INTRODUCTION

An outbreak of autochthonous dengue fever occurred in the summer of 2014 in Tokyo, Japan. Numerous participants and spectators from abroad are expected to visit Tokyo in the summer of 2020. This study aims to analyze the risk of autochthonous dengue infections in Tokyo in summer and also assess the additional risk in the Olympiad using a mathematical model. A stochastic transmission model was developed with the cooperation of seasonal factors that greatly influence the transmission cycle of dengue virus, and stochastic simulations were conducted for each scenario provided adequately. This study found that (i) the incidence of dengue autochthonous infections is predicted to occur in a small number of cases; (ii) the local climate greatly influences the scale of dengue autochthonous infections; (iii) the incidence reaches its peak in August and early September; and (iv) the possibility of progressing to dengue outbreak is rare. In the Olympiad to be held in the summer of 2020, an additional risk of dengue autochthonous infections will amount to double compared with that in other years.

SUMMARY: An outbreak of autochthonous dengue fever occurred in the summer of 2014 in Tokyo, Japan. Numerous participants and spectators from abroad are expected to visit Tokyo in the summer of 2020. This study aims to analyze the risk of autochthonous dengue infections in Tokyo in summer and also assess the additional risk in the Olympiad using a mathematical model. A stochastic transmission model was developed with the cooperation of seasonal factors that greatly influence the transmission cycle of dengue virus, and stochastic simulations were conducted for each scenario provided adequately. This study found that (i) the incidence of dengue autochthonous infections is predicted to occur in a small number of cases; (ii) the local climate greatly influences the scale of dengue autochthonous infections; (iii) the incidence reaches its peak in August and early September; and (iv) the possibility of progressing to dengue outbreak is rare. In the Olympiad to be held in the summer of 2020, an additional risk of dengue autochthonous infections will amount to double compared with that in other years.
function to satisfy that its value rises in proportion to $d$ for small $d$ and saturates for large $d$ (18). Therefore, a hyperbolic function $f(d) = \frac{3bd}{(2d_{\text{mean}}+d)}$ ($d_{\text{mean}} = 4.29$, the mean number of captured mosquitoes) is employed, where $b$ stands for the scale parameter that will be assigned in scenarios based on human behavioral patterns.

**Imported dengue cases:** The yearly number of imported cases confirmed as dengue fever ranges between 150 and 350 nation-wide or between 50 and 100 in Tokyo in the last 5 years (2012-16); the confirmed cases in Tokyo were 25–30 of those in nation-wide (3–5, 19).

For the risk assessment of autochthonous dengue fever, three assumption levels for yearly number of imported dengue cases in Tokyo (NID) were used, i.e., low (50), middle (70), and high (100), where middle stands for the mean number in the past five years (2012-16); each monthly imported number in the assumption is assigned in proportion to the transitions of mean monthly confirmed cases in 2012–2016 in Tokyo.

During the Olympiad season, many participants and spectators are expected to visit Tokyo intensively, and most of them will be in the open air. Mizuho Research Institute (20) estimated the number of foreign spectators to be approximately 810,000, whereas the number of participants will be approximately 11,000. An estimation of the additional number of dengue cases in the Olympiad (additional NID) ranges from 10 (low) to 23 (high) where an average stands at 14 (middle) according to the ratio of the number of confirmed dengue cases and number of tourists from other countries in recent 5 years (2012-16) (3–5, 21).

**Natural history of dengue fever:** Some persons infected with DENV for the first time remain asymptomatic and thus they play an important role in DENV infection to mosquitoes. Especially in Japan, most symptomatic cases are referred to the hospital for treatment; as a consequence, they cannot become the source DENV-infection. Duong et al. (22) reported that asymptomatic cases were always significantly more infectious to mosquitoes than the symptomatic cases (odds ratio, 10.05) and that 50% of mosquito infectious doses (viremia level) in asymptomatic cases was approximately a hundredth as much as in symptomatic cases. Therefore, we assume that only asymptomatic cases can transmit DENV to *Ae. albopictus* in this study.

In stochastic process, a decision on asymptomatic or symptomatic infection for infected person is assumed to be governed by the binomial distribution with success rate of 0.6 (23, 24).

**Influence of temperature on the progress of dengue infection in *Ae. Albopictus*:** Xiao et al. (25) investigated the effect of temperature on the infection rate of DENV in *Ae. albopictus* by infection experiments. The regression curve $\text{Inf}(T)$, the success rate of infection in the salivary grand at temperature ($T$) is provided by the data:

$$\text{Inf}(T) = -0.0001291T^3 + 0.005735T^2 + 0.008916T - 1.5258 (R^2 = 0.990)$$

Several studies demonstrated on the relationship between temperature and extrinsic incubation period.
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(EIP) of DENV in *Aedes* mosquitoes (10). Regression curves for mean EIP and lower bound EIP are provided based on the data (10,25):

Mean\( EIP(T) = 91.524 \exp(-0.073T), \quad (R^2 = 0.994)\)

Lower\( EIP(T) = 38.134 \exp(-0.07655T), \quad (R^2 = 0.8999)\)

In the stochastic process, an event of successful infection in *Ae. albopictus* at \( T \) is expected to be governed by the binomial distribution of success rate \( \text{Inf}(T) \), and that the EIP distribution at \( T \) is governed by the gamma distribution with mean = Mean\( EIP(T) \), variance = \( (\text{Mean} EIP(T) - \text{Lower} EIP(T))^2 \).

**Stochastic transmission model of DENV:** A stochastic transmission model of DENV between humans (imported dengue cases or inhabitants) and *Ae. albopictus* mosquitoes was constructed. The population of inhabitants is divided into five epidemiological classes, i.e., (i) negative, (ii) exposed, (iii) viremia and symptomatic, (iv) viremia and asymptomatic, and (v) recovered, whereas imported dengue cases are divided into every class, except negative class. On the contrary, *Ae. albopictus* mosquitoes are divided into (i) negative, (ii) exposed, and (iii) infectious classes (Fig. 2). Table 1 summarizes epidemiological and entomological parameters with probability distribution and their estimated or assumed parameter values used in this model. Stochastic events such as infection and mosquitoes’ death progress on daily interval, while length of incubation and infectious period, choice of symptomatic or asymptomatic infection for humans, or length of EIP for mosquitoes, are randomly decided by the probability distributions in Table 1 at the time of infection to humans, or to mosquitoes, respectively.

**Scenarios:** We provide several assumptions for indefinite factors. As has been mentioned, NID in the normal year and of the additional NID in the Olympiad are each provided for three levels. For a person, the number of mosquito bites per day highly depends on his/her daily life. Based on the behavioral pattern, human population is classified into (i) indoor (living mostly indoor), (ii) outdoor (exposed outdoor for some hours), (iii) open-air (participating in an open-air event for many hours; only applied to the additional NID in the Olympiad), and (iv) normal (any other situation) types. The composition ratio among indoor, normal, and outdoor types is assumed to be 0.1, 0.8, and 0.1, respectively, whereas the composition ratio among normal, outdoor, and open-air types is assumed to be 0.5, 0.4, and 0.1 for the additional imported dengue cases in the Olympiad, respectively. The scale parameter \( b \) in conversion function is assigned to 1, 2, 0.1, and 0.01 for outdoor, open-air, normal, and indoor types, respectively.

We investigated three levels of climate situation: low (2008), middle (2014), and high (2010) temperature patterns. Daily survival rate of *Ae. albopictus* (DSR) depends on the climate; however, the influence of temperature on DSR for the interval of 20–30°C is limited (Fig. 1); then, three levels of DSR were investigated, independent of temperature: low (0.75), middle (0.80), and high (0.85) (8, 26, 27). For human bait index of *Ae. albopictus* (HBI), three levels were identified: low (0.3), middle (0.5), and high (0.8).

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Fig. 2. Scheme of the stochastic model of DENV transmission between humans (inhabitants or imported dengue cases) and *Ae. albopictus* mosquitoes. Gray arrows show the progress of infection, onset, and recovery, and black arrows show infection between humans and *Ae. albopictus*. 

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RESULTS

Stochastic simulations: Trial stochastic simulations were carried out 10,000 times for each 81 combinations of assumptions about the NID in normal year or the additional NID according to the Olympiad, climate situation, DSR, and HBI of mosquitoes with each three level in Scenarios. Simulation results for the middle level of HBI situation are summarized in Table 2.

Risk assessment for autochthonous dengue infections in Tokyo in normal year: The transition of the mean number of daily infected and onset autochthonous dengue cases in 10,000 iterations is shown in Fig. 3 on selecting the middle level for all assumptions in Scenarios; both of the mean numbers remain low in July, increase from the beginning of August, reach its peak in late August, and decrease throughout the other months. The occurrence probability of one more autochthonous dengue cases is highly influenced by climate; this probability holds under 5% for low climate situation, but increases over 10% for high climate situation when two entomological factors (DSR and HBI) were selected as the middle level situation. However, most simulation trials on autochthonous infection showed one (approximately 70%) or less than two cases (approximately 90%), and only 1–2% of trials had more than 5 cases of dengue infection.

Additional risk for autochthonous dengue infections in Tokyo due to the additional NID in the 2020 Olympiad: Transitions of the mean number of daily onset autochthonous dengue cases reaches its peak on August 20 or thereabouts and falls in the middle of September. The mean number of autochthonous dengue cases is approximately 3 (2.6–3.83), 2.5 (1.93–2.84), and 1.7 (1.57–1.92) times higher than that in normal year for the selection of low, middle, and high level climate situation, respectively (values in parenthesis being lower and upper bounds of 95% CI) (Table 2). The probability of occurrence of one more autochthonous dengue cases is also highly influenced by climate; this probability holds under 10% for low climate situation but climbs over 25% for high climate situation when two entomological factors (DSR and HBI) were selected as the middle level. The distribution of trials with one more autochthonous cases is similar to the distribution in the normal year mentioned above.

DISCUSSION

A stochastic model for the DENV transmission was proposed between humans (imported dengue cases or inhabitants) and mosquitoes (Ae. albopictus) according to transitions of temperature and density of Ae. albopictus in Tokyo. For most epidemiological and entomological parameters in the model, their values were estimated based on the literatures. However, other parameters were provided with the three level values (low, middle, and high) in the simulation scenarios, their values were estimated based on the literatures. However, other parameters were provided with the three level values (low, middle, and high) in the simulation scenarios because their values cannot be fixed due to the influence of environmental factors or overseas prevailing affairs. Consequently, an adoption of three levels would cover a wide range of fluctuations. This model can be modified to apply to other imported infectious diseases, Chikungunya and Zika fever, that are transmitted by Ae. albopictus.

The source of DENV infection in mosquitoes in

| Probability distribution | Descriptions | Parameters of probability distribution |
|--------------------------|--------------|---------------------------------------|
| Gamma                    |              | Average | Variance | Range  |
| Humans                   | Intrinsic incubation period (days) | 6.11     | 4.11     | 2-12   |
|                          | Infectious period (days)           | 5        | 1        | 3-7    |
| Ae. albopictus           | Extrinsic incubation period $^1$ (days) | Mean EIP(T) | (Mean EIP(T) - Lower EIP(T))$^2$ | 3-30 |
| Binomial                 | Probability of success rate        | 0.4      | see text | see text |
| Humans                   | Rate of symptomatic infections     | 0.4      | see text | see text |
| Ae. albopictus           | Daily survival rate                |          |          |        |
|                          | Human bait index                   |          |          |        |
|                          | Success rate of infection in salivary gran$^1$ | Inf(T)  |          |        |
| Poisson                  | Average                             |          |          |        |
| Humans and Ae. albopictus| Number of bites/day/person$^2$      |          |          |        |
| Stable                   | Ae. albopictus                      | Estimated value |          |        |

$^1$: Depending on temperature (T).
$^2$: Depending on number of captured Ae. albopictus (d).

Table 1. List of epidemiological and entomological parameters used in the stochastic model with probability distributions and their estimated or assumed parameters.
Table 2. Summary of simulation results for autochthonous dengue fever in normal year and in the 2020 Olympiad

| Assumptions (Level) | Climate condition | Number of imported dengue cases | Daily survival rate of Ae. albopictus | Number of autochthonous dengue cases | Probability of one more autochthonous dengue cases (%) |
|---------------------|-------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------------------------|
|                     |                   |                                  |                                      | Mean | Minimum | 1st quartile | Median | 3rd quartile | Maximum |                                      |
| Normal year         |                   |                                  |                                      |      |         |             |        |             |         |                                      |
| Low (2008)          | Low               | 0.012                           | 0 0 0 0 3                           | 1.0  |
|                     | Middle            | 0.016                           | 0 0 0 0 3                           | 1.3  |
|                     | High              | 0.024                           | 0 0 0 0 4                           | 2.0  |
| Middle (2014)       | Low               | 0.024                           | 0 0 0 0 4                           | 1.8  |
|                     | Middle            | 0.042                           | 0 0 0 0 7                           | 3.1  |
|                     | High              | 0.059                           | 0 0 0 0 6                           | 4.4  |
| High (2010)         | Low               | 0.077                           | 0 0 0 0 8                           | 4.9  |
|                     | Middle            | 0.101                           | 0 0 0 0 7                           | 6.4  |
|                     | High              | 0.155                           | 0 0 0 0 8                           | 9.9  |
| Middle (2014)       | Low               | 0.088                           | 0 0 0 0 7                           | 5.9  |
|                     | Middle            | 0.103                           | 0 0 0 0 5                           | 7.5  |
|                     | High              | 0.165                           | 0 0 0 0 5                           | 11.4 |
| High (2010)         | Low               | 0.198                           | 0 0 0 0 8                           | 12.2 |
|                     | Middle            | 0.263                           | 0 0 0 0 8                           | 16.6 |
|                     | High              | 0.408                           | 0 0 0 0 9                           | 23.7 |
| The Olympiad        | Low (2008)        | 0.035                           | 0 0 0 0 6                           | 2.7  |
|                     | Middle            | 0.05                            | 0 0 0 0 5                           | 3.9  |
|                     | High              | 0.092                           | 0 0 0 0 6                           | 7.2  |
| Middle (2014)       | Low               | 0.085                           | 0 0 0 0 6                           | 5.9  |
|                     | Middle            | 0.130                           | 0 0 0 0 5                           | 9.5  |
|                     | High              | 0.209                           | 0 0 0 0 7                           | 13.6 |
| High (2010)         | Low               | 0.173                           | 0 0 0 0 6                           | 12.1 |
|                     | Middle            | 0.252                           | 0 0 0 0 8                           | 16.8 |
|                     | High              | 0.357                           | 0 0 0 0 7                           | 23.0 |
|                     | Low               | 0.219                           | 0 0 0 0 8                           | 13.2 |
|                     | Middle            | 0.33                            | 0 0 0 0 13                          | 19.5 |
|                     | High              | 0.515                           | 0 0 0 1 9                           | 28.7 |
| High (2010)         | Low               | 0.07                            | 0 0 0 0 5                           | 5.4  |
|                     | Middle            | 0.115                           | 0 0 0 0 6                           | 8.7  |
|                     | High              | 0.179                           | 0 0 0 0 7                           | 13.0 |
| Middle (2014)       | Low               | 0.169                           | 0 0 0 0 6                           | 11.7 |
|                     | Middle            | 0.248                           | 0 0 0 0 7                           | 16.8 |
|                     | High              | 0.399                           | 0 0 0 1 6                           | 25.3 |
|                     | Low               | 0.419                           | 0 0 0 0 9                           | 23.9 |
|                     | Middle            | 0.642                           | 0 0 1 10                           | 33.9 |
|                     | High              | 1.03                            | 0 0 2 12                           | 49.0 |
|                     | Low               | 0.133                           | 0 0 0 5                            | 9.8  |
|                     | Middle            | 0.184                           | 0 0 0 7                            | 13.6 |
|                     | High              | 0.308                           | 0 0 0 7                            | 21.6 |
| High (2010)         | Low               | 0.282                           | 0 0 0 7                            | 18.7 |
|                     | Middle            | 0.419                           | 0 0 1 6                            | 26.9 |
|                     | High              | 0.682                           | 0 0 1 9                            | 39.7 |
|                     | Low               | 0.678                           | 0 0 1 11                           | 35.0 |
|                     | Middle            | 1.031                           | 0 0 2 13                           | 48.8 |
|                     | High              | 1.572                           | 0 0 1 14                           | 64.7 |

1: The assumption about HBI is set to be middle.
Tokyo is different from that in overseas with endemic regions because it is limited to asymptomatic cases only. Majority of dengue patients must consult the doctor in Tokyo. Any inpatient cases are unable to contact mosquitoes, and also outpatients in homes can escape from mosquito bites because almost all homes are air-conditioned.

Two entomological factors, DSR and HBI, directly influence the infectivity of DENV in *Ae. albopictus*. Furthermore, the climate condition can indirectly
influence through EIP and the success rate of infection in salivary grand that also increases the number of *Ae. albopictus*. Therefore, these three factors have an impact on the occurrence of autochthonous dengue cases. On the contrary, NID has an absolute impact on the occurrence of autochthonous dengue. Four factors were compared through an analysis of variance using the linear model of the total number (μ) of autochthonous dengue cases in 10,000 trials:

\[
\mu_{i,j,k,l} = \mu_0 + \text{HBI}_i + \text{Climate}_j + \text{DSR}_k + \text{NID}_l,
\]

where

\[
\sum_j \text{HBI}_i = \sum_j \text{Climate}_j = \sum_k \text{DSR}_k = \sum_l \text{NID}_l = 0, \quad (i,j,k,l = \text{Low,Middle,High})
\]

The analysis for autochthonous dengue infections in normal year showed that an impact of DSR is similar to that of climate, and that NID has a half impact of them. Chung et al. (9) found that dengue transmission in southern Taiwan could be affected by climate. From the theoretical viewpoint of modeling, Siraj et al. (28) supported the impact of temperature on DENV transmission. However, the analysis in the Olympiad showed that DSR has a stronger impact than the other three factors with nearly similar impact. The restriction to a short summer period in the Olympiad may relatively reduce the impact of climate. The climate or HBI cannot be changed by anyone. Neither can NID because it comes from an incidence in endemic countries. Moreover, asymptomatic dengue cases from abroad are difficult to determine at quarantine inspection. On the contrary, suppression measures against mosquitoes allow reduction DSR and increase number of *Ae. albopictus*, which leads to reduced occurrence of autochthonous infections in a view of ANOVA. Furthermore, Yanagisawa et al. (6) suggested the reinforcement of early detection of dengue infection to prevent further transmission in the Olympiad.

Simulations on our scenarios showed that a big outbreak of autochthonous dengue infections rarely occurs. Our previous study (13) showed that an existence of lodgers in Yoyogi Park was necessary for the occurrence of the 2014 dengue outbreak. They played a role in determining the source of infection to mosquitoes, and consequently, a transmission cycle of DENV was established. This study did not adopt scenarios that lodgers in parks participate in DENV transmission because of few limited parks occupied by lodgers, besides progressing preventive measures against mosquitoes in parks after the 2014 dengue outbreak.

This study has some limitations. The human behavioral pattern will affect possible contacts between humans and mosquitoes. However, knowledge of human behavioral pattern is poor in Tokyo. Therefore, this study adopted a simple assumption about it. Hereafter, it is desirable to precisely assess human behaviors based on the progress of human ecological study. Imported dengue cases in reports (3–5) were all Japanese national, except for very few cases (29). Although quarantines occasionally find dengue cases among foreign visitors with fever, the dengue situation of foreign visitors in Japan remains unclear. The number of the additional NID in the Olympiad was calculated based on the number of foreign visitors because additional dengue cases will result from spectators abroad in Japan. Although simulation scenarios adopted three levels, a possibility of overestimation remains.

In conclusion, we found that the incidence of dengue autochthonous infections is predicted to be small, that the local climate greatly influences the scale of dengue autochthonous infections, and that the incidence reaches its peak in August and early September. We also found that development into dengue outbreak is barely possible, but that such possibility increases in a particular situation, such as the existence of lodgers in parks who play a role as a source of infection to mosquitoes. When the 2020 Tokyo Olympic Games will be held during summer, an additional risk of dengue autochthonous infections will approximately double the risk in normal years. In the prevention viewpoint against dengue autochthonous infections, swift suppression measures against mosquitoes should be maintained for the early detection of dengue cases and to control lodgers in parks.

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**Conflict of interest** None to declare.

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