Vaccination Against Hepatitis B Virus: Are Thai Medical Students Sufficiently Protected?

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Medical students are frequently at risk of being infected by hepatitis B virus (HBV) via occupational exposure to infected blood or body fluids. In 2002, the Faculty of Medicine Siriraj Hospital provided screening tests for HBV serology to all medical students for a vaccination campaign against the infection. There were 1,165 medical students tested. Eight hundred and eleven (69.6%) students had immunity by previous vaccination, but more importantly 212 (18.2%) had no immunity and required vaccination. Most of the students who needed to be vaccinated were in the pre-clinical year (82.5%). Moreover, the students in the pre-clinical year who had previous vaccination had a 2.2 times greater risk of having negative anti-HBs than the students in the clinical year (OR = 2.2, 95%CI = 1.4-3.5). This is because they might have been vaccinated when they were young and the antibody waned overtime.

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Hepatitis B viral infection (HBV) is a well-known occupational risk for healthcare workers (HCW)[1]. A serological study conducted in the United States reported HCW had a prevalence of HBV infection approximately 10 times higher than the general population[2]. The risk of HBV infection is related to the degree of contact with infected blood or body fluids and also the presence of the hepatitis B e antigen (HBeAg) of the source person[3]. Several studies of HCW who had sustained injuries from needles contaminated with blood containing HBV showed the risk of developing clinical hepatitis when the blood was both hepatitis B surface antigen (HBsAg)-and HBeAg-positive of 22%-31%, and the risk of developing serological evidence of HBV infection was 37%-62%[1]. HBV can survive in dried blood at room temperature on environmental surfaces for at least 1 week[4]. As a result, HCW can be infected from infected blood or body fluid exposures that inoculate HBV into cutaneous scratches, abrasions, or on mucosal surfaces.

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Thailand has been classified to be an intermediate endemic country for HBV infection, classified by prevalence of HBsAg of 2-7%[5]. Thus, HCW would have more potential exposure to HBV-contaminated blood or body fluids. Since 2001, more than 200 occupational exposures to blood or body fluids per year among HCW have been reported in Siriraj Hospital. Medical students are among those at high risk of exposure, because they are relatively inexperienced. During 1994-2001 in Siriraj Hospital, medical students and nurses reported occupational exposures more than other HCW either by needle-stick injury or mucosal exposure[6]. According to hepatitis B (HB) vaccination, Thailand has integrated the vaccine as part of an expanded programme on immunization (EPI) since 1992. Subsequently, the study from five representative provinces showed an average of HB vaccine coverage of 82.3%[7]. Medical students, however, who were born before 1992 have not been vaccinated in EPI. Catch-up vaccination was not adequate, since only educated and wealthy families would have vaccinated their children. Therefore, some of the medical students would have not received HB vaccination.

Given the universal recommendation of hepatitis B vaccination for all HCW at risk, the high incidences of occupational exposure, and potential of non-vaccination among Siriraj medical students, the Faculty of Medicine Siriraj Hospital have encouraged vaccination against HBV for all students since 2002. In the initial phase, all serological tests for HBV were supported by the hospital. In the present study, the authors reported the HBV serological status of all students in 2002 prior to a mass vaccination campaign to ensure sufficient protection against HBV.

Material and Method

At the beginning of the first semester 2002, all of the 1st year to the 6th year medical students were asked to be tested for hepatitis B immunity on a voluntary basis. Their histories of previous hepatitis B vaccination were recorded using self-report questionnaire. Blood samples were collected from May to June 2002. Sera were separated by centrifugation and frozen at -20 C until tested. All sera were first tested for hepatitis B surface antibody (anti-HBs) by a Microparticle Enzyme Immunoassay (MEIA) (AxSym AUSAB , Abbott Laboratories Diagnosis Division, Abbott Park, IL, USA). The anti-HBs-negative sera were further assayed for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) by MEIA (AxSym HBsAg (V2) and AxSym CORE , Abbott Laboratories Diagnosis Division, Abbott Park, IL, USA, respectively). Subsequently, the anti-HBs-positive sera from the students who could not remember previous vaccinations or had no vaccination were tested for anti-HBc. The anti-HBs titer of greater than 10 mIU/ml was considered protective[8,9].

Based on the results of sera and history of previous hepatitis B vaccination, the hepatitis B serological statuses of students were classified into 5 groups: 1) "Immune by vaccination" was a student with anti-HBs-positive alone regardless of history of previous vaccination, 2) "Waning protective antibody after vaccination" was a student, with negative for all tests, who had previous vaccination, 3) "No immunity" was a student, with negative for all tests, who had no vaccination or cannot remember the previous vaccination, 4) "Immune by natural infection" was a student with anti-HBs-and anti-HBc-positive, and 5) "Chronic infection" was a student with HBsAg- and anti-HBc-positive. The hepatitis B serological statuses of students were compared by each medical year. In addition, the anti-HBs titers of students in the pre-clinical year were compared with those in the clinical year.

A booster dose was given to the students who had waning protective antibody after vaccination. The authors were not sure if they really received the vaccine, because their vaccination records cannot be traced. These students were subsequently tested for anti-HBs at 1-2 months after a booster dose. The authors also asked the students who needed HB vaccination to have post-vaccination anti-HBs testing after completing a primary course 1-2 months. The students with chronic infection were examined and tested for liver function and HBeAg.

Frequency tables were classified by medical year and history of vaccination against Hepatitis B virus as well as anti-HBs status were analyzed. Odd ratio and 95% confidence interval were presented as the risk factor.

Results

In the academic year of 2002, there were 1,299 medical students, including the 1st year to the 6th year students, in the Faculty of Medicine Siriraj Hospital. One thousand one hundred and sixty five students (89.7%), comprised of 592 males and 573 females, were tested. The mean age was 20.5 years old (SD = 1.6). Eight hundred and eleven (69.6%) had immunity against HBV by previous vaccination, 83 (7.1%) had waning antibody although they had already been vaccinated, and 59 (5.1%) had been infected naturally. Seventeen (1.5%) with chronic infection were found to be chronic carriers with all negative for HBeAg but one. More importantly, 212 (18.2%) had no immunity and needed to be vaccinated. Most of them were studying in the pre-clinical year. The details of hepatitis B serological status by medical year are shown in Table 1.

Table 2 shows the levels of anti-HBs titer of those who had previous vaccination divided according to each medical year. Eighty four (9.4%) of 894 had negative anti-HBs, anti-HBs titer less than 10 mIU/ml, and 531 (59.4%) had anti-HBs titer greater than 100 mIU/ml. However, when the authors reclassified the medical year to be pre-clinical (1st to 3rd year) and clinical (4th to 5th year) year, the authors found the risk to have negative anti-HBs was 2.2 times greater in the pre-clinical year than in the clinical year (OR = 2.2, 95%CI = 1.4-3.5) shown in Table 3.

In the present study, 417 (35.8%) could not remember whether or not they had previously been vaccinated, and 223 (53.5%) of 417 were found to be immune by the previous vaccination given anti-HBs-positive and anti-HBc-negative results shown in Table 4. Nine students reported no previous vaccination,

but serological test showed immunity by vaccination. Surprisingly, 5 students who were naturally infected and 5 students who were chronic carriers reported that they had previously been vaccinated.

Of 83 students who had waning of antibody after vaccination, 68 students came for a booster dose, and only 41 came back for antibody testing. Thirty five students had seroconversion with high titer of

Table 1. Hepatitis B serological status of the 1st to 6th year Siriraj medical students in 2002

Hepatitis B Serological Status	Medical Year						Total n (%)
	1st n (%)	2nd n (%)	3rd n (%)	4th n (%)	5th n (%)	6th n (%)	
1. Immune by vaccination	104(59.4)	135 (62.8)	106(51.7)	142(74.7)	154(81.5)	170(89)	811 (69.6)
2. Waning protective antibody after vaccination	15(8.6)	22(10.2)	14(6.8)	8(4.2)	14(7.4)	10(5.2)	83 (7.1)
3. No immunity	49(28.0)	53(24.7)	73(35.6)	23(12.1)	14(7.4)	0(0.0)	212 (18.2)
4. Immune by natural infection	5(2.9)	5(2.3)	8(3.9)	9(4.7)	6(3.2)	9(4.7)	42 (3.6)
5. Chronic infection	2(1.1)	0(0.0)	4(2.0)	8(4.2)	1(0.5)	2(1.0)	17 (1.5)
Total	175(100.0)	215(100.0)	205(100.0)	190(100.0)	189(100.0)	191(100.0)	1165 (100.0)

Table 2. Anti-HBs titers among the 1st to 6th year Siriraj medical students in 2002 who had previous vaccination

Anti-HBs Titer	Medical Year						Total n (%)
	1st n (%)	2nd n (%)	3rd n (%)	4th n (%)	5th n (%)	6th n (%)	
1. < 10 mIU/ml	15(12.6)	22(14.0)	15(12.5)	8(5.3)	14(8.3)	10(5.6)	84(9.4)
2. 10-100 mIU/ml	41(34.5)	47(29.9)	41(34.2)	52(34.7)	34(20.2)	64(35.6)	279(31.2)
3. 101-1,000 mIU/ml	36(30.3)	56(35.7)	46(38.3)	44(29.3)	62(36.9)	79(43.9)	323(36.1)
4. > 1,000 mIU/ml	27(22.7)	32(20.4)	18(15.0)	46(30.7)	58(34.5)	27(15.0)	208(23.3)
Total	119(100.0)	157(100.0)	120(100.0)	150(100.0)	168(100.0)	180(100.0)	894(100.0)

Table 3. Anti-HBs status of Siriraj medical students who had previous vaccination by the pre-clinical year and clinical year

Medical Year	Anti-HBs Status			Odds ratio (95%CI)
	Negative n (%)	Positive n (%)	n (%)	
Pre-clinical year (1st to 3rd year)	52 (61.9)	344(42.5)	396(44.3)	2.2 (1.4-3.5)
Clinical year (4th to 6th year)	32 (38.1)	466(57.5)	498(55.7)	
Total	84 (100.0)	810(100.0)	894(100.0)	

Table 4. Hepatitis B serological status of Siriraj medical students in 2002 and history of previous vaccination

Hepatitis B Serological Status	History of Previous Hepatitis B Vaccination			Total n (%)
	Not Remember n (%)	Not Vaccinated n (%)	Vaccinated n (%)	
1. Immune by vaccination	223 (53.5)	9 (11.3)	579 (86.7)	811 (69.6)
2. Waning protective antibody after vaccination	4 (1.0)	0 (0.0)	79 (11.8)	83 (7.1)
3. No immunity	163 (39.1)	49 (61.3)	0 (0.0)	212 (18.2)
4. Immune by natural infection	19 (4.6)	18 (22.5)	5 (0.7)	42 (3.6)
5. Chronic infection	8 (1.9)	4 (5.0)	5 (0.7)	17 (1.5)
Total	417 (100.0)	80 (100.0)	668 (100.0)	1165 (100.0)

anti-HBs at approximately 1-2 months after a booster dose. In the meantime, the authors found 6 students had anti-HBs titer less than 10 mIU/ml at 1 month after a booster dose. They continued to complete two more doses, and two of them had finally seroconverted. The authors also found a non-responder who did not respond to the second course of hepatitis B vaccine. The rest did not come for repeat anti-HBs. Only 26 of 212 students who completed their primary course of HB vaccination after the campaign had a post vaccination test for anti-HBs. All were seroprotective.

Discussion

Medical students are a high risk group for blood-borne infections including human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV). Among these three viral infections, HBV is the most infectious, and persistent infection may lead to the development of chronic hepatitis, cirrhosis, and hepatocellular carcinoma[10]. However, HBV can be protected by effective vaccination. According to the recommendation of post exposure prophylaxis for persons who have no immunity against HBV, both active immunization with HB vaccine and/or passive immunization with hepatitis B immune globulin (HBIG) are recommended[1]. Recently, HBIG is not only expensive, but also usually lack of supply. When a medical student with no history of HB vaccination and serological status sustains a needle stick injury, it is a disturbing situation to get a serological test either for the student or the source person even in a teaching hospital setting. Thus, there is no doubt that HB vaccination in medical students is cost-effective in general practice.

In the present study, 1,165 (89.7%) out of all students in 2002 were tested which might represent the HB seroprevalence of Thai medical students. Overall, 811 (69.6%) had immunity against HBV from previous vaccination, 42 (3.6%) had immunity by natural infection. Seventeen students (1.5%) were chronic carriers which were lower than the prevalence of Thai general population. Our group reported the prevalence of HBsAg at Thai central region and Bangkok of 3.6% in 13-25 years old age group[11]. The students who knew their chronic infection status would not have come for the screening causing the low prevalence in the presented data. Catch-up HB vaccination was quite inadequate in students prior to entrance for medical school, because the presented data showed 212 (18.2%) of all students had no immunity, especially students in the pre-clinical year. The percentages of no immunity ranged from 24.7-35.6% in each pre-clinical year higher than each clinical year. A study from Chulalongkorn University showed fewer than 50% of pre-clinical year students had been vaccinated[12]. This emphasizes the need for catch-up vaccination in the first year of medical school.

The students in the pre-clinical year who had previous vaccination had a 2.2 times greater risk to have negative anti-HBs, which was < 10 mIU/ml, than the students in the clinical year (OR = 2.2, 95%CI = 1.4-3.5). The explanation was that the students in the pre-clinical year would have been vaccinated when they were young, and the antibody level waned over time. The authors have also learned that a lot of students in the 5th and 6th medical years had their catch-up vaccination after entering the medical school, so their antibody should have been detectable. Anti-HBs concentrations decrease more quickly during the first few years after vaccination than they do later on[13], and the persistence of antibody is related to the peak response of vaccine responders[14]. After vaccination of approximately 5 years, the levels of antibody in some individuals decline to low or undetectable levels[15]. However, the antibody level above 10 mIU/ml is not essential for protection against significant breakthrough infection, because rapid and effective anamnestic response via pool of memory B lymphocytes will emerge after exposure to HBV within days[16]. Long-term follow-up of vaccine recipients among hospital employees in the Netherlands indicated that immune memory persisted up to 15 years[17]. In addition, no published vaccine responder who had benign breakthrough infection developed chronic infection. Therefore, the routine booster is not recommended for healthy HCW[18,19].

The post-vaccination testing for anti-HBs is not routinely practiced given the fact that HB vaccine has more than 90% efficacy in HCW[20]. Also vaccination record is not usually kept by vaccine recipients. Therefore, most of them would not remember their histories of vaccination. The present data showed that of 417 students who could not remember their histories of previous vaccination, 223 (53.5%) were found to have immunity by having solely positive anti-HBs indicated past vaccination. The students who could not remember their HB vaccination would cost us a lot of budget to test for anti-HBs and unnecessary vaccination when occupational exposure occurs.

After a booster dose all 35 students with waning antibody who came for antibody testing had

robust anamnestic response within 1-2 months determining the recognition of antigen by the memory B lymphocyte pool. There were 6 students who had a very low response after a booster dose, who might be non-responders. Five were not really sure about their vaccination in the past, because no records could be traced. Thus, they would have been non immunized persons. Only one was a real non-responder after a second course of vaccine without antibody response.

In summary, vaccination against hepatitis B viral infection among medical students is very important. Students in the pre-clinical year at risk are not sufficiently protected because catch-up vaccination is not enough before entering medical school. Therefore, the authors need to continue HB vaccine campaign in the pre-clinical year at least until 2010 when the children born after 1992 and received HB vaccine in EPI enter medical school. However, further studies are needed in medical students, especially those who had been vaccinated more than 15 years ago, to determine the duration of immunological memory and whether and when a booster dose should be recommended?

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วัคซีนป้องกันการติดเชื้อไวรัสตับอักเสบบี: นักศึกษาแพทย์ไทยได้รับการป้องกันเพียงพอหรือไม่?

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นักศึกษาแพทย์เป็นกลุ่มเสี่ยงสำคัญที่มีโอกาสติดเชื้อไวรัสตับอับเสบบีจากอุบัติเหตุทางการแพทย์โดยสัมผัสเลือด หรือ สิ่งคัดหลั่งที่ติดเชื้อ ในต้นปีการศึกษา 2545 คณะแพทยศาสตร์ศิริราชพยาบาลได้ทำการตรวจเลือดหาภูมิคุ้มกัน หรือ การติดเชื้อไวรัสตับอักเสบบีของนักศึกษาแพทย์ศิริราชทุกชั้นปีเพื่อให้วัคซีนป้องกันการติดเชื้อ พบว่าจากจำนวนนักศึกษาแพทย์ 1,165 ราย ที่เข้ารับการตรวจ นักศึกษา 811 ราย (69.6%) มีภูมิคุ้มกันแล้วจากการได้รับวัคซีนมาก่อน แต่มีอีก 212 ราย (18.2%) ยังไม่มีภูมิคุ้มกัน และจำเป็นต้องได้รับวัคซีน โดยส่วนใหญ่กำลังศึกษาในชั้นปรีคลินิก (82.5%) นอกจากนี้นักศึกษาในชั้นปรีคลินิกที่มีประวัติเคยรับวัคซีนมาก่อนมีระดับ anti-HBs เป็นลบมากกว่านักศึกษาในชั้นคลินิก 2.2 เท่า (OR = 2.2, 95%CI = 1.4-3.5) สาเหตุอาจเกิดจากนักศึกษาในชั้นปรีคลินิกได้รับวัคซีนตอนอายุน้อยทำให้ภูมิคุ้มกันลดลงเมื่อเวลาผ่านมานาน