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Original Article

Diseases affecting patients returning from abroad: Experience of a travel clinic in Japan from 2004 to 2014

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ABSTRACT

The number of patients returning from or staying abroad is likely to increase in the future. We performed a retrospective study of patients returning from abroad in our travel clinic in Japan. All patients presenting within 6 months of traveling abroad between 2004 and 2014 were included in the present study. A total of 2374 (mean age, 35 years) patients were seen by doctors specializing in treating infectious diseases. Of these, 918 were females and 87 of them lived abroad. Diagnoses and exposure regions were recorded for all patients. The most frequent region visited before attending our clinic was Southeast Asia ($n = 1050$, 44%), with a median duration for staying abroad of 8 days. The major purposes for overseas travel were tourism ($n = 1302$, 55%) and business ($n = 684$, 29%). Of the 2399 individual diagnoses made, the most frequent were diseases of the gastrointestinal system ($n = 1083$, 45%), skin and soft tissue ($n = 440$, 18%), systemic febrile disease without specific systems (419, 18%), and the respiratory system (353, 15%). The relative incidences of specific diseases changed drastically due to significant disease outbreaks, such as pandemic influenza in 2009. Exposure regions remained relatively constant throughout the study period, except for Japan. Vaccine-preventable diseases accounted for 5.3% of all the diseases, and 402 (26%) patients received pre-travel consultation and prophylaxis with vaccines and/or anti-malarial drug. We should make an effort to make more people notice the risk of travel and properly perform prophylaxis.

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1. Introduction

Each year, more than 16 million Japanese residents travel abroad and more than 19 million foreign people visit Japan according to Japan National Tourism Organization. The number of foreign tourists traveling to Japan has been increasing, with more patients visiting clinics in Japan after or during travel. There is a lack of published small case series regarding infectious and non-infectious diseases among patients visiting travel clinics in Japan [1–3]. Our clinic is a member of the global travel-associated disease surveillance network “GeoSentinel,” which has recently reported large-scale studies on ill travelers [4]. However, most of the data are provided by European and North American clinics, and the report

does not reveal the patients and diseases in real settings, such as the travel clinics in Japan. Accordingly, we evaluated the characteristics of patients visiting our travel clinic following recent travel abroad to help improve the clinical practice of Japanese doctors and establish prevention strategies.

2. Patients and methods

We performed a retrospective study of patients attending our clinic between 2004 and 2014 who had a history of abroad travels within 6 months of their initial presentation. Our clinic is located in Yokohama, Japan's second most populated city (over 3 million residents), approximately 40 km south of Tokyo. Our hospital is a 650-bed community-based acute care teaching facility, and our clinic is run by 2–4 doctors for infectious disease, with inputs from other specialties, such as dermatology and pediatrics. We obtained data regarding patient demographics, travel histories, reasons for most recent overseas travel, and pre-travel vaccinations using a

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questionnaire for all patients (pre-travel information was added to the questionnaire in 2006). Regions were classified as East Asia (except Japan), Southeast Asia, South Asia, Oceania, Middle East, Europe, Africa, North America, and Latin America. Reasons for traveling abroad included tourism, business, study, missionary or volunteer work, visiting friends and relatives (VFR), and immigration or residence. VFR is defined as a condition when people visit a foreign country to see friends, family, or relatives; it does not depend on where they were born, how developed the foreign country is or which they migrated or not. In cases where there were multiple reasons, the most important reason was considered. Physicians determined exposure regions according to clinical course, travel history, and infection window periods. Therefore, potential exposure regions included Japan, airplanes, or none (disease not associated with any specific exposure). Diagnoses were made according to clinical, laboratory, and imaging findings, with every effort taken to determine the underlying etiologies. For example, in cases where acute bacterial colitis was suspected but no pathogen was detected, the final diagnosis was recorded as acute colitis of unknown etiology. Diseases were classified according to organ system as systemic febrile (no specific organ), respiratory, gastrointestinal, skin and soft tissue, hepatobiliary, genitourinary, and neurological diseases. When patients attended our clinic in the recovery phase, we used information from clinical correspondence to determine their underlying etiology. Real-time PCR was used to detect the pathogenic gene of diarrheagenic *Escherichia coli* strains.

This study is performed independently of GeoSentinel, which collects information only on travel-associated diseases. This study was approved by our institutional review board.

3. Results

A total of 2374 patients were seen at our clinic during the study period (Table 1). The mean age of patients was 35 ± 14 years, with 918 people female (39%). Of the 2374 included patients, 2251 (95%) were Japanese, 120 (5.1%) were born in foreign countries (2 Japanese) and 87 (3.7%) lived abroad (57 Japanese). The most frequently

Table 1
Demographic data.

Number of patients	2374
Age [years old]	35 ± 14
Female	918 (39%)
Born abroad	120 (5.1%)
Living abroad	87 (3.7%)
Staying regions	
Southeast Asia	1050 (44%)
South Asia	367 (15%)
Africa	281 (12%)
East Asia	245 (10%)
North America	94 (4.0%)
Europe	84 (3.5%)
Oceania	72 (3.0%)
Latin America	68 (2.9%)
Middle East	8 (0.34%)
Multiple	104 (4.4%)
Unknown	2 (0.08%)
Median staying duration [days]	8 (1–27480)
Staying purpose	
Tourism	1302 (55%)
Business	684 (29%)
Visiting friends and relatives	209 (8.8%)
Study	66 (2.8%)
Missionary/volunteer	43 (1.8%)
Residence	39 (1.6%)
Immigrant	5 (0.21%)
Unknown	26 (1.1%)

\pm SD, a–b: minimum to maximum.

traveled region before clinic visit was Southeast Asia ($n = 1050$, 44%), whilst 102 patients (4.3%) had traveled to multiple regions. The median duration of overseas travel was 8 days (0–27480 days). The predominant reasons for overseas travel were tourism ($n = 1302$, 55%), business ($n = 684$, 29%), and VFR ($n = 209$, 9%).

The highest number of patients seen per year was in 2007, with the lowest number seen in 2010. The number of patients has increased since 2012 (Table 2). Of the 2399 diagnoses made in our clinic, the most frequently affected organ system was the gastrointestinal system, followed by skin and soft tissue, and systemic febrile diseases. Acute and chronic diarrhea were the most frequently observed gastrointestinal diseases, with fewer cases of enteric fever, esophagitis, and gastritis (Table 3). Causative agents identified in cases of gastrointestinal disease included *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., and diarrheagenic *E. coli*, with *Giardia intestinalis* being the most frequently observed parasitic infection (Table 3). Three cases of irritable bowel syndrome and one case of drug-induced (atovaquone/proguanil) diarrhea were also observed. The majority of skin/soft tissue diseases were caused by animal exposure with or without post-exposure prophylaxis against rabies, insects bite, and lymphadenitis (Table 4). The predominant sources of animal exposure were dogs, monkeys, and cats, with squirrels, sheep, lions, donkeys, bats, and boars identified as less frequent sources. Systemic febrile diseases are shown in Table 5. A total of 81 cases of dengue fever, 76 cases of malaria, 4 cases of measles, 4 cases of chikungunya fever, 4 cases of leptospirosis, and 1 case of murine typhus were diagnosed. Respiratory diseases were predominantly unspecified upper respiratory infections or influenza (Table 6). Bronchitis and pneumonia were observed in 34 and 26 cases respectively. Frequent causative agents identified in cases of pneumonia included *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*. Cases of genitourinary diseases included 10 cases of urinary tract infection and 2 cases of prostatitis (Table 7). There was one case of a foreign doctor developing acute pseudomonas prostatitis. Hepatobiliary diseases included hepatitis and biliary infection (Table 8). Hepatitis A virus was the most frequent cause of hepatitis. The predominant neurological disease was aseptic meningitis (Table 9). The case of rabies developed right shoulder pain, cough, anxiety, and confusion 3 months after a dog bite in the Philippines. He was diagnosed with rabies and provided with intensive care, although eventually died. Data pertaining to infrequent diseases, such as endocrine, bone/joint, ophthalmological, otological, and other diseases, are shown in Table 10. There were 2 cases of newly diagnosed HIV infection. Diseases rarely diagnosed in Japan but observed in the present study included rabies, cutaneous leishmaniasis, melioidosis, and murine typhus. The most frequent regions of exposure were Southeast Asia ($n = 1014$, 43%), South Asia ($n = 377$, 16%), Africa ($n = 259$, 11%), East Asia ($n = 225$, 9.4%), and “unspecified” ($n = 106$, 4.5%; Table 11). Outcomes were generally good in the present study, with only one fatal case of rabies and 220 (9.5%) patients admitted to hospital. Pre-travel vaccination or anti-malarial chemoprophylaxis was performed in 394 (25%) and 13 (0.8%) patients, respectively. Vaccine-preventable diseases were diagnosed in 127 cases, including influenza (81), typhoid fever (17), hepatitis A (7), rubella (6), varicella (5), measles (4), pneumococcal pneumonia (3), tuberculosis (2), mumps (1) and rabies (1).

4. Discussion

To our knowledge, this is the largest study of patients presenting at a Japanese travel clinic with a history of traveling abroad. A 12-year study of infectious diseases in travelers presenting to a Japanese clinic was published although this study was not comprehensive [2]. The majority of studies evaluating travel-associated

Table 2
Organ-system syndrome by year.

Systems	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Gastrointestinal	118	131	145	145	78	68	59	90	76	88	85	1083 (45%)
Skin/soft tissue	13	24	38	78	52	33	38	44	43	28	49	440 (18%)
Systemic febrile	36	37	32	41	39	25	29	34	35	50	61	419 (18%)
Respiratory	30	17	35	29	38	77	18	18	23	23	45	353 (15%)
Genitourinary	1	1	5	2	1	0	0	2	1	3	2	18 (0.75%)
Hepatobiliary	2	2	3	2	4	2	2	0	0	0	0	17 (0.71%)
Neurological	0	1	2	0	2	0	1	2	0	2	3	13 (0.54%)
Other	2	2	0	3	2	2	2	3	1	2	2	21 (0.88%)
Healthy	2	5	2	0	4	4	4	6	2	2	4	35 (1.5%)
Total	204	220	262	300	220	211	153	199	181	198	251	2399

Table 3
Gastrointestinal diseases.

Syndromic diagnosis		
	Esophagitis	1
	Gastritis	4
	Enterocolitis	1043
	Enteric fever	33
	Others	2
	Subtotal	1083
Causative agents		
Bacteria	<i>Campylobacter</i> spp.	
	<i>C. jejuni</i>	113
	<i>C. coli</i>	5
	<i>C. sp. unknown</i>	4
	<i>Salmonella</i> spp.	
	Non Typhi <i>Salmonella</i> spp.	26
	<i>S. enterica</i> serotype Typhi	17
	<i>S. enterica</i> serotype Paratyphi A	16
	<i>Shigella</i> spp.	
	<i>S. sonnei</i>	45
	<i>S. flexneri</i>	8
	<i>S. dysenteriae</i>	1
	Diarrheagenic <i>Escherichia coli</i>	
	Enterotoxigenic <i>E. coli</i> (ETEC)	39
	Enteroaggregative <i>E. coli</i> (EAggEC)	3
	Enteropathogenic <i>E. coli</i> (EPEC)	2
	Enterohemorrhagic <i>E. coli</i> (EHEC)	2
	Enteroinvasive <i>E. coli</i> (EIEC)	1
	<i>Plesiomonas shigelloides</i>	26
	<i>Vibrio</i> spp.	
	<i>V. parahaemolyticus</i>	10
	<i>V. cholerae</i> O1 (cholera toxin+)	7
	<i>V. cholerae</i> non O1 & O139	2
	<i>V. sp. unknown</i>	1
	<i>Aeromonas</i> spp.	
	<i>A. hydrophila</i>	6
	<i>A. sobria</i>	2
	<i>A. sp. unknown</i>	1
	Protozoa	
	<i>Giardia intestinalis</i>	24
	<i>Entamoeba histolytica</i>	22
	<i>Blastocystis hominis</i>	2
	<i>Endolimax nana</i>	2
<i>Cryptosporidium parvum</i>	1	
Helminth		
<i>Ascaris lumbricoides</i>	4	
<i>Taenia saginata</i>	3	
<i>Trichuris trichiura</i>	2	
<i>Heterophyes heterophyes</i>	1	
<i>Enterobius vermicularis</i>	1	
<i>Schistosoma</i> sp.	1	
Tape worm	1	
<i>Metagonimus yokogawai</i>	1	
Drug-induced		
Atovaquone/proguanil	1	

Table 4
Skin/soft tissue diseases.

Animal bite/scratch	388
Dog	304
Monkey	39
Cat	38
Others	7
Insect bite	10
Lymphadenitis	6
Toxicoderma	4
Subcutaneous abscess	4
<i>Streptococcus pyogenes</i>	2
<i>Bacteroides</i> sp.	1
<i>Staphylococcus aureus</i>	1
Cutaneous larva migrans	3
Cutaneous injury	3
Urticaria	3
Tick bite	2
Cellulitis	2
Sun burn	2
Cutaneous leishmaniasis	1
Others	8

Although the total number of patients visiting our clinic changed year by year, no correlation was observed between the number of patients leaving and coming to Japan over the years. The highest number of patients was seen in 2007, which may have been influenced by 2 deaths due to rabies in Japan in 2006. The lowest number of patients was seen in 2010, and this may be attributed to the H1N1 influenza pandemic in 2009. Many factors likely underlie the changes in the numbers of patients presenting to our clinic, with public awareness of disease pandemic likely being a major contributor. We included patients living in foreign countries, with their median duration of staying abroad influenced by this.

The most frequently involved organ system was the gastrointestinal system over the entire study period, with the majority of cases diagnosed as enterocolitis. The ratio is much more than that of GeoSentinel's report (34%) [4]. The variety and frequency of causative agents identified in the present study were comparable to previous reports, except for strongyloides [4,7,8]. Regarding *Vibrio cholerae* serotype O1/non-O1 infections, no cases were observed after 2007. This finding may be attributable to infectious disease law revision in 2007, by which quarantine stations have not tested *Vibrio cholerae* since then. With regard to parasites, giardia species and *Entamoeba histolytica* were the most common causative agents, with other helminths, such as, strongyloides, rarely identified. Cases of helminthic infection may be rare due to a relatively short duration of stay and low-risk behavior in foreign countries.

Skin and soft tissue diseases are commonly associated with animal exposure. The large number of patients with animal exposure in the present study may be attributed to poor knowledge of the risk of animal bites among the Japanese population. The number of cases with animal exposure was the greatest in 2007 and

diseases were conducted in the United States or Europe, with few reports of diseases specific to Japan or non-travel-associated diseases [4–6]. The present report provides a comprehensive and longitudinal study of diseases presenting at a Japanese clinic for patients with a history of overseas travel.

Table 5
Systemic febrile disease.

Viral infection	284
Bacterial infection	11
Parasitic infection	76
Others	7
Unknown	41
Etiologic diagnosis	
Dengue fever	81
Epstein-Bar virus infection	11
Rubella	6
Varicella	5
Measles	4
Chikungunya fever	4
Cytomegalovirus infection	2
Hand foot mouth disease	2
Bacteremia	4
<i>Salmonella</i> spp.	2
<i>Enterobacter cloacae</i>	1
<i>Escherichia coli</i>	1
Leptospirosis	4
Melioidosis	1
Lyme disease	1
Rickettsial diseases	4
<i>Rickettsia typhi</i>	1
<i>Rickettsia rickettsii</i>	1
Unknown	2
Malaria	76
<i>Plasmodium falciparum</i>	41
<i>P. vivax</i>	26
<i>P. ovale</i>	7
Unknown	6
Multiple species	4
Malignant lymphoma	1
Adult-onset Still's disease	1
Polymyalgia rheumatica	1

Table 6
Respiratory diseases.

Pneumonia	26
<i>Haemophilus influenzae</i>	6
<i>Streptococcus pneumoniae</i>	4
<i>Mycoplasma pneumoniae</i>	3
<i>Chlamydia pneumoniae</i>	1
<i>Staphylococcus aureus</i>	1
<i>Pneumocystis jirovecii</i>	1
<i>Mycobacterium tuberculosis</i>	2
Bronchitis	34
<i>Haemophilus influenzae</i>	1
Upper respiratory infection	205
<i>Streptococcus pyogenes</i>	8
Group C streptococcus	1
Influenza	81
Type A influenza	60
Type B influenza	19
Sinusitis	5
Bronchial asthma	1
Atopic cough	1

Table 7
Genitourinary diseases.

Urinary tract infection	10
<i>Escherichia coli</i>	4
<i>Streptococcus agalactiae</i>	1
Prostatitis	2
<i>E. coli</i>	1
<i>Pseudomonas aeruginosa</i>	1
Phallitis	1
Pelvic inflammatory disease	1
Genital herpes	1
Epididymitis	1
Genital warts	1
Pyosalpinx	1
<i>Streptococcus pyogenes</i>	1

Table 8
Hepatobiliary diseases.

Biliary infection	2
Hepatitis	15
Hepatitis A virus	7
Hepatitis E virus	2
Hepatitis B virus	1
Epstein-Bar virus	1
Mefloquine-induced	1
Unknown	3

Table 9
Neurological disease.

Aseptic meningitis	8
Coxsackievirus B5	1
Toxoplasma encephalitis	1
Rabies	1
Tension headache	1
Migraine	1
Drug-induced headache	1

Table 10
Infrequent diseases.

Endocrine diseases	
Adrenal dysfunction	2
Hyperthyroidism	2
Hypothyroidism	1
Subacute thyroiditis	1
Otological disease	
Otitis media	3
Bone/joint diseases	
Bacterial spondylitis	1
Reactive arthritis	1
Eye diseases	
Corneal ulcer	1
Conjunctivitis	1
Others	
HIV infection	2
Fatigue	2
Dehydration	1
Insomnia	1
Vaccine adverse reaction	1
Vertigo	1

declined thereafter. This number was likely considerably influenced by 2 cases of Japanese individuals who contracted rabies abroad and died in Japan in 2006. These 2 deaths increased awareness and education regarding rabies among the Japanese population; however, this awareness may have subsequently declined as no cases have since been observed in Japan. Therefore, when people were injured during contact with animals abroad, only a small fraction of them might have attended clinics. Among all sources of animal exposure, monkeys were the second most prominent. The high number of individuals injured by monkeys may be attributed to individuals being less wary of monkey attacks than of dog attacks, particularly in wildlife parks. These findings indicate Japanese

travelers should be more cautious when dealing with animals likely to carry rabies.

The underlying etiology in cases of systemic febrile disease was not determined in more than half of cases. For example,

Table 11
Exposure region.

Region	Number	Ratio %
Southeast Asia	1014	42.7
South Asia	377	15.9
Africa	259	10.9
East Asia	225	9.5
Unspecified	106	4.5
Japan	78	3.3
Europe	77	3.2
North America	74	3.1
Latin America	69	2.9
Oceania	65	2.7
None	19	0.8
Middle East	9	0.4
Airplane	2	0.1

chikungunya fever outbreaks had been identified in countries in Africa, Asia, Europe, America, and the Indian and Pacific Oceans [9]; however, there were only 4 cases of chikungunya fever in the present study. We do not routinely test for chikungunya virus in patients with mild symptoms as diagnostic tests are unavailable in Japanese clinics. The major exposure region for malaria was Africa, with one case from East Asia (South Korea). It should be noted that South Korea, North Korea, and China, the nearest countries to Japan, had endemic malaria outbreaks in 2013 [10]. The number of malaria cases was the lowest in 2013, which is in agreement with the national surveillance data [11]; however, the reasons for this low number remain unclear.

Upper respiratory infection was the most frequent respiratory diagnosis, followed by influenza. The H1N1 influenza pandemic occurred in 2009, and our clinic also experienced a large number of suspected cases. Although 23 of the 81 cases of influenza observed in the present study were diagnosed in 2009, influenza A/B was diagnosed in every year of the study period. As previous studies have reported year-round circulation of influenza viruses in tropical countries [12], influenza should be included as a differential diagnosis in all seasons in patients with a history of travel to tropical areas. The causative agent was confirmed in 16 of 23 cases of pneumonia. Four of these 16 cases were atypical pneumonia (*M. pneumoniae* in 3 cases and *Chlamydia pneumoniae*), which has a longer incubation period and predominantly affects younger people compared to the typical pneumonia. Two cases of pulmonary tuberculosis, with longer incubation periods, were also observed. These results corroborate those of a previous report [4,13].

Regarding diseases that are rarely observed in Japan, we experienced cases of rabies, melioidosis, murine typhus, and cutaneous leishmaniasis. No cases of Ebola virus disease, yellow fever, Zika virus infection, Middle East respiratory syndrome, plague, or anthrax were encountered; however, appropriate preparations should be in place for such lethal and/or highly infectious diseases.

Vaccine-preventable diseases, excluding tuberculosis, were observed in 127 (5.3%) cases [14]. The proportion of patients receiving pre-travel consultation with vaccination/anti-malarial chemoprophylaxis was similar to a previous report [3] and was relatively low compared with that in foreign countries, where 20–40% of travelers undergo prophylaxis [4,15–17]. Therefore, greater awareness among Japanese travelers is required regarding travel-associated diseases and the importance of prophylaxis.

The limitations of the present study were the inclusion of patients from a single center and uncertainty regarding some diagnoses. First, single-center studies are subject to selection bias.

Second, diagnostic laboratory techniques were limited at our facility, with viral culture, PCR, and many serological tests unavailable at our hospital, with these techniques only performed in highly suspected or severe cases. Third, the quality of diagnosis may have varied according to physicians' skill and experience.

In conclusion, we report the findings of a longitudinal study of diagnoses in a real-world travel clinic setting in Japan. Gastrointestinal and skin and soft tissue diseases were the most common among patients with a history of overseas travel. Further, the incidence of diseases changed year by year and may have been influenced by specific disease outbreaks. As a low proportion of patients had received vaccination or pre-travel consultation before travel, Japanese travelers should be better informed regarding travel-related health risks.

Conflict of interest

All authors have declared no conflicts of interest.

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