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Case report

The 2014 autochthonous dengue fever outbreak in Tokyo: A case series study and assessment of the causes and preventive measures

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ABSTRACT

Objective: In 2014, an autochthonous dengue fever outbreak occurred around the Yoyogi Park in Japan for the first time in 70 years. Despite no local cases reported since then, the risk of another outbreak remains high. This study reviews the autochthonous dengue fever cases of the outbreak, investigates its causes, and delineates preventive measures against autochthonous dengue epidemics.
Methods: We conducted a case series study of 15 patients who visited our institution during the 2014 outbreak. We collected and evaluated data on the surveillance of vector mosquitoes, weather, pest control, travelers' origins and destinations, and imported dengue fever cases using reports made by public institutions.
Results: All patients recovered with supportive treatments and none met the diagnostic criteria for severe dengue infection. Twelve patients with positive real-time polymerase chain reactions were confirmed as having dengue virus-1 infections. We found no obvious associations between the number of mosquitoes and the weather, or between the number of imported dengue fever cases and that of travelers. Insect growth regulator (IGR) against vector mosquitoes has been used since 2014 for pest control, but the number of larvae has not declined in the Yoyogi Park, although that of imagoes has been relatively suppressed.
Conclusion: The 2014 outbreak emerged without particularly favorable climate conditions for vector mosquitoes. We found no obvious associations between the number of travelers or the imported dengue fever cases and the outbreak, but the increasing number of travelers may contribute to another outbreak. Pest control, including IGR, remains essential for infection control.

1. Introduction

Dengue fever is the most prevalent mosquito-borne viral infection in the world, transmitted between humans by *Aedes* (Ae.) mosquitoes, with an estimated 390 million infections each year [1,2]. The virus is endemic to the tropical belt of Asia, but dengue has expanded globally due to many factors, including population growth, increased number of travelers, global warming, and insufficient vector control [3–5]. In Japan, no locally acquired cases had been reported since the outbreak from 1942 to 1945 [6], although approximately 200–300 imported cases are reported annually [7]. However, in 2014, an autochthonous dengue fever outbreak was reported for the first time in 70 years, and our institution experienced the second largest number of cases among all the medical facilities.

Dengue virus (DENV) has four serotypes (DENV1–4) and is transmitted by *Ae. aegypti* and *Ae. albopictus* mosquitoes [8]. Among these vectors, only the *Ae. albopictus* species is confirmed to have settled in Japan [9]. Studies focused mostly on *Ae. aegypti* have shown that climate factors such as temperature, humidity, and precipitation influence the number of mosquitoes by multiple means: biting rate, survival, incubation period, and development of both the virus in the mosquito and the mosquito itself [10–13]. Imagoes cannot survive the winter season in Japan, and the incidence of DENV carried to the next generation is negligibly low [14]. Therefore, autochthonous DENV infections are

Abbreviations: DENV, dengue virus; Ae, Aedes; NSI, non-structural protein; RT-PCRs, real-time polymerase chain reactions; ELISAs, enzyme-linked immunosorbent assays; IGR, insect growth regulator.

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likely to be caused by newly imported DENV in a given year.

Many studies have attempted to discover the causes of the outbreak of 2014 using mathematical models [15,16], but no explanations exist for the lack of single autochthonous cases since then. Although a report found that the estimated risk of dengue infection among Japanese travelers closely reflects local dengue trends, seasonally and annually [17], the influence of the number of travelers as a risk factor for autochthonous infections has never been examined. Moreover, the effects of mosquito-control measures started after the 2014 outbreak has not been evaluated. With the Olympiad close at hand, an epidemic from imported and autochthonous cases is of great concern, and a multifaceted evaluation of the pathogen, vector, host, and environment is required.

We aimed to describe the cases of autochthonous DENV infections that we encountered during the 2014 outbreak. Moreover, we analyzed data on the weather, travelers, pest control strategies, and surveillance of vector mosquitoes to identify local outbreak causes and delineate preventive measures.

2. Materials and methods

2.1. Case series

We collected a case series of 15 patients with autochthonous dengue fever who visited our institution from August 16, 2014 to September 29, 2014. We extracted information on the following clinical features: age, gender, past medical history, estimated latent period, symptoms, laboratory findings (including leukocytes, platelets, and C-reactive protein), and clinical course. We tested the blood samples of patients with suspected dengue fever using the non-structural protein (NS1) antigen assay (Dengue NS1 AgStrip, Bio-Rad Laboratories, Marnes-la-Coquette, France), real-time polymerase chain reactions (RT-PCRs) (TaqMan RT-PCR, Life Technologies, Grand Island, NY, USA), and dengue IgM enzyme-linked immunosorbent assays (ELISAs) (Panbio Dengue IgM Capture ELISA, Alere, Florida, USA or SD BIO-LINE Dengue Duo Dengue NS1 Ag + IgG/IgM, Standard Diagnosis, Gyeonggi-do, Korea) at the public health care center of Shibuya or Tokyo Metropolitan Institute of Public Health [18].

2.2. Mosquito surveillance

Surveillance on mosquito imagoes, including *Ae. albopictus* and *Ae. aegypti,* has been conducted by the Tokyo Metropolitan government, from June to October every year, and the numbers of mosquitoes caught in collection devices installed at 15 major parks in Tokyo are counted (wide-area surveillance) [19]. Captured mosquitoes are checked for particular mosquito-borne pathogens, including DENV. When the first patient with autochthonous dengue fever was confirmed in 2014, the Ministry of Health, Labor, and Welfare ordered the Tokyo Metropolitan authorities to perform an emergency survey at the Yoyogi Park in which the mosquitoes were inspected for DENV positivity. We collected the data from the additional surveillance, focusing not only on larvae but also on imagoes (focused surveillance started in 2015). The numbers of larvae per 100 mL of water samples from rainwater inlets in the parks have been counted and checked for DENV presence, from April to November each year since then.

2.3. Local climate of the Tokyo Metropolitan area

We assessed the climate in Tokyo using data accumulated by the Japan Meteorological Agency [20], which include mean temperatures, mean humidity, and total precipitation every two weeks from May to October, every other year from 2010 to 2018.

2.4. Pest control

The Tokyo Metropolitan authorities had ordered public health centers to take measures to prevent mosquito breeding in major parks in Tokyo. We analyzed the efficacy of these measures based on those of other studies and public reports [18,19].

2.5. Numbers of imported/autochthonous dengue infection cases and travelers

We evaluated how the number of travelers to and from Japan affected the number of autochthonous and imported cases of DENV infection. We used annual reports made by the National Institute of Infectious Diseases to discover trends of DENV infections [7].

We calculated numbers of visitors to Japan from dengue-endemic countries or areas per year from 2011 to 2018, together with the number of tourists from Japan to dengue-endemic countries or areas [21]. We selected countries and areas for aggregation based on information by the Centers for Disease Control and Prevention and the Japanese Ministry of Health, Labor, and Welfare [22,23].

2.6. Ethics statement

The Ethical Committee for Clinical Studies, Japanese Red Cross Medical Center approved this study (No. 1038). We disclosed the study's information on the website of our institution, and the requirement for individual informed consent was waived as we removed any patient identifiers from the dataset prior to analysis. For all data sources, permissions to reproduce and republish were obtained from respective publishers or copyright owners.

3. Results

3.1. Case series

Out of 162 autochthonous dengue fever cases in Japan in 2014, 15 cases were confirmed at our institution. Tables 1 and 2 show the clinical course and characteristics of these patients. None of them had traveled abroad within 3 weeks before the onset of symptoms. The median age of the patients was 37 years (range, 6–77 years), and 9 (60%) were female patients. All of them lacked former dengue infection episodes or underlying diseases, except for one patient with rheumatoid arthritis. None of the patients met the diagnostic criteria for dengue hemorrhagic fever or dengue shock syndrome. The mean levels of minimum white blood cells, minimum platelets, and maximum C-reactive protein were 1800 cells/μL, 7.3×10^4/μL, and 0.28 mg/L, respectively.

The dates and places of exposure to mosquito bites were investigated for all patients. Ten patients had one or more recent mosquito bites (within 5–9 days of symptom onset), and the dates of exposures could not be predicted for three patients because they had visited the park several times or lived close to it. Sites of exposures were also inferred; 12 at or near the Yoyogi Park, and 3 at other places, namely, Meiji Jingu Shrine, Shinjuku Central Park, and Komazawa Park, all of which were reported as the epidemic focus. The mean latent period was 5.5 days.

Diagnoses were made for patients positive for one or more of the following: NS1 antigen assay, RT-PCR, or dengue IgM ELISA test. Of the 14 patients whose blood samples were assayed for NS1 antigen and RT-PCR, 14 and 12 cases were positive, respectively. All of the positive RT-PCR cases were confirmed as presenting DENV-1 infections. The remaining case had a primary DENV infection with positive IgM and IgG ELISA tests.

Out of the 15 patients, 11 were admitted to our hospital and were cured with symptomatic treatment alone, except for 2 patients: one fulfilled the diagnostic criteria for disseminated intravascular coagulation, and intravenous thrombomodulin alfa was administered; the other was initially diagnosed with febrile neutropenia due to methotrexate as

Table 1
Case Series of 15 patients with dengue fever, August–October 2014.

Case	age	gender	latent period (days)	place of exposure	rash onset (day)	min. WBC (/μL)	min. Plt (× 10^4/μL)	max. CRP (mg/L)	NS1	RT-PCR	serotype	IgM
1	45	F	6	Yoyogi Park	8	700	5.1	0.16	no	no		+
2	29	M	?	Yoyogi Park	7	1300	3.0	0.86	+	+	1	no
3	6	M	5	Yoyogi Park	5	1600	9.0	0.17	+	+	1	no
4	37	F	?	Yoyogi Park	6	1600)	8.9	0.14	+	+	1	no
5	25	F	5	Yoyogi Park	5	2100	4.7	0.21	+	+	1	no
6	20	F	5	Yoyogi Park	4	2400	11.2	1.6	+	–		+
7	62	M	?	Yoyogi Park	4	1800	7.3	0.1	+	–		+
8	46	F	7	Yoyogi Park	4	900	4.8	0.1	+	+	1	–
9	47	F	5–8	Yoyogi Park	5	2800	14.0	0.19	+	+	1	–
10	72	F	5	Meiji Jingu Shrine	5	2600	8.2	0.04	+	+	1	–
11	77	M	3	Yoyogi Park	–	3900	9.8	0.65	+	+	1	–
12	35	F	5	Yoyogi Park	6	1400	4.9	0.28	+	+	1	+
13	24	F	9	Yoyogi Park	1	2000	5.2	0.67	+	+	1	–
14	47	M	5–7	Shinjuku Central Park or Meiji Jingu Shrine	1	2300	10.4	0.52	+	+	1	–
15	28	M	9	Komazawa Park	7	1400	5.4	1.22	+	+	1	+
median	37		5.5		5	1800	7.3	0.28				

Abbreviations: M, male; F, female; min, minimum; max, maximum; WBC, white blood cells; Plt, platelet; NS1, non-structural protein 1; RT-PCR, real-time polymerase chain reaction; IgM, immunoglobulin M (against dengue infection).

Table 2
Symptoms of 15 patients with dengue fever (August–October 2014).

Symptom	Number of patients	Frequency (%)
Fever	15	100.0
Headache	12	80.0
Arthralgia	6	40.0
Myalgia	8	53.3
Nausea	6	40.0
Stomachache	2	13.3
Vomiting	1	6.7
Diarrhea	5	33.3
Rash at first visit	6	40.0
Rash during the infection course	14	93.3
Sore throat	1	6.7
Cough	1	6.7
Sputum	2	13.3
Orbital pain	4	26.7
Nose bleeding	3	20.0
Night sweats	2	13.3

treatment for rheumatoid arthritis and was started on antibiotics. All patients recovered without subsequent complications.

3.2. Data from the mosquito surveillance and climate change

Figs. 1 and 2 show the mean numbers of mosquitoes caught every two weeks in major parks of Tokyo and at the Yoyogi Park, respectively. The wide-area surveillance data shows numbers for every other year from 2010 to 2018. The focused surveillance presents the data from 2015 to 2017. Only *Ae. albopictus* was detected during the surveillance. The surveillance results showed that the number of mosquitoes in an individual park (Yoyogi Park) did not correlate with those of the overall number of mosquitoes. In addition, the number of larvae was not associated with the number of imagoes. Although anti-larvae measures have been repeatedly applied in Yoyogi Park every year since 2015, the number of larvae has kept increasing every year. However, the number of imagoes has not risen accordingly with the increasing numbers of larvae. The mosquitoes were positive for DENV in the emergency surveys in 2014, but were otherwise negative [19]. No imagoes were DENV carriers in the surveillances since their initiation.

Fig. 3 shows the climatic factors assessed for every other year. We could not detect obvious correlations between the numbers of mosquitoes and each climatic factor (mean temperature, mean humidity, and total precipitation). For example, many mosquitoes were caught in

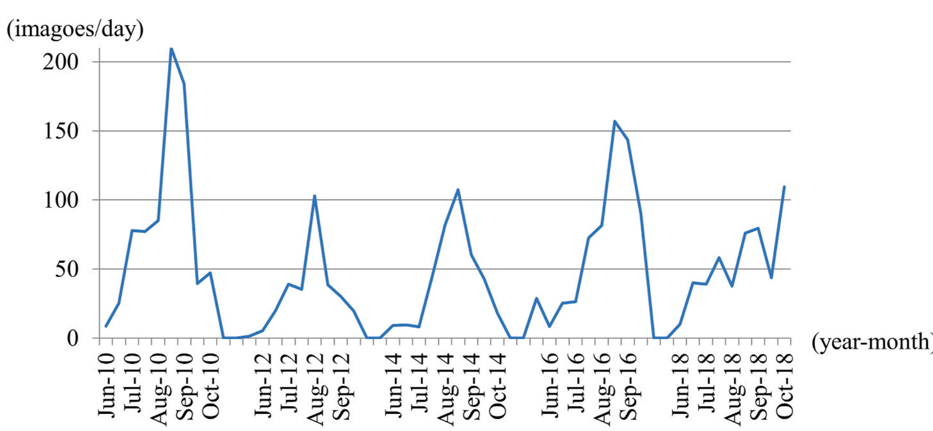

Fig. 1. Numbers of *Ae. Albopictus* imagoes in major parks of Tokyo were calculated every two weeks from June to October, every other year from 2010 to 2018. Mean numbers of mosquitoes caught per day in the 15 major parks in Tokyo. We did not detect significant increases or decreases in the numbers of imagoes over the years. Moreover, when the autochthonous outbreak occurred in 2014, the number of mosquitoes was similar to those of other years.

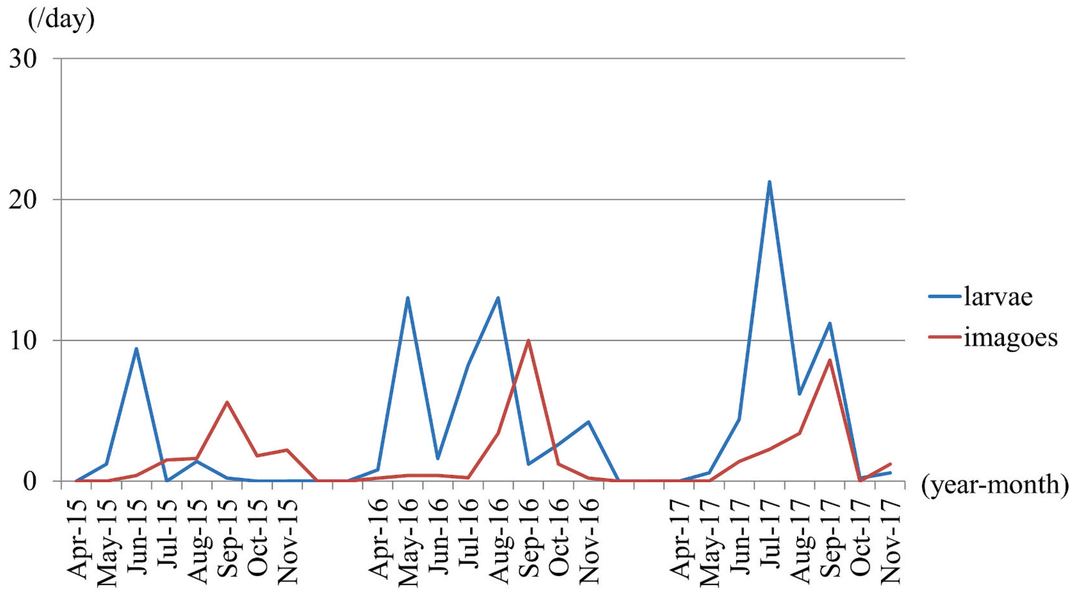

Fig. 2. Numbers of *Ae. Albopictus* larvae and imagoes captured at the Yoyogi Park from April to November, from 2015 to 2017. The blue and red lines show the mean numbers of larvae and imagoes caught per day, respectively. The numbers of larvae increased every year, but the numbers of imagoes remained constant. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2016, although the temperature was relatively low that year. Moreover, in 2014, when the big outbreak occurred, the temperature and humidity in Tokyo were not relatively high compared with those in other years. Although gradually higher humidity values are apparent, the numbers of imagoes have not risen accordingly.

3.3. Pest control

Besides mowing grass and bamboo trees, as per Tokyo Metropolitan authorities' instructions, the public health care center and the major parks in Tokyo started a campaign for prevention and extermination of *Ae. albopictus* in 2014; that year, pesticides using pyrethroid insecticide against mosquitoes and insect growth regulator (IGR) against larvae were applied, in addition to water drainage from ponds and rainwater inlets and cleaning of fountains inside the parks, which have been carried out every year since then. Moreover, some areas of Yoyogi Park were closed in 2014, and users were notified about the risk of DENV infection inside the park [19].

Thereafter, the major parks in Tokyo have continuously taken countermeasures against mosquito-borne infections voluntarily or under instructions from the Tokyo Metropolitan government. Yoyogi Park, which was the central location of the 2014 transmission, has continued all the efforts mentioned above except for spraying pyrethroid insecticide. Moreover, branches of bushes and groves have been cut off to improve ventilation and reduce the habitats for mosquitoes. However, larvae numbers have kept increasing each year (Fig. 2).

3.4. Numbers of imported/autochthonous dengue infection cases and travelers

More and more people have been visiting Japan from abroad, although the numbers of people traveling to dengue-endemic countries or areas have not risen as much. Among the East Asian areas with continuous or frequent dengue risks, visitors from Taiwan and Hong Kong account for the majority (Fig. 4). In addition, the number of travelers from Thailand has increased in the last 10 years. On the other hand, the major high dengue risk destinations for Japanese travelers represent popular tourist spots, including many island areas such as Hawaii and Guam [24,25].

The number of imported dengue cases have ranged from approximately 200 to 300 (Fig. 5), and have not been consistent with the increases in the number of travelers. In 2014, when the outbreak occurred, the number of imported infections did not show relative increase; in fact, it was smaller than that on average.

4. Discussion

In this study, we assessed the autochthonous dengue cases that we encountered in 2014 and analyzed correlations between the numbers of mosquitoes and the weather that season, as well as between the numbers of imported dengue fever cases and the number of travelers. We also evaluated the effects of preventive measures against autochthonous dengue infections.

Many patients with autochthonous DENV infection visited our institution located near Yoyogi Park, which was the epidemic focus of the outbreak. NS1 antigen assay and RT-PCR are effective diagnostic tests during the acute phase of infection, within the initial one to seven days after the symptom onset [22]. The serotype of DENV in all positive RT-PCR patients was 1, which was consistent with other reports [20,26].

Analysis of the data we gathered did not show significant associations between the numbers of mosquitoes and the weather, nor between the numbers of imported dengue infection cases and the number of travelers. Despite the greater risk for DENV infection caused by higher humidity values and increasing numbers of travelers, no autochthonous infections have been reported after 2014. Our study indicates that the outbreak of 2014 occurred without a favorable environment for mosquitoes or high inflow of travelers, and other unknown factors may have led to the autochthonous infection. Some reports have found that most of the cases in the outbreak were caused by a single strain that shared high identity (99.7% and 99.3%, respectively) with the envelope protein genome sequence of a DENV strain isolated in China and Indonesia [18,27,28]. In 2013, a year before the outbreak, a German tourist was diagnosed with dengue fever after he left Japan, and the site of exposure was presumed to be Japan, considering the incubation period [29,30]. However, an RT-PCR of the sample obtained from this patient revealed a DENV-2 infection, which was different from the serotype that caused the 2014 outbreak. On the other hand, *Ae. albopictus* imagoes cannot survive the Japanese winter, and the possibility of a DENV carried to the next generation of mosquitoes is known to be extremely low. In fact, a previous study found that larvae collected at

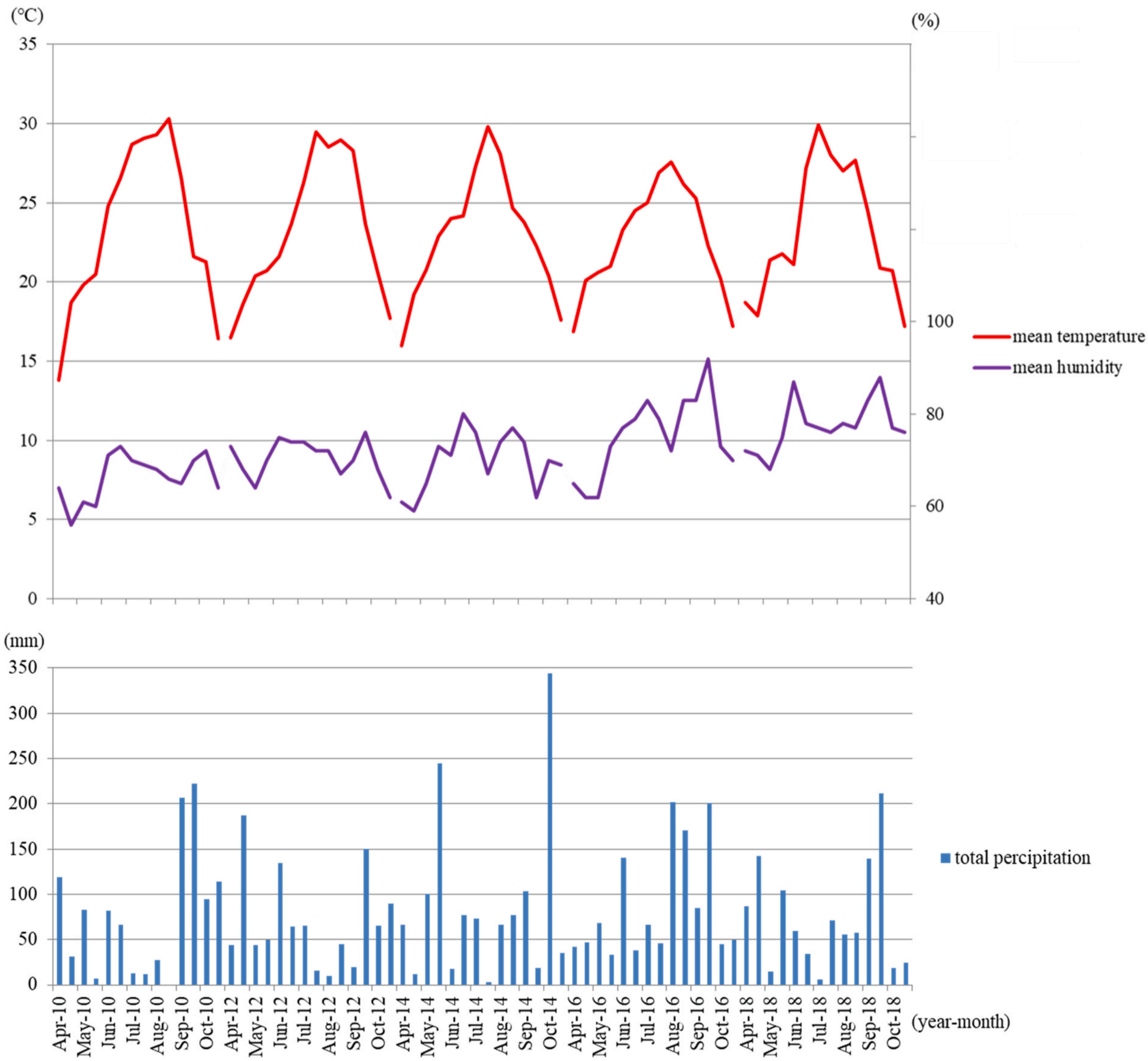

Fig. 3. Temperature, humidity, and precipitation variables in Tokyo from April to October every other year from 2010 to 2018. The red and purple lines show the mean temperature and humidity every two weeks, respectively. The blue bar charts show the total precipitation every two weeks. The temperature showed a similar trend each year, but the humidity has gradually risen over the years. We did not identify any of these three factors as players during the outbreak year of 2014. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

some of the central locations of the 2014 outbreak in April 2015 were negative for DENV [27]. Considering these facts, the outbreak could have been caused by a newly imported strain of DENV-1. Although risks for autochthonous infections (such as increased numbers of *Ae. albopictus*, improved living environments for mosquitoes in terms of weather, or elevated numbers of imported dengue cases) were not detected in 2014, a single case of imported DENV infection may have led to the infection of *Ae. albopictus* at Yoyogi Park and caused an extensive outbreak. Notably, Brazilian and Thai festivals were held at Yoyogi Park in late July with many Brazilian and Thai individuals participating in these events. Considering the onset of the first case of autochthonous dengue fever, the imported infection that led to the outbreak may have happened during these festivals. The higher risk of imported dengue infections posed by mass gatherings is clear [31], and increased imported cases may contribute to indigenous infections. Therefore, countermeasures to prevent DENV infections from expanding, for example, environmental improvements (including the measures taken at Yoyogi Park), and public education regarding the risk and prevention of mosquito-borne infectious diseases, are essential.

Pest control, including IGR, may have played a role in controlling the number of imagoes because of its effect on larvae (inhibition of the formation of the epidermis, thereby stopping the molting, pupation, and eclosion). Unlike pyrethroid insecticide, which was used in the outbreak in 2014, IGR does not accumulate in the environment and can be safely applied. The increases in the numbers of imagoes during the years after the outbreak were relatively smaller than in those of the larvae (Fig. 2), and, therefore, IGR may be effective in controlling the number of mosquitoes. However, the numbers of larvae have risen each year. Since the climatic environment of Tokyo in summer is generally favorable for mosquitoes and more and more travelers are visiting, autochthonous outbreaks could happen any time. Our analysis in this study could not explain the absence of autochthonous DENV infections since 2014 despite growing numbers of travelers to and from Japan and the increasing numbers of larvae in Yoyogi Park that have thrived in spite of the continuous pest control.

We are aware of the limitations of this study. First, we did not detect nucleotide sequences of the DENV in our institution because sequencing was not available at the time, and we were unable to confirm the origin of the virus strains. Second, we did not obtain precise information about pest control because the main information source was the internet.

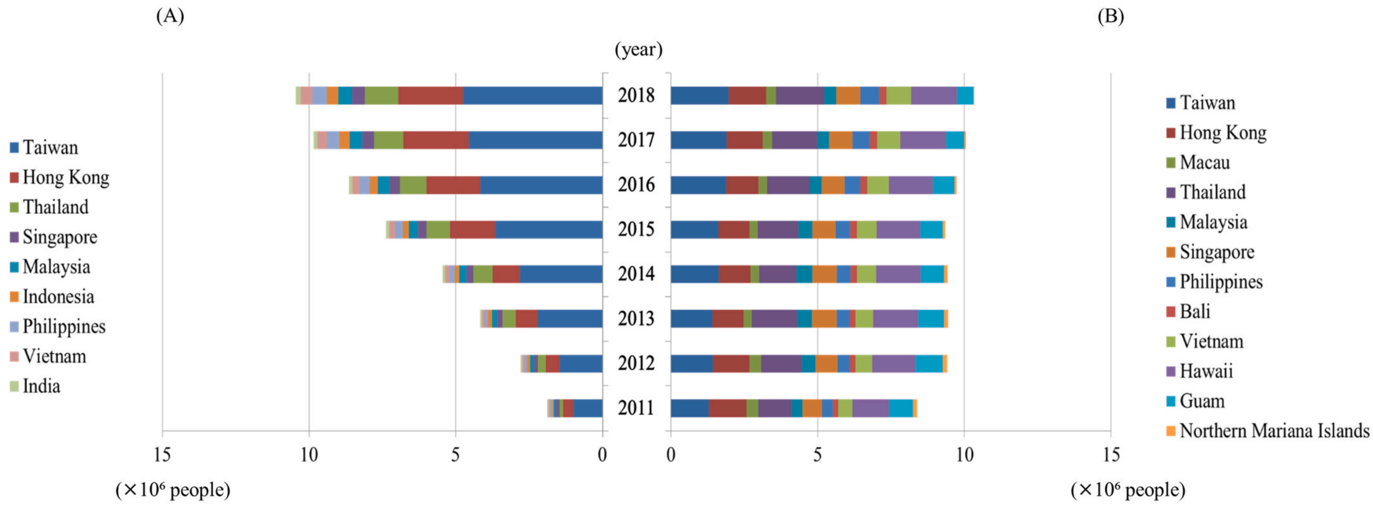

Fig. 4. Numbers of travelers from high dengue risk areas to Japan per year (A), and numbers of travelers from Japan to high dengue risk areas (B), from 2011 to 2018. Each bar chart is color-coded by area or country. The number of people visiting Japan from dengue-endemic areas has increased compared with the number of people traveling to dengue-endemic areas from Japan. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

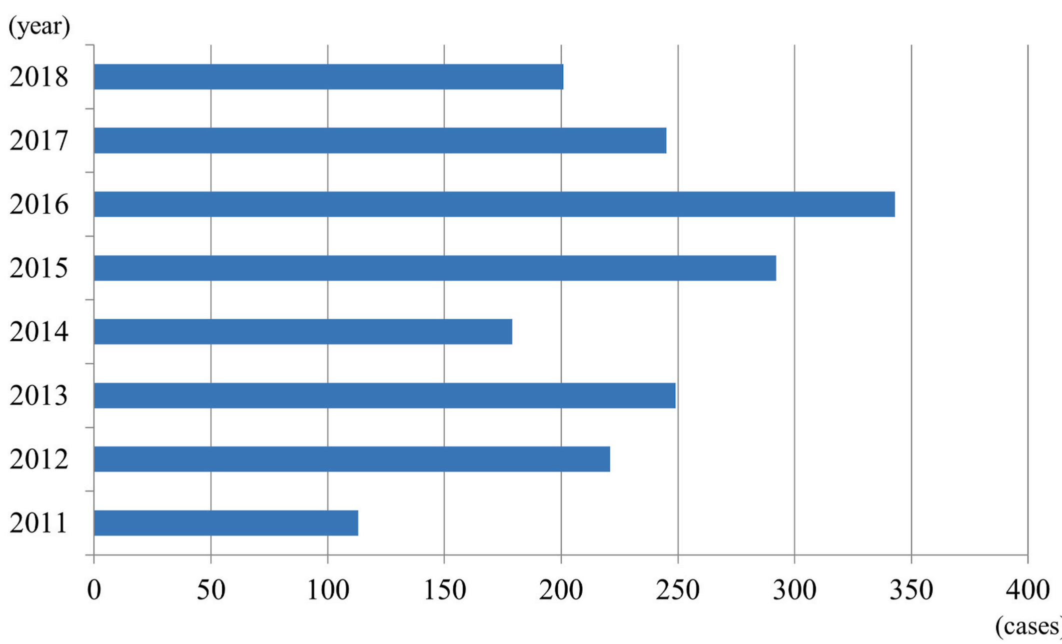

Fig. 5. Numbers of imported dengue fever cases in Japan each year from 2011 to 2018. The total number of imported cases has fluctuated between 113 and 343.

Details about pest control (site, frequency, and timing of implementation) were not fully available, probably because the instructors for each countermeasure differed. Lastly, the mosquito surveillance should have been larger in scale, targeting more parks throughout the country, so that not only vectors but also pathogens could have been investigated. Unfortunately, the numbers of mosquito larvae had not been surveyed before the outbreak, disabling the accurate examination of the effect of IGR against mosquitoes.

5. Conclusion

We conducted a case series study on autochthonous dengue cases that we treated in 2014 and investigated the causes of the outbreak. Our results show that the weather conditions were not especially favorable for vector mosquitoes in that year and that the number of travelers, imported dengue cases did not show remarkable associations. However, the increasing numbers of travelers expected pose increased risks for both imported and autochthonous DENV infections. Considering the upcoming mass gatherings such as the Tokyo Olympic Summer Games, measures to control mosquitoes as well as alerting people to the danger of mosquito-borne infections will be necessary to reduce the high risk of a next dengue fever outbreak in Japan.

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None.

Declaration of competing interest

The authors declare that they have no competing interest.

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