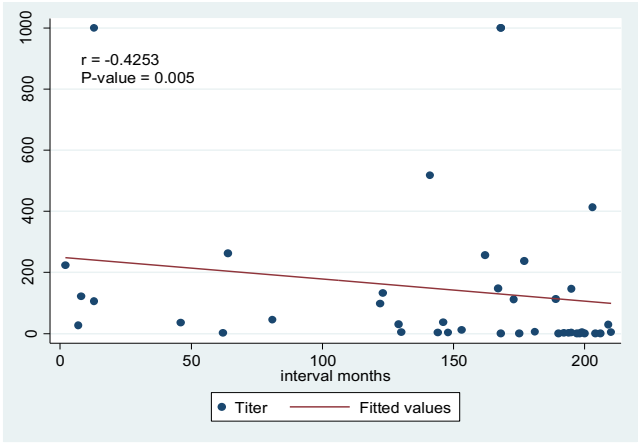

Figure 4. Scatter plot of time elapsed from the last hepatitis B booster dose (in months) and anti-HBs titer

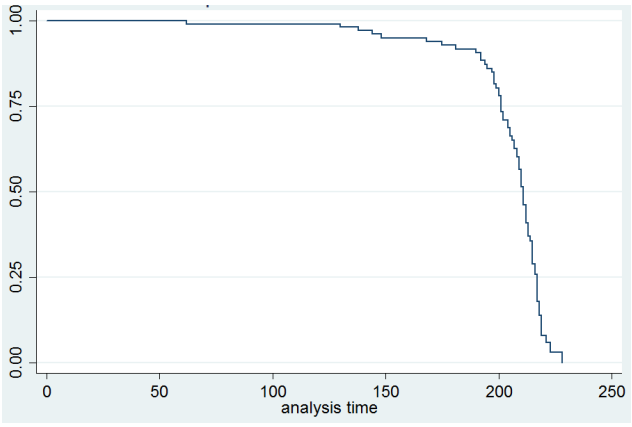

Figure 5. Kaplan Meier Survival Estimate

Figure 5 shows the probability of anti-HBs seropositivity at a given time. At 190 months (15.8 years), the seropositivity rate declines to 90.56%. At 210 months (17.5 years), only 51.35% of the patients remained seropositive. By 223 months (18 years), only 2.97% are seropositive.

DISCUSSION

The Centers for Disease Control and Prevention (CDC) reported that a three-dose series of Hepatitis B vaccine induces seroprotective levels in more than 95% of infants, children, and young adults.[17] While research has shown that Hepatitis B vaccine remains effective over time, the levels of protective antibodies tend to decline. A Gambian study with a 19-year follow-up showed high vaccine efficacy up to 20 years despite decreasing anti-HBs levels.[18] According to Bialek, antibody titers wane from birth, with only 5-20% maintaining protective levels 13-15 years later.[19] A Korean study found that anti-HBs titers in children decrease over time, with 50% of the subjects over seven years old becoming seronegative and titers reaching zero by 13 years old.[20] Protective anti-HBs levels are achieved within 1 month in 48% of neonates after the first dose. Two months after the second dose, 91% of neonates have detectable anti-HBs titers, which rise to 96% at 6 months. The persistence of anti-HBs is influenced by the initial concentration achieved post-vaccination. Immunity from perinatal HBV vaccination diminishes 10-15 years after initial immunization, with 62.4% of adolescents aged 15 years old losing the protective levels.[14] An Italian prospective cohort study revealed a greater reduction in anti-HBs geometric mean concentrations in the boosted group (17.5-fold) compared to the unboosted group (2.5-fold reduction). This suggests that the kinetics of anti-HBs decay and the antibody persistence depend on the magnitude of the peak antibody level achieved after the primary immunization rather than on the peak reached after booster administration.[21] An Alaskan study likewise revealed a sharp decline in post-booster antibody levels, with only 41% of vaccine recipients maintaining seroprotection one year following booster administration.[22] Therefore, this antibody decline strongly suggests that post-booster and anti-HBs concentrations tend to wane rapidly and eventually return to the levels detected before the booster dose.

There has been limited research conducted in the Philippines on the long-term immunogenicity of vaccines. Children from Manila in 2002 demonstrated reactive anti-HBs levels 8-15 years after receiving their primary vaccination.[47] In 2018, subjects from different regions of Luzon had 52% anti-HBs reactivity, but with seroprotection declining over time.[9] In Northern Mindanao, 56.8% of the subjects, including the one that is infected, did not seroconvert, despite completion of the primary vaccination series from the local health center.[23] In our study, college students in the health-related courses exhibited low anti-HBs titers with a median of 2.9 mIU/mL several years after completion of the primary hepatitis B vaccination series. Our results are consistent with McMahon in 2005 which showed that protection from Hepatitis B vaccine remained robust for at least 15 years (84% of the subjects still had anti-HBs present). The inverse relationship observed between the time elapsed since the last vaccine dose and anti-HBs titers in our study corresponds with the result of Barroza-Cendaña, who also demonstrated that intervals between vaccination and titer measurement correlated with lower anti-HBs levels.[24,25] These results suggest a gradual decline in antibody levels to the hepatitis B surface antigen over time.

The American Academy of Pediatrics and Advisory Committee for Immunization Practices recommend the 0-1-6 month hepatitis B schedule to provide seroprotection for more than 10 years.[11] The dosing schedule of our country's National Immunization Program is at 6-10-14 weeks, which is roughly equivalent to the 0-1-2 month hepatitis B schedule.[26,27] Internationally, studies have demonstrated the efficacy of 0-1-6 schedule in achieving higher seroconversion rates and sustaining

higher anti-HBs titers. In 1989, Jilg compared the anti-HBs concentrations of adults who received hepatitis B vaccination schedule as follows: 0-1-2 months, 0-1-6 months, and 0-1-12 months.[16] Results showed that the anti-HBs titers increase and tend to persist with longer intervals between the last two doses. However, our study showed that there is no significant difference between the 0-1-6-month and 0-1-2-month schedule in terms of seropositivity and anti-HBs titer.

The CDC does not routinely recommend booster doses of the vaccine for any age group with normal immune status because they have long-term protection.[11] The observation that specific immune memory for HBsAg can persist beyond the presence of vaccine-induced antibodies is consistent with the outcomes of long-term studies conducted in countries with high HBV endemicity.[29-33] Hence, persistence of anti-HBs titer ≥10 mIU/mL is not necessary for protection, because of this anamnestic response. The duration of protection is at least 15 years and lifelong. After 40 years, protection after the primary vaccination series drops below 90%. By 60 years old, antibody levels are achieved in only 65–75% of the recipients. Though booster doses are unnecessary for most, it is important to consider the response to vaccination in high-risk groups, such as healthcare personnel, infants born to HBsAg-positive mothers and immunocompromised individuals.[34] Completely vaccinated healthcare personnel with low anti-HBs (<10 mIU/mL) should receive an additional dose of hepatitis B vaccine, followed by anti-HBs testing 1-2 months later. Additionally, a study by Samandari found that the anamnestic response rate at 2 weeks post-booster among participants with antibodies to hepatitis B surface antigen was inversely related to age, with 97% of 5-year-olds responding compared to only 60% of 14-year-olds. This suggests that immune memory may wane with age.[12] Similarly, McMahon in 2009 demonstrated that participants with low pre-booster anti-HBs levels had a significantly higher likelihood of achieving a booster response compared to those with undetectable anti-HBs levels.[22] This emphasizes the importance of monitoring antibody levels in certain populations.

CONCLUSION

While Hepatitis B vaccine provides robust and long-lasting protection for majority of individuals, the decline in antibody levels over time, particularly among high-risk groups, highlights the importance of continued monitoring and potential booster doses for those with waning immunity. Students in the health care field, who are at risk for acquiring hepatitis B infection during their clinical training, are particularly affected. This study infers that despite completion of the primary hepatitis B vaccination during infancy, anti-HBs titers start to decline after 15 years. Subjects in the booster group had the highest antibody seropositivity. There is no significant difference between the two primary vaccination dosing schedules. There is an inverse relationship between the anti-HBs titer and elapsed time after the last hepatitis B vaccine dose. The longer the time elapsed after the last dose of hepatitis B vaccine, the lower is the anti-HBs titer.

RECOMMENDATIONS

A larger prospective study with equal proportions in the dosing groups and long-term follow-up is recommended to validate the results of this study. Monitoring anti-HBs titers at different period is proposed to determine the duration of protection after completion of the primary hepatitis B vaccination series and the rate of decline over time. Future research may also evaluate the anamnestic response in individuals vaccinated against Hepatitis B by measuring their antibody response to a booster dose, which can help identify true non-responders. Further investigation is recommended to explore factors impacting seropositivity despite long-term immune memory, to develop more effective strategies for maintaining long-term immunity.

CONFLICT OF INTEREST

None declared.

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