Typhoid Vaccination among Japanese Travelers to South Asia and the Factors Associated with Compliance

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Abstract:
Objective  In 2010, candid advice concerning the low rate of typhoid vaccination among Japanese travelers was received from Nepal. Recently, progressive Japanese travel clinics have encouraged Japanese travelers to be vaccinated against typhoid fever in conjunction with officially approved vaccines, such as hepatitis A vaccine. We herein report the status of typhoid vaccinations for Japanese travelers to the most endemic area (South Asia) and describe the factors associated with compliance.

Methods  In the travel clinic at Kurume University Hospital, we used the following criteria to retrospectively extract the records of new pre-travel Japanese clients between January 2011 and March 2015: hepatitis A vaccine administered, traveling to South Asian countries, and ≥2 years of age. We first summarized the participants and then divided them into typhoid-vaccinated and typhoid non-vaccinated groups for a comparative analysis.

Results  This study included 160 clients. A majority (70.0%) of these clients traveled for business. The duration of trips was long (≥1 month) (75.0%), and India was a popular destination (90.6%). A comparative study between the vaccinated group (n=122) and the non-vaccinated group (n=38) revealed that the two factors most positively associated with typhoid vaccination were business trips (adjusted odds ratio [aOR] 3.59, 95% confidence interval [CI] 1.42-9.06) and coverage by a company/organization payment plan (aOR 7.14, 95% CI 2.67-20.3).

Conclusion  The trend toward typhoid vaccination among Japanese travelers to South Asia with pre-travel consultation is correlated with business trips and coverage by a company/organization payment plan. If problems concerning the cost of vaccines were resolved, more travelers would request typhoid vaccination.

Key words: Japanese travelers, pre-travel consultation, typhoid vaccine, Typhim Vi⁷, typhoid fever, hepatitis A

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Introduction

Typhoid fever is endemic in developing countries, particularly in South Asia, and the risk of acquiring typhoid fever among travelers to South Asia is greater than in travelers to other areas (1, 2). More than 16 million Japanese travel abroad annually, and travel to tropical areas (e.g. South Asia) endemic for hepatitis A and typhoid fever (3, 4), has increased (5). Recently, 20-65 typhoid cases per year have been reported to Japanese national surveillance, and most cases were imported (6, 7). Furthermore, some Japanese long-term travelers acquire typhoid fever and must be treated abroad (8). Those cases fall outside the data collected by Japanese national surveillance unless they visit healthcare facilities in Japan. Therefore, typhoid vaccines are recommended for Japanese travelers<5 to South Asia, regardless of trip duration (9).

A report by the Nepal International Clinic described that 95% of their Japanese patients had not been vaccinated...
against either hepatitis A or typhoid fever (10). Ten years later, another report by the same clinic favorably described that Japanese authorities had begun to encourage hepatitis A vaccinations for travelers to endemic areas (8). They warned, however, that the status of typhoid vaccination remained insufficient (8). While hepatitis A vaccines, which are the core vaccines for travelers to developing countries, were administered to 54.8% of Japanese long-term travelers to South Asia (11), the prevalence of typhoid vaccination among the same population was estimated to be as low as 23.4% (11). The main reason for this discrepancy can be attributed to the official disapproval of such typhoid vaccines in Japan.

Some travel clinics in Japan have recently introduced typhoid vaccines (9). The introduction of typhoid vaccine in Japan is an urgent matter. Our travel clinic initiated pre-travel consultations beginning in 2007, and began to import typhoid polysaccharide vaccine in 2011. Our clinical question was, “What are the factors that influence hepatitis A-vaccinated travelers to request the optional typhoid vaccination before visiting endemic countries?”

We analyzed the clinical characteristics of pre-travel clients with hepatitis A vaccinations who planned to travel to South Asia (endemic area for hepatitis A and typhoid fever), and examined the factors that contributed to compliance with typhoid vaccination. This survey of the current status of typhoid vaccination in Japan will clarify the status of typhoid vaccination in Japan.

### Patients and Methods

This research involved a single-center study that was conducted by the Department of Infection Control and Prevention, which manages a travel clinic in Kurume University Hospital, a tertiary-care medical center. On the first day of consultation, our doctors explain the risks of particular destination countries and recommended vaccines using the Japanese vaccine guideline for overseas tourists 2010 (Japanese Society of Travel and Health) and Tropimed (http://www.tropimed.com/en/index.html). Our explanation is not confined to the vaccines that clients request, and the first consultation requires 45 minutes per client. We use AIM-MUGEN (KAKETSUKEN, Kumamoto, Japan) and HAVRIX (GlaxoSmithKline Biologicals SA, Rixensart, Belgium) as hepatitis A vaccines, and Typhim Vi (Sanofi Pasteur, Lyon, France) as typhoid vaccine. The safety of this imported typhoid polysaccharide vaccine has been confirmed among the Japanese population in previous studies (12, 13). The Kurume University Research Ethics Committee has approved the use of these imported vaccines (HAVRIX and Typhim Vi).

Between January 2011 and March 2015, there were 1,003 new pre-travel Japanese clients (without other travel clinic’s consultation) who visited our clinics. For the present study, we included participants who met all of the following criteria: hepatitis A vaccine administered, traveling to South Asian countries, and ≥2 years of age.

Among 1,003 pre-travel Japanese clients, 160 were chosen to participate in this study, according to the criteria. We retrospectively reviewed their medical records and classified their factors as follows: age, sex, typhoid vaccine administered or not, purpose of travel (business, leisure, accompanying family members, education, volunteer work, visiting friends and relatives [VFRs]), destination country, interval between the first consultation and the intended departure time (<1 month and ≥1 month), scheduled duration of travel (<1 month and ≥1 month), and payment for vaccines (cost was covered by a company/organization payment plan or not). If a company/organization paid a portion of the cost, the participants were categorized as follows: “company/organization pays.” We summarized the characteristics of the clients and performed a comparative study: a typhoid-vaccinated group was compared with an unvaccinated group.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.2.3) (14). Categorical data were tested using Fisher’s exact test, and continuous data were tested using Student’s t-test. Multiple logistic regression analyses were performed with adjustment for age and sex for each of the factors showing p values of <0.10 in the univariate analyses.

The Kurume University Research Ethics Committee approved this study (Research No. 15214).

### Results

A summarized clinical profile of the participants appears in Table 1. Most of our clients traveled for business (70.0%). The duration of most trips was long (≥1 month) (51.3%), and India was the most popular destination (90.6%). Typhoid vaccine was administrated to 122 clients (75.8%).

A univariate comparison between the vaccinated group (n =122) and the non-vaccinated group (n=38) among travelers going to South Asia is shown in Table 2. In this analysis, there were statistically significant differences in the proportions of sex, the purposes of travel (business, accompanying family members, education, volunteer work), the scheduled duration of travel, and the existence of a company/organization payment plan.

Multiple logistic regression analyses adjusting for age and sex between the vaccinated group and the non-vaccinated group among travelers to South Asia were also performed. We evaluated each of the factors that showed P <0.10 in the univariate analysis. The results are presented in Table 3. Factors positively associated with the administration of typhoid vaccine were business trips (adjusted odds ratio [aOR] =3.59, 95% confidence interval [CI] 1.42-9.06) and the existence of a company/organization payment plan (aOR=7.14, 95% CI 2.67-20.3).
**Table 1.** the Characteristics of the Participants. (n=160)

|                          | Typhoid vaccinated group (n=122) | Typhoid non-vaccinated group (n=38) | p value |
|--------------------------|----------------------------------|-------------------------------------|---------|
| Age, mean±SD (year)      | 38.9±14.8                        | 35.6±14.9                           | 0.242   |
| Sex (male)               | 109 (89.3)                       | 27 (71.1)                           | 0.009   |
| Typhoid vaccine administration | Yes 122 (75.8)            | (Unknown) 6 (3.8)                   |         |
| Purpose of travel        |                                  |                                     |         |
| Business                 | 112 (70.0)                       | Company/organization pays 87 (51.9) |         |
| Leisure                  | 25 (15.6)                        | Clients pay 42 (26.3)               |         |
| Accompanying family members | 10 (6.3)                       | (Unknown) 31 (19.4)                 |         |
| Education                | 7 (4.4)                          | Destination country                 |         |
| Volunteer                | 6 (3.8)                          | India 145 (90.6)                    |         |
| VFRs                     | 5 (3.1)                          | Pakistan 3 (1.9)                    |         |
| Interval between consultation and departure | Nepal 5 (3.1)  | Buran 3 (1.9)                       |         |
| <1 month                 | 74 (46.3)                        | Sri Lanka 3 (1.9)                   |         |
| ≥ 1 month                | 82 (51.3)                        | Bangaldesh 2 (1.3)                  |         |
| (Unknown)                | 4 (2.5)                          |                                     |         |

SD: standard deviation, VFRs: visiting friends and relatives

**Table 2.** the Comparison between a Typhoid-vaccinated Group and Typhoid Non-vaccinated Group among Travelers Visiting South Asia.

|                          | Typhoid vaccinated group (n=122) | Typhoid non-vaccinated group (n=38) | p value |
|--------------------------|----------------------------------|-------------------------------------|---------|
| Age, mean±SD (year)      | 38.9±14.8                        | 35.6±14.9                           | 0.242   |
| Sex (male)               | 109 (89.3)                       | 27 (71.1)                           | 0.009   |
| Purpose of travel        |                                  |                                     |         |
| Business                 | 95 (77.9)                        | 17 (44.7)                           | <0.001  |
| Leisure                  | 17 (13.9)                        | 8 (21.1)                            | 0.311   |
| Accompanying family members | 5 (4.1)                        | 5 (13.2)                            | 0.058   |
| Education                | 3 (2.5)                          | 4 (10.5)                            | 0.055   |
| Volunteer                | 2 (1.6)                          | 4 (10.5)                            | 0.029   |
| VFRs                     | 5 (4.1)                          | 0 (0)                               | 0.340   |
| Interval between consultation and departure | 62 (52.5)  | 20 (52.6)                           | 1.000   |
| ≥ 1 month                |                                  |                                     |         |
| Scheduled duration of travel | 96 (82.1)           | 24 (64.9)                           | 0.040   |
| Payment for vaccines     | 78 (77.2)                        | 9 (32.1)                            | <0.001  |

1) Student’s t-test, 2) Fisher’s exact test, SD: standard deviation, VFRs: visiting friends and relatives

The present study also demonstrated that business trips and the existence of a company/organization payment plan were important factors for ensuring compliance with typhoid vaccination (Table 3). Only nine participants who traveled for business purposes had not received a typhoid vaccination, despite the fact that their company/organization had a payment plan. In Japan, travel medicine doctors must personally import typhoid vaccines. This has led to negative consequences such as a high cost and insufficient compensation schemes. For example, many students who travel for vaccine. This was a result of the countermeasures for the infection risk in the most endemic areas.

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**Discussion**

The risks of acquiring typhoid fever are known to vary depending on a client’s travel destination. In the U.S., the results of national surveillance data have shown that approximately half of U.S. typhoid patients have traveled to India, followed by other South Asian countries (Pakistan and Bangladesh) (2). Other surveillance studies have also established a high risk for travel to India and South Asian countries (1, 15). Our study indicated that most clients traveling to South Asia (75.8%) tended to be vaccinated with typhoid...
To promote the prevalence of typhoid vaccination, clients to South Asia comply with vaccination. Therefore, Iners to endemic areas has been encouraged, and most of our addition to hepatitis A vaccination) among Japanese travel-
would cover the cost of vaccines were positive factors for

In conclusion, the designation of a business trip and the existence of a company/organization payment plan that would cover the cost of vaccines were positive factors for typhoid vaccination among travelers to South Asia, which is the most endemic area. Typhoid vaccine administration (in addition to hepatitis A vaccination) among Japanese travelers to endemic areas has been encouraged, and most of our clients to South Asia comply with vaccination. Therefore, In order to promote the prevalence of typhoid vaccination, travel medicine doctors should continue to emphasize the importance of typhoid vaccination for all Japanese companies and organizations.

The authors state that they have no Conflict of Interest (COI).

References
1. Ekdahl K, de Jong B, Andersson Y. Risk of Travel-Associated Typhoid and Paratyphoid Fevers in Various Regions. J Travel Med 12: 197-204, 2005.
2. Lynch MF, Blanton EM, Bulens S, et al. Typhoid fever in the United States, 1999-2006. JAMA 302: 859-865, 2009.
3. Basnyat B, Maskey AP, Zimmerman MD, Murdoch DR. Enteric (typhoid) fever in travelers. Clin Infect Dis 41: 1467-1472, 2005.
4. Mohd Hanafiah K, Jacobsen KH, Wiersma ST. Challenges to mapping the health risk of hepatitis A virus infection. Int J Health Geogr 10: 57, 2011.
5. Japan Association of Travel Agents. Destination Countries for Japanese travelers: Top 50. Available at: http://www.jata-net.or.jp/d ata/stats/2015bis/05.html (in Japanese) (Accessed 2016 May 20).
6. National Institute of Infectious Diseases. NESID Annual Surveillance Data (Notifiable Diseases) 2014-1. Available at: http://www.nih.go.jp/niid/en/survei/2015-idw/data/6057-report-ea2014-10.html (Accessed 2016 May 20).
7. National Institute of Infectious Diseases. Typhoid fever -The increase of the cases with no travel history (after 34th week later in 2014). IDWR 2014; 38. Available at: http://www.nih.go.jp/niid/ja/d engue-m/dengue-idwr/5032-idwr-1438.html (in Japanese) (Accessed 2016 May 23).
8. Thapa R, Banskota N, Pokharel J, Subedi BH, Basnyat B. Another typhoid patient from Japan. J Travel Med 17: 199-200, 2010.
9. Hamada A, Fukushima S. Present situation and challenges of vaccinations for overseas travelers from Japan. J Infect Chemother 21: 405-409, 2015.
10. Basnyat B, Pokhrel G, Cohen Y. The Japanese need travel vaccinations. J Travel Med 7: 37, 2000.
11. Hamada A, Koga T, Fukushima S. Traveler’s Vaccine Use Among Japanese Expatriates in Developing Countries. Kansenshogaku zasshi (The Journal of the Japanese Association for Infectious Diseases) 83: 375-379, 2009 (in Japanese).
12. Miyagi K, Nakano T, Ishizaki A, et al. The safety and efficacy of typhoid vaccine and meningococcal vaccine in Japan. Nihon Tokou Igakkaishi (Journal of Japanese Society of Travel and Health) 2: 19-23, 2008 (in Japanese).
13. Miyazu M, Kikuchi H, Hamada A, et al. A Japanese study to assess immunogenicity and safety of a typhoid Vi polysaccharide vaccine. Vaccine 33: 6697-6702, 2015.
14. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 48: 452-458, 2013.
15. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. A study of typhoid fever in five Asian countries Disease burden and implications for controls. Bull World Health Organ 86: 260-268, 2008.
16. Yaita K, Yahara K, Sakai Y, et al. Hepatitis B Vaccination Status among Japanese Travelers. Kurume Med J 63: 69-76, 2016.

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