

Anti-Hepatitis B surface Titer as Indicator in Faculty of Medicine Universitas Riau Hepatitis B Vaccination Program

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ABSTRACT

Indonesia is endemic for hepatitis B virus infection. However, the prevalence has decreased which might be contributed to national immunisation programme starting in 1997. As a protective effort, since 2014, Faculty of Medicine Universitas Riau (FK UNRI) has implemented mandatory hepatitis B vaccination programme for students enrolling into clinical rotation who have anti-Hepatitis B surface (anti-HBs) titer less than 10 IU/mL. However, post-vaccination anti-HBs titer has never been measured. This research aimed to analyse post-vaccination anti-HBs titer on FK UNRI students enrolling in the vaccination programme. Surveyed respondents claimed to have been vaccinated on < 1 year old (40 people, 34,2%) or >1 year old (0,8%), while 77 people (65,8%) did not know or could not remember their vaccination status. Pre-programme initial screening showed that more than 80% students were nonreactive for anti-HBs. Followup anti-HBs titer measurement post-programme was conducted on 24 out of 42 students who have received third doses in FK UNRI hepatitis B vaccination programme. Result showed that all tested respondents have protective anti-HBs titer (≥ 100 IU/mL) within at least 2 months post-vaccination. Until now, Hepatitis B vaccination program has not been mandatory for healthcare workers or students working in various medical institutions. Therefore, a mandatory hepatitis B vaccination programme policy could be implemented by medical institutions to minimize hepatitis B infection cases among healthcare workers and students.

Keywords: *Anti-Hepatitis B surface, hepatitis B, vaccination program, vaccine.*

1. INTRODUCTION

Hepatitis B is a disease caused by hepatitis B virus infection which can lead to liver inflammation. Chronic infection can cause hepatic cirrhosis, portal hypertension, liver failure, and malignancies. In Indonesia, national prevalence of hepatitis B surface antigen (HBsAg) carrier in 2013 (7.1%) was decreased compared to 2007 (9.4%). Meanwhile, HBsAg prevalence varies across regions, ranging from 4% to 20.3% [1,2].

One of the main factors contributing to the decrease of hepatitis B incidence is the success of hepatitis B vaccination programme. Hepatitis B has been included in national infant immunisation programme since 1997. However, prevalence of HBsAg among children under 5 years old is still around 5% [3]. Low coverage of vaccination in several areas as well as high prevalence of

HBsAg-reactive pregnant women are suspected to contribute to high HBsAg prevalence among infants. A study in Makassar showed that 6.8% from 943 pregnant women were HBsAg reactive [4]. Studies in Jakarta as well as West Java-Bali-West Nusa Tenggara reported HBsAg prevalence of 2.2% and 1.9-4.7%, respectively, among pregnant women [5,6]. High prevalence of HBsAg-reactive pregnant women increases the risk of HBsAg-reactive infants through vertical transmission. Infection occurring in infancy has significantly higher risk to develop into chronic hepatitis B in adulthood compared to infection occurring in adulthood [7].

Healthcare workers, including medical students, have high risk of hepatitis B virus infection. Exposure to patient's blood products and bodily fluids, directly or indirectly, increases the infection risk. Study in one

medical education institution in Bali reported 0.7% of students were reactive to HBsAg [8]. Another study in medical students in Faculty of Medicine Universitas Riau (FK UNRI) in 2018 showed 0.6% of students were HBsAg-reactive. In Kariadi Hospital, Semarang, 3.9% of students in medical residency programme had HBsAg-reactive. Hepatitis B exposure risk was higher among medical doctor who have been practicing ≥ 3 years (5.1%) compared to those practicing < 3 years (1.6%) [9].

In order to provide protection for our students, starting from 2014, all medical students of FK UNRI is required to undergo hepatitis B vaccination prior to starting clinical rotations. Before vaccination, immunity status was screened based on anti-Hepatitis B surface (anti-HBs) titre where anti-HBs < 10 IU/L was classified as non-protective, 10-99 IU/L was low-protective, and > 99 IU/L was protective. In 2011, 35.9% of FK UNRI medical students had non-protective anti-HBs titre (< 10 IU/L) while reporting vaccination history during infancy [10]. Similar pattern was observed in Semarang, where 39.8% of medical students had non-protective anti-HBs titer [11]. Several factors that might contribute to anti-HBs titre decrease are timeframe of more than 10 years without booster, inadequate vaccination, or genetic factors affecting immune system modulation against vaccine [12]. Since the initiation of mandatory Hepatitis B vaccination for FK UNRI medical students, we have not evaluated protective effect to the given vaccination. Therefore, this study aimed to evaluate anti-HBs titre post-vaccination among FK UNRI medical students.

2. METHODS

The study was cross-sectional involving 117 students from cohort 2016. Samples were all students meeting the inclusion criteria. Inclusion criteria were age of > 18 years old, nonreactive for HBsAg screening, had received final dose of hepatitis B vaccine for at least 2 months, and provided informed consent to be involved in the study. The research has been given ethical clearance from Unit Etika Penelitian Kedokteran dan Kesehatan FK UNRI (No:).

Respondents were provided information regarding the study and asked to provide informed consent. Around 5 ml of blood were drawn into EDTA tube and stored at -80°C until further analysis. Blood sampling was conducted by trained staff from private clinical lab. Measurement of anti-HBs titre was conducted using Enzyme Linked Fluorescent Assay (ELFA, Mini Vidas®) on blood serum in private clinical lab. Respondents were also asked to fill online questionnaire regarding vaccination history by self-recall.

3. RESULTS

Screening was conducted for all 117 students of FK UNRI cohort 2016 prior clinical rotations. There were 27

(23.1%) males and 90 (76.9%) females with the age range of 21-22 years old. There were 35% students self-reported having hepatitis B vaccination at < 1 year old, 10.3% self-reported having vaccination history but could not recall the time, and 54.7% self-reported having no hepatitis B vaccination history.

Initial screening for anti-HBs titre showed most students had non-protective titer (Figure 1). There were 95 (81.2%) students had non-protective anti-HBs titer (< 10 IU/ml), 21 (17.9%) had low protective titre (10-100 IU/ml) and only 1 (0.9%) had protective titre (> 100 IU/ml). Based on sex, 77.8% male students had non-protective titre, 22.2% had low protective titre, while none had protective titre. Among female students, there were 82.2% had non-protective titre, 16.7% low protective, and 1.1% protective. Presence of zero value hindered statistical analysis on sex variable.

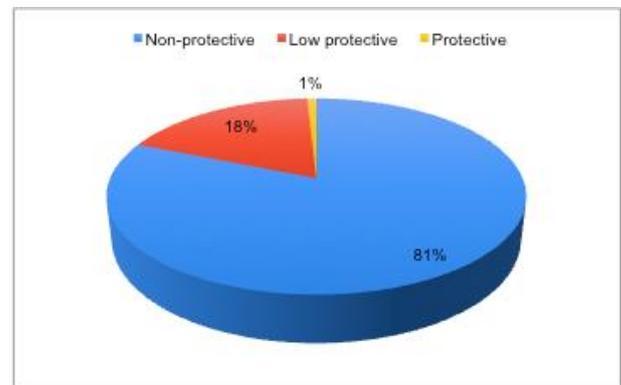


Figure 1 Result of initial anti-HBs screening among cohort 2016 FK UNRI medical students

Further analysis was conducted on sub-group reporting hepatitis B vaccination history. Result showed that 77.4% students reported having vaccination history had non-protective anti-HBs titre, 20.8% had low protective titre, and only 1.9% had protective titre. Among the low protective group, 9 people (81,8%) reported vaccination at < 1 year old while 2 people (18,2%) reported not knowing vaccination history or not knowing the time of hepatitis B vaccination. One student having protective anti-HBs titre reported having hepatitis B vaccination at < 1 year old.

Table 1. anti-HBs status on initial screening

Anti-HBs status	Male	Female	Total
Non-protective	21 (77.8%)	74 (82.2%)	95 (81.2%)
Low protective	6 (22.2%)	15 (16.7%)	21 (17.9%)
Protective	-	1 (1.1%)	1 (0.9%)
Total	27 (23.1)	90 (76.9%)	117 (100%)

Based on FK UNRI regulation, all students with non-protective anti-HBs titre was provided and required to undergo hepatitis B vaccination prior clinical rotations. Vaccination for students with low-protective titre (10-100 IU/mL) was also offered but was not mandatory. In a follow-up survey in the second semester of 2020 (Figure 2), there were 42 of 77 (54.5%) students responded as had received third dose of vaccine, 23 (29.9%) students only received the second dose, 1 (1.3%) students just started the first dose, and 11 (14.3%) students reported not required to undergo mandatory hepatitis B vaccination. Eleven students reported not required to undergo mandatory hepatitis B vaccination had protective anti-HBs titre (1 person) and low-protective titre (10 people) from initial screening programme.

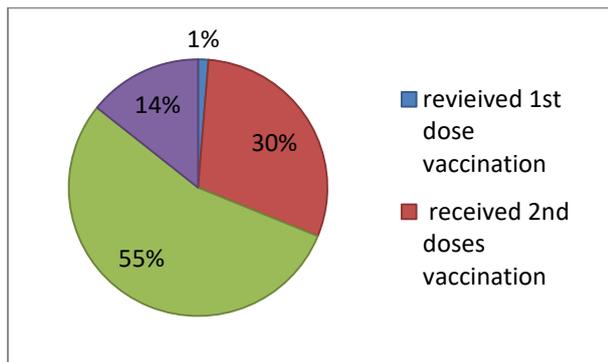


Figure 2 Result of initial anti-HBs screening among cohort 2016 FK UNRI medical students

Among 42 students who had received the third dose, only 24 students showed up for follow-up anti-HBs titre measurement post vaccination. The result showed that all 24 students had protective anti-HBs titre. There were 79.2% students had anti-HBs titer >1000 IU/ml. Others had <1000 IU/ml titer with the lowest titre was 202,33 IU/ml. There were no students with non-protective titre. Among 24 followed-up students, there were 12 (50%) people reported having hepatitis B vaccination history during the initial screening while the others reported not having vaccination history. Among students with initial low-protective anti-HBs titre, only 14% decided to repeat hepatitis B vaccination and 43% decided to not repeat vaccination while other 43% have not responded regarding vaccination or booster.

4. DISCUSSION

Healthcare workers at risk of blood exposure at work need to be vaccinated against hepatitis B [13]. One of the at-risk groups was medical students in clinical rotations. In a hospital in Bali, 42.3% syringe injuries happened in medical students in 2013 [14]. Therefore, FK UNRI feels the urgency of providing protection for its students by providing hepatitis B vaccination.

High prevalence of non-protective anti-HBs titre (<10 IU/mL) might due to titre decrease post-vaccination which has been observed by other study reporting 20% and 27% respondents had non-protective anti-HBs status after 5 and 10 years post vaccination, respectively [12].

Literature showed no association between anti-HBs titre decrease with sex [12]. In our study, one female student had protective titre while no male students had protective titre during the initial screening. Immune reactivity was observed to be higher among women vaccinated above 1 year old, but no sex difference was observed between those vaccinated under 1 year old [15].

Follow-up anti-HBs screening was conducted at least 2 months after the third dose, based on WHO guideline for healthcare workers [13]. In our study, we did not find non-responders with non-protective antibody, thus all followed-up students have developed immunity against hepatitis B [13]. The result was in line with a study observing increase of respondent with anti-HBs titre ≥10 mIU/mL on 1 – 5 months after third dose [16].

Only 14% students with initial low-protective titre responded of repeating vaccination. The low participation among those with low-protective anti-HBs titre to obtain vaccination booster is concerning. The mean anti-HBs titre among low-protective group was 28.8 IU/ml with highest titer of 75.5 mIU/ml and lowest titre of 11.06 IU/mL. Anti-HBs decrease was more pronounced among individuals without booster dose [17].

Antibody titre decrease post-vaccination is affected by many factors, from genetic predisposition to lifestyle such as smoking and obesity [18]. Other studies have also shown that anti-HBs titre post-vaccination will decrease naturally over time. Study in India showed that medical students and healthcare workers having protective immunity after <5 years post-vaccination was 94.1%, which then decreased into 79.7% in 5-10 years post-

vaccination, and 72,7% in >10 years post-vaccination.¹² Study in Palestinian children at 0-19 years old showed similar pattern. Decrease of anti-HBs titer was significant starting at 5-6 years old which only 66.7-69.2% children still had protective titre [19].

This study limitation was the self-recall method to collect vaccination history without supporting document. It might cause recall bias where students with no prior vaccination history reported presence of vaccination history. Most of students from cohort 2016 were born in 1998 when the national hepatitis B immunisation programmes was just started, which presented possibility of uneven programme coverage. However, the self-recalled vaccination history did not affect screening or follow-up vaccination programme. This is in line with WHO guideline to provide 3 doses of hepatitis B vaccine followed by check-up after 1-2 months after the third dose for healthcare workers who self-recalls hepatitis B vaccination history without supporting documents [13].

Due to their frequency of blood and bodily fluids exposure, medical students, especially in clinical rotation, are at high risk of hepatitis B virus infection. Hepatitis B vaccination programme for healthcare workers and medical students have not been mandatory for teaching hospitals and their networks. Regulation from Ministry of Health or from local government was also lacking. Regulation for mandatory hepatitis B vaccination programme can be implemented locally by each health and medical institutes, including medical faculties, to minimalise hepatitis B infection risk among students, thus controlling hepatitis B incidence among medical students.

5. CONCLUSION

Screening and evaluation of hepatitis B vaccination programme for FK UNRI medical students were conducted by anti-HBs measurement. Initial screening showed 81.2% students had non-protective anti-HBs titre (<10 IU/ml), 17.9% had low-protective titre (10-100 IU/ml), and only 0.9% had protective titre (>100 IU/ml). The profile did not reflect hepatitis B vaccination history reported by 45.3% students. After hepatitis B vaccination programme, 24 students were followed up at least 2 months after third dose. Among those, 79.2% students had anti-HBs titre >1000 IU/ml, while the rest had titre >200-1000 IU/ml. However, only 14% students with low-protective anti-HBs titre during initial screening reported to undergo vaccination programme. Therefore, there is a need for mandatory hepatitis B vaccination or booster followed by anti-HBs measurement post-vaccination in medical education institutions such as medical faculties to minimalise hepatitis B virus infection risk among medical students.

AUTHORS' CONTRIBUTIONS

DA, HM, FMS, and RAK designed the study and collected the data. HM and RAK wrote the initial manuscript draft. All authors read and approved the final manuscript.

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REFERENCES

- [1] Mulyanto et al. A nationwide molecular epidemiological study on hepatitis B virus in Indonesia: Identification of two novel subgenotypes, B8 and C7. *Arch. Virol.* 154, 1047–1059 (2009).
- [2] Muljono h, D. Epidemiology of Hepatitis B and C in Republic of Indonesia. *Euroasian J. Hepato-Gastroenterology* 7, 55–59 (2017).
- [3] Gunardi, H. et al. Current prevalence of hepatitis B infection among parturient women in Jakarta, Indonesia. *Acta Med. Indones.* 46, 3–9 (2014).
- [4] Fujiko, M. et al. Chronic hepatitis B in pregnant women: Is hepatitis B surface antigen quantification useful for viral load prediction? *Int. J. Infect. Dis.* 41, 83–89 (2015).
- [5] Reniers, J., Vranckx, R., Ngantung, W., Sugita, E. & Meheus, A. Prevalence and determinants of hepatitis B virus markers in pregnant women in West Java, Indonesia. *J. Trop. Med. Hyg.* 90, 249–53 (1987).
- [6] Surya, I. G. P. et al. Serological markers of hepatitis B, C, and E viruses and human immunodeficiency virus type-1 infections in pregnant women in Bali, Indonesia. *J. Med. Virol.* 75, 499–503 (2005).
- [7] Trépo, C., Chan, H. L. Y. & Lok, A. Hepatitis B virus infection. *Lancet* 384, 2053–2063 (2014).
- [8] Murprayana, K. & Budayanti, N. N. S. Prevalensi HBsAg, anti HBs, dan anti HCV pada mahasiswa fakultas kedokteran preklinis di Bali periode Januari 2013-Juni 2014. *E-Jurnal Med.* 6, 1–5 (2017).
- [9] Purwono, P. B. et al. Hepatitis B virus infection in Indonesia 15 years after adoption of a universal infant vaccination program: Possible impacts of low birth dose coverage and a vaccine-escape mutant. *Am. J. Trop. Med. Hyg.* 95, 674–679 (2016).
- [10] Kemaladina, I., Masdar, H. & Efendi, D. Identifikasi status vaksinasi hepatitis B dan kadar anti-HBs pasca vaksinasi pada mahasiswa kepaniteraan klinik

Fakultas Kedokteran Universitas Riau. J. Online Mhs. Univ. Riau 1–10 (2012).

- [11] Kasih, T. & Hapsari, R. Profil anti-HBs sebagai penanda kekebalan terhadap infeksi virus hepatitis B pada mahasiswa kedokteran. J. Kedokt. Diponegoro 6, 1279–1289 (2017).
- [12] Sahana, H. V, Sarala, N. & Prasad, S. R. Decrease in Anti-HBs Antibodies over Time in Medical Students and Healthcare Workers after Hepatitis B Vaccination. *Biomed Res. Int.* 2017, 1–5 (2017).
- [13] World Health Organization. 2019. Hepatitis B and the health care worker. https://www.who.int/occupational_health/activities/3hepatiti.pdf
- [14] Sudiantara, P. H. & Somia I. K. A. Karakteristik pajanan jarum suntik pada tenaga kesehatan di Rumah Sakit Sanglah Denpasar. *E-Jurnal Medika Udayana.* 4(1), (2015).
- [15] Trevisan A. et al. Sex disparity in response to hepatitis B vaccine related to age of vaccination. *Int J Environ Res Public Health* 17(1): 327
- [16] Nagashima, S. et al. Acquisition rate of antibody to hepatitis B surface antigen among medical and dental students in Japan after three-dose hepatitis B vaccination. *Vaccine* 37, 145-151 (2019).
- [17] Verso M. G. et al. Kinetics of anti-Hepatitis B surface antigen titers in nurse students after a two-year follow-up. *Vaccine* 8, 467 (2020).
- [18] Walayat S, Zohair A, Daniel M, Srinivas P, Michael C, Suno D. Recent Advances in Vaccination of Non-Responders to Standard Dose Hepatitis B Virus Vaccine. *World J Hepatol* 2015;7: 2503-2509.
- [19] Qawasmi M, Samuh M, Glebe D, Gerlich WH, Azzeh M. Age dependent decrease of anti-HBs titer effect of booster doses using 2 different vaccines in Palestinian children vaccinated in early childhood. *Human Vaccines & Immunotherapeutics.* 2015. 11(7):1717-1724.