

Hepatitis B Vaccination Status among Japanese Travelers

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Summary: This study clarified the characteristics of travelers who received hepatitis B vaccinations. Subjects were 233 Japanese travelers who visited our clinic prior to travel. We summarized the characteristics of the clients and performed two comparative studies: first, we compared a hepatitis B-vaccinated group with an unvaccinated group; second, we compared a group that had completed the hepatitis B vaccine series with a group that did not complete the series. The hepatitis B vaccine was administered to 152 clients. Factors positively associated with the hepatitis B vaccination (after adjusting for age and sex) included the following: travel for business or travel as an accompanying family member; travel to Asia; travel for a duration of a month or more; and, inclusion of the vaccine in a company or organization's payment plan. Meanwhile, factors negatively associated with the vaccination were travel for leisure or education, and travel to North America or Africa. Among 89 record-confirmed cases, only 53 completed 3 doses. The completion rate was negatively associated with the scheduled duration of travel if it was from a month to less than a year (after adjusting for age and sex). The present study provides a basis for promoting vaccination compliance more vigorously among Japanese adults.

Key words Japanese travelers, pre-travel consultation, hepatitis B vaccine, completion rate

INTRODUCTION

Traveling abroad is now popular among Japanese individuals; approximately 16 million Japanese travel abroad annually [1]. The use of travel clinics has been increasing, particularly in urban areas [2], although pre-travel health consultations remain insufficient. The clients of travel clinics who attend pre-travel health consultations in Japan are mainly long-term travelers [3]; approximately 60% of long-term travelers receive some form of vaccination before departure [2]. In pre-travel health consultations, the hepatitis A and typhoid fever vaccines are recommended for short-term travelers, while hepatitis B and rabies vaccines are additionally recommended for long-term travelers [2].

The efficacy and safety of the hepatitis B vaccine is well established, and its use is universal in most developed countries [4-6]. The 3-dose vaccine series provides protective antibodies to 30-55% after the first dose, 75% after the second dose, and >90% after the third dose among healthy adults aged <40 years [4]. Japan is considered to be a low/intermediate area for hepatitis B virus infection [6,7], which means that the universal prevalence of vaccinations is also effective from the viewpoint of economics [8]. Universal vaccinations for infants in Japan are now planned to start in October 2016, but universalization is not the rule among adults. Among hepatitis B patients, the prevalence of genotype A is increasing in Japan [9]. And the tendency to develop chronic of hepatitis is higher in

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Abbreviations: CI, confidence interval; OR, odds ratio; SBHCs, two school-based health centers.

genotype A than in other genotypes. Under these conditions, Japanese travel clinics have an important role to play in increasing hepatitis B vaccine coverage among adults, regardless of their travel characteristics.

Although Japanese pre-travel consultations have previously been described in the literature [10-12], no reports have focused on the hepatitis B virus vaccination. Kurume University Hospital is located in Kurume City (Fukuoka Prefecture, Japan). In 2007, our travel clinic initiated pre-travel consultations at the university hospital. As of August 2015, more than 10,000 clients had consulted our clinic for vaccinations. We herein report our practice, with a focus on hepatitis B vaccination, in order to clarify the characteristics (including the vaccine completion rate) of Japanese pre-travel clients.

MATERIALS AND METHODS

This present study involved Kurume University Hospital, a 1,025-bed tertiary care medical center, and was conducted by the Department of Infection Control and Prevention, which manages the travel clinic. Our two travel doctors present and explain in detail the vaccines that we recommend and/or the client (individual/company/organization) requests, on the first day of consultation. Between January and December 2013, our clinic served 233 new pre-travel Japanese clients. We retrospectively reviewed their medical charts and classified their factors as follows: age, sex, hepatitis B vaccine status (administered or not), purpose of travel, interval between consultation and departure, scheduled duration of travel, area of destination(s), cost of vaccines (whether the cost was covered by a company/organization payment plan or not), the client's (including company/organization) request for hepatitis B vaccination when making the reservation for consultation, and their residence (Kurume city or elsewhere; analyzed in the study of completion rates). In addition, we performed a telephone survey to establish how many times a patient had received a hepatitis B vaccination if there were no documents related to the second or third doses in our medical charts. We summarized the characteristics of the clients and performed two comparative studies: first, comparing a hepatitis B-vaccinated group with an unvaccinated group; second, comparing a group that completed the hepatitis B vaccine series with a group that did not complete the series.

All analyses were performed using JMP (version 11.0), R (version 3.1.3), and EZR software program (Saitama Medical Center, Jichi Medical University,

Saitama, Japan). EZR is a graphical user interface for the R [13]. Univariate analysis was conducted using Fisher's exact test and Wilcoxon's rank sum test for categorical and continuous data, respectively. Multiple logistic regression analyses adjusting for age and sex were also performed, for each of the factors showing P values < 0.05 (comparison between groups with and without hepatitis B vaccination) or < 0.10 (comparison between a group that completed the hepatitis B vaccine series and an uncompleted group) in the univariate analyses.

The present study was approved by the Kurume University Research Ethics Committee (<http://www.med.kurume-u.ac.jp/med/joint/rinri/>) (Research No. 15035).

RESULTS

Our clinic served 233 Japanese pre-travel clients during the study period. The characteristics of the clients are summarized in Table 1. Most of the travelers who visited our clinic were long-term business travelers. Asia was the major travel destination (175 cases, 75%): Southeast Asia (96 cases), South Asia (52 cases), and East Asia (28 cases). A total of 152 travelers (65%) received hepatitis B vaccinations.

Results of a univariate analysis comparing the hepatitis B-vaccinated group with the unvaccinated group are shown in Table 2. Factors positively associated with the hepatitis B-vaccinated group were age, sex (male), the purpose of travel (business and, accompanying family members), the areas of destination (Asia), the scheduled duration of travel (1 month \leq , or 1 year \leq), clients who belonged to a company/organization paying for the vaccines, and clients (company/organization) who requested hepatitis B vaccination when they were reserving their consultation. Meanwhile, factors negatively associated with the hepatitis B-vaccinated group were the areas of destination (North America and Africa) and scheduled duration of travel (< 1 month).

Next, by multiple logistic regression adjusted for age and sex, which were biased between the hepatitis B-vaccinated group and the unvaccinated group, we evaluated each of the factors that were significant ($P < 0.05$) in the univariate analysis. Table 3 shows that the same factors were still significantly associated with the difference between the vaccinated and unvaccinated group. Regarding the purposes of travel, business or accompanying family members was positively associated with vaccination (odds ratio [OR] = 16.9, (95% confidence interval [CI] 7.1-40.0) and OR=7.0 (95% CI 2.4-20.4)) while leisure or education was

TABLE 1.
The characteristics of the Japanese Pre-travel clients (n=233)

	(%)			(%)	
Age, mean \pm SD (year)	33.2	\pm 16.1	Interval between consultation and departure		
Sex (male)	158	(68)	< 1 week	4	(2)
Hepatitis B virus vaccine administration			1 week \leq and < 1 month	90	(39)
Yes	152	(65)	1 month \leq and < 6 months	127	(55)
No	81	(35)	6 months \leq	11	(5)
Purpose of travel			(Unknown)	1	
Leisure	30	(13)	Scheduled duration of travel		
Business	119	(51)	< 1 month	45	(19)
Education	32	(14)	1 month \leq and < 1 year	84	(36)
Volunteer	5	(2)	1 year \leq	87	(37)
Accompanying family members	33	(14)	(Unknown)	17	
VFRs	9	(4)	Cost of vaccines		
Mission	5	(2)	Company/organization pays	131	(56)
Area of destination(s)			Clients pay	101	(43)
Asia	175	(75)	(Unknown)	1	
Africa	16	(7)	Client requested hepatitis B vaccination by reservation		
Europe	2	(1)	Yes	121	(52)
North America	17	(7)	No	112	(48)
Central and South America	15	(6)			
Around the world	8	(3)			

SD, standard deviation; VFRs, visiting friends and relatives

negatively associated with vaccination (OR=0.12 (95% CI 0.04-0.30) and OR=0.08 (95% CI 0.03-0.22)). Regarding the areas of destination, Asia had a positive association (OR=3.3 (95% CI 1.7-6.3)) while North America and Africa both had a negative association (OR=0.10 (95% CI 0.03-0.38) and OR=0.09 (95% CI 0.02-0.34)). In addition, positive associations were found for travel with a duration longer than 1 month (OR=20.4 (95%CI 7.6-54.9)), inclusion of the vaccine in a company or organization's payment plan (OR=21.5 (95% CI 9.6-48.4)), and client's request for hepatitis B vaccine at the time of booking (OR=74.0 (95% CI 23.8-230.3)).

Furthermore, we also examined the proportion of cases that had completed the series of vaccinations. The number of clients who got 1, 2, or 3 vaccinations is shown in Fig. 1. Among the 89 cases in which the number of doses of vaccine was confirmed (dark gray area in Fig. 1), 36 (40%) did not complete all three doses. Table 4 shows results comparing the group that completed the hepatitis B vaccine series with the group that did not. Statistically significant differences ($P < 0.05$) were found only in sex (male) and scheduled travel duration (from 1 month to less than 1 year). Mul-

tiple logistic regression analysis showed a negative association of scheduled travel duration (from 1 month to less than 1 year) with the completion of the series of hepatitis B vaccination (OR=0.4 (95% CI 0.1-0.9), $P = 0.03$) after adjusting for age and sex (Table 5). In addition, more than 6 months interval between the first consultation and departure showed a trend of positive association with the completion of the vaccine series (OR=6.4, 95% CI 0.8-55.7, $P = 0.09$)

DISCUSSION

Sixty-five percent of the clients in the present study underwent hepatitis B vaccination; however, the completion rate of the vaccine series was only 60%. Since 73% of our participant's travel was long-term (1 month \leq), the high proportion of hepatitis B vaccination was not surprising. Namikawa et al. found that only 4.3% of Japanese tourists and individual short-term travelers [10] had been vaccinated for hepatitis B. In 2009, Hamada et al. found that 38.1% of long-term Japanese travelers who were traveling to developing countries had been vaccinated for hepatitis B [11]. Although the populations of those reports included overall travelers,

TABLE 2.
Comparison between groups with and without hepatitis B vaccination

	Hepatitis B unvaccinated group (n = 81)	(%)	Hepatitis B vaccinated group (n = 152)	(%)	P value
Age, median (25%-75%), years	26.0 (21.0-39.0)	–	34.0 (26.0-42.3)	–	0.02 ¹⁾
Sex (male)	40	(49.4)	118	(77.6)	< 0.0001 ²⁾
Purpose of travel					
Business	13	(16.0)	106	(69.7)	< 0.0001 ²⁾
Accompanied family	6	(7.4)	27	(17.8)	0.03 ²⁾
Leisure	23	(28.4)	7	(4.6)	< 0.0001 ²⁾
Education	26	(32.1)	6	(3.9)	< 0.0001 ²⁾
Mission	4	(4.9)	1	(0.7)	0.05 ²⁾
Volunteer	3	(3.7)	2	(1.3)	0.34 ²⁾
VFRs	6	(7.4)	3	(2.0)	0.07 ²⁾
Area of destinations					
Asia	48	(59.3)	127	(83.6)	< 0.0001 ²⁾
Central and South America	2	(2.5)	13	(8.6)	0.09 ²⁾
North America	14	(17.3)	3	(2.0)	< 0.0001 ²⁾
Africa	13	(16.0)	3	(2.0)	< 0.0001 ²⁾
Europe	1	(1.2)	1	(0.7)	1.00 ²⁾
Around the world	3	(3.7)	5	(3.3)	1.00 ²⁾
Interval between consultation and departure					
< 1 week	2	(2.5)	2	(1.3)	0.61 ²⁾
1 week ≤ and < 1 month	36	(44.4)	54	(35.5)	0.20 ²⁾
1 month ≤ and < 6 months	42	(51.9)	85	(55.9)	0.58 ²⁾
6 months ≤	1	(1.2)	10	(6.6)	0.10 ²⁾
1 month ≤	43	(53.1)	95	(62.5)	0.16 ²⁾
Scheduled duration of travel					
< 1 month	38	(46.9)	7	(4.6)	< 0.0001 ²⁾
1 month ≤ and < 1 year	25	(30.9)	59	(38.8)	0.25 ²⁾
1 year ≤	15	(18.5)	72	(47.4)	< 0.0001 ²⁾
1 month ≤	40	(49.4)	131	(86.2)	< 0.0001 ²⁾
Payment for vaccines					
Company/organization	12	(14.8)	119	(78.3)	< 0.0001 ²⁾
Client's request for hepatitis B vaccine when reserving	4	(4.9)	117	(77.0)	< 0.0001 ²⁾

1) Wilcoxon's rank sum test, 2) Fisher's exact test. VFRs: visiting friends and relatives

and were not limited to the clients of travel clinics, the reported trend in hepatitis B vaccination among travelers is compatible with our results.

Long-term travel (1 month ≤), travel due to business or accompanying family members, travel to Asian countries, and belonging a company/organization that would pay for vaccines were positively associated with hepatitis B vaccination compliance. Hepatitis B vac-

cination is thought to be of a lower priority for short-term travelers (< 1 month) than hepatitis A or tetanus vaccination [2], and is recommended particularly for long-term travelers. Among our participants, the proportion of long-term travel (1 month ≤) was positively associated with the other factors: business trips (95/117 cases, 81%), accompanying family members (25/33 cases, 76%), travel to Asia (126/175 cases, 72%), and a

TABLE 3.
Factors influencing hepatitis B vaccination (after adjusting for age and sex)

	OR	95% CI	P value
Purpose of travel			
Business	16.9	7.1-40.0	<0.0001
Accompanied family	7.0	2.4-20.4	0.0003
Leisure	0.12	0.04-0.30	<0.0001
Education	0.08	0.03-0.22	<0.0001
Area of destinations			
Asia	3.3	1.7-6.3	0.0003
North America	0.10	0.03-0.38	0.0007
Africa	0.09	0.02-0.34	0.0005
Scheduled duration of travel			
< 1 month	0.05	0.02-0.13	<0.0001
1 year ≤	5.8	2.8-12.0	<0.0001
1 month ≤	20.4	7.6-54.9	<0.0001
Payment for vaccines			
Company/organization	21.5	9.6-48.4	<0.0001
Client's request for hepatitis B vaccine when reserving	74.0	23.8-230.3	<0.0001

Each factor was evaluated by logistic regression adjusting for age and sex. CI: confidence interval, OR: odds ratio, VFRs: visiting friends and relatives

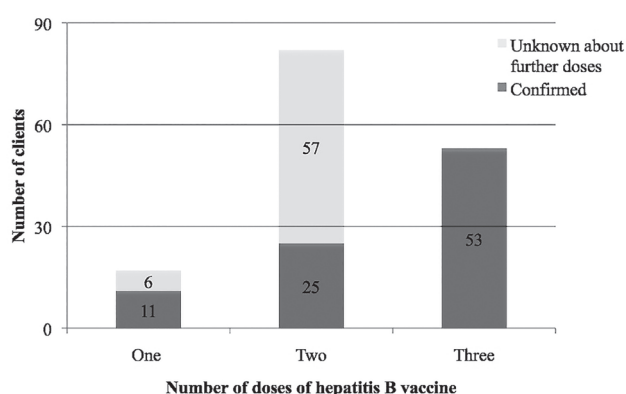


Fig. 1. The number of confirmed/possible hepatitis B-vaccinated clients.

company/organization's payment plan for vaccination (102/131 cases, 78%).

On the other hand, short-term travel (< 1 month), travel due to leisure or education, and travel to North America or Africa were negatively associated with hepatitis B vaccination compliance. Types of vaccines among clients who were traveling with educational entities had been decided by either the school/agency for the study abroad program or by the company. This type of inflexibility could explain the lower proportion of hepatitis B vaccination among the participants who

traveled due to education. Leisure travel is relatively short and the vaccine cost might be a barrier for clients. In addition, such short-term clients might consider themselves to be at a "low risk" of contracting sexually transmitted or blood-borne infections. However, short-term travel is also a risk factor for hepatitis B infection [14]. In the Western Pacific and South East Asian regions (hepatitis B virus hyperendemic areas), which are popular destinations, there are only three countries (Australia, Nepal and Malaysia) in which the estimated prevalence of hepatitis B virus carriers is lower than that of Japan [7]. Despite the fact that Africa is also an endemic area, most travelers visiting Africa were short-term (10/16 cases), and for leisure (9/16 cases), which might be reasons for the low proportion of hepatitis B vaccination. However, most of the participants return to Japan, which has a low/intermediate number of hepatitis B carriers. The Ministry of Health, Labor and Welfare (Japan) as well as a recent study [7] estimates that there are more than 1 million hepatitis B virus carriers in Japan. Hepatitis B virus infection was previously mostly a matter of mother-to-child transmission; however, sexual transmission has become more frequent among the younger generations in Japan [15]. Moreover, a genotypic shift in the hepatitis B virus (from C to A) has been documented. Kobayashi et al. summarized the cases of 4,430 acute and chronic hepatitis patients who were treated at a single tertiary

TABLE 4.
Comparison between a group that completed the hepatitis B vaccine series and an uncompleted group

	Series uncompleted group (n = 36)	(%)	Series completed group (n = 53)	(%)	P value
Age, median (25%-75%), years	35.5 (28.0-42.8)	—	31.8 (26.0-40.0)	—	0.19 ¹⁾
Sex (male)	33	(91.7)	38	(71.7)	0.03 ²⁾
Purpose of travel					
Business	29	(80.6)	32	(60.4)	0.06 ²⁾
Accompanied family	4	(11.1)	13	(24.5)	0.17 ²⁾
Leisure	0	(0.0)	3	(5.7)	0.27 ²⁾
Education	2	(5.6)	2	(3.8)	1.00 ²⁾
Mission	1	(2.8)	0	(0.0)	0.40 ²⁾
Volunteer	0	(0.0)	1	(1.9)	1.00 ²⁾
VFRs	0	(0.0)	2	(3.8)	0.51 ²⁾
Area of destinations					
Asia	33	(91.7)	44	(83.0)	0.35 ²⁾
Central and South America	2	(5.6)	5	(9.4)	0.70 ²⁾
North America	0	(0.0)	1	(1.9)	1.00 ²⁾
Africa	1	(2.8)	0	(0.0)	0.40 ²⁾
Europe	0	(0.0)	1	(1.9)	1.00 ²⁾
Around the world	0	(0.0)	2	(3.8)	0.51 ²⁾
Interval between consultation and departure					
< 1 week	1	(2.8)	0	(0.0)	0.40 ²⁾
1 week ≤ and < 1 month	14	(38.9)	18	(34.0)	0.66 ²⁾
1 month ≤ and ≤ 5 months	20	(55.6)	27	(50.9)	0.83 ²⁾
6 months ≤	1	(2.8)	8	(15.1)	0.08 ²⁾
1 month ≤	21	(58.3)	35	(66.0)	0.51 ²⁾
Scheduled duration of travel					
< 1 month	2	(5.6)	2	(3.8)	1.00 ²⁾
1 month ≤ and < 1 year	22	(61.1)	16	(30.2)	0.005 ²⁾
1 year ≤	10	(27.8)	26	(49.1)	0.05 ²⁾
1 month ≤	32	(88.9)	42	(79.2)	1.00
Payment for vaccines					
Company/organization	30	(83.3)	45	(84.9)	1.00 ²⁾
Clients request for hepatitis B vaccine when reserving	29	(80.6)	42	(79.2)	1.00 ²⁾
Residing in Kurume city	4	(11.1)	11	(20.8)	0.27 ²⁾

1) Wilcoxon's rank sum test, 2) Fisher's exact test. VFRs: visiting friends and relatives

care hospital in Tokyo over a 35-year period [16]. They found that approximately 40% of acute hepatitis was caused by genotype A, despite the fact that the prevalence of genotype A in the 1976-1990 period was 8%. Another study reported that 23% of patients with genotype A, advance to a chronic state [9]. Therefore the risk of hepatitis B virus infection also exists in Ja-

pan. In consideration of the possibility of the forms of hepatitis B virus transmission in Japan, Japanese travel doctors should consider recommending hepatitis B vaccinations to all unvaccinated clients, regardless of the characteristics of their travel.

A scheduled duration of travel of 1 month ≤ and < 1 year was associated with a low completion rate of

TABLE 5.
Factors influencing completion of the series of hepatitis B vaccination (after adjusting for age and sex)

	OR	95% CI	P value
Purpose of travel			
Business	0.8	0.2-2.7	0.71
Interval between consultation and departure			
6 months \leq	6.4	0.8-55.7	0.09
Scheduled duration of travel			
1 month \leq and $<$ 1 year	0.4	0.1-0.9	0.03
1 year \leq	2.1	0.8-5.5	0.12

Each factor was evaluated by logistic regression adjusting for age and sex. CI: confidence interval, OR: odds ratio

hepatitis B vaccination. And there was a trend whereby travelers with long intervals between consultation and departure (6 months \leq) tended to complete the series of hepatitis B vaccination. Clients with a scheduled duration of travel \geq 1 year were more likely to receive vaccinations, probably during a temporary return or during their visit to foreign countries. More than half of vaccination record-confirmed clients with a scheduled travel duration of less than 1 year (24 out of 42) did not get the third dose of hepatitis B vaccine, despite the fact that they had come back to Japan, possibly because they may have underestimated the risk of hepatitis B infection in Japan.

In our consultation, we emphasize that the completion of the series of hepatitis B vaccinations is more important than in the case of hepatitis A, because of the low positive rate of protective antibodies against hepatitis B virus after 1 or 2 doses of vaccination [4]. As far as we could ascertain, only one previous report has focused on the rate of hepatitis B vaccination completion in the setting of a travel clinic [17]. In other settings such as primary care clinics or sexually transmitted diseases clinics, there are reports of approaches for improving the completion rate [18,19]. Reminders (mail, telephone, and postcards) and unusual vaccine schedules (accelerated schedules and two-visit schedules) have been discussed in the literature [17-20]. Lancman et al. compared facilities (two school-based health centers (SBHCs), and one hospital-based adolescent health center) which provided health services, including hepatitis B vaccinations [18]. The completion rate of vaccinated students at one particular center (SBHC-A), which only used reminder postcards, was higher (76%) than that in the other centers (approximately 20%). The Wong's study was the only report that focused on a travel clinic setting [17]. They investigated a two-visit schedule (a double-dose on day 0

and a single-dose at 4-12 months), and found that only 32.6% of clients completed the schedule, and that the completion rate at a clinic that reminded clients by telephone was higher (48.9%) than at other clinics. We usually administer hepatitis B vaccine on day 0, then at 1 month, and 6 months. Because accelerated schedules and two-visit schedules are not officially approved in Japan, the administration of a second dose at 2 or 3 weeks is sometimes unavoidable due to the lack of a sufficient interval before departure. The results in the literature suggest that a reminder might improve the completion rates of Japanese travelers.

This study has some limitations. First, the number of definite vaccinations could only be confirmed by a telephone survey and chart review in 38% (89 cases) of our 233 participants (Fig. 1). Second, we were not able to consider some human factors (e.g., the personality of the clients, the existence of vigorous occupational health practitioners in the clients' companies, and the differences in our travel doctors' recommendations about hepatitis B vaccination). Third, we did not remind clients in this retrospective study. A prospective interventional study is required to determine the usefulness of a reminder method in a travel clinic setting.

In conclusion, hepatitis B vaccine was administered to many of our clients, but the vaccine series completion rate was only 60%. Long-term travel and business trips and accompanied family members, travel to Asia, and company or organization's payment plan were positively associated with vaccination compliance; short-term travel ($<$ 1 month), travel due to leisure or education, and travel to North America or Africa were negatively associated with hepatitis B vaccination compliance. Scheduled travel duration of 1 month \leq and $<$ 1 year was negatively associated with the completion of the vaccine series. Because we are con-

cerned about the rate of hepatitis B virus carriers and the threat to adolescents and young adults both within and outside Japan, we advise Japanese travel doctors to explain the need for hepatitis B vaccination and to consider its administration to travelers, regardless of the characteristics of their travel. To promote the completion of the vaccine series, a reminder process should be considered. Pre-travel consultation is one of the few opportunities to screen Japanese individuals who have not received hepatitis B vaccinations. Finally, because not all Japanese visit travel clinics, catch-up immunizations for hepatitis B virus should be considered for adolescents and young adults after the introduction of universal childhood hepatitis B immunization.

CONFLICTS OF INTEREST

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