



# Identifying geographic areas at risk of rubella epidemics in Japan using seroepidemiological data



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## ARTICLE INFO

### Article history:

Received 21 August 2020

Received in revised form 23 September 2020

Accepted 23 September 2020

### Keywords:

Rubella virus

Importation

Statistical model

Travel

Epidemiology

Vaccination

## ABSTRACT

**Objective:** Even with relatively high vaccination coverage, Japan experienced rubella epidemics in 2012–2014 and 2018–2019, which were fueled by untraced imported cases. We aimed to develop a risk map for rubella epidemics in Japan by geographic location via analysis of seroepidemiological data and accounting for the abundance of foreign visitors.

**Methods:** Geographic age distribution and seroprevalence were used to compute the age- and sex-dependent next-generation matrix in each region. We computed the probability of a major epidemic using the assumed number of untraced imported rubella cases proportionally modeled to the number of foreign travelers.

**Results:** Risks of a major epidemic were high in areas with capital cities, while areas with a greater fraction of older people yielded smaller effective reproduction numbers, a lower volume of foreign travelers, and thus a lower probability of a major epidemic. The volume of susceptible adult males was larger in urban geographic regions, having a greater number of foreign travelers than remote areas.

**Conclusions:** Our findings are consistent with the observation of multiple large clusters of rubella cases in urban areas during 2012–2014 and 2018–2019. Should a future rubella epidemic occur, it will likely be in geographic areas with capital cities.

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## Introduction

Rubella, sometimes known as German measles, is an infectious disease caused by the rubella virus, generally involving a mild febrile disease accompanied by rash and lymphadenopathy (Menser et al., 1978; Lambert et al., 2015). While rubella is mostly self-limiting and is asymptomatic for 25%–50% of infections, pregnant women infected in the first trimester can suffer a variety of complications, including miscarriage, stillbirth, and congenital rubella syndrome (CRS) (Panagiotopoulos et al., 1999; Lambert et al., 2015). When it comes to prevention, rubella is certainly a vaccine-preventable disease, and having substantial herd immunity at the population level can eventually lead to its elimination (Nokes and Anderson, 1988; Plans-Rubió, 2012).

Japan has enjoyed coverage of greater than 90% for the measles and rubella (MR) vaccine from the late 1990s (Kinoshita and

Nishiura, 2016); however, rubella control has been a continuous challenge. In fact, the country has recently been forced to introduce supplementary immunization among young adults. The vaccination target was changed from only junior high school girls to both male and female pre-school children in 1995, but the past policy has meant present-day adult males are largely susceptible (Nishiura et al., 2015; Kinoshita and Nishiura, 2016). There was an epidemic from 2012 to 2014 involving more than 12,000 confirmed cases that were dominated by adult males aged 30–59, and there were as many as 45 confirmed CRS cases during the epidemic (Kinoshita and Nishiura, 2016; Kayano et al., 2019). A similar outbreak recurred in 2018–2019, also involving CRS cases (Lee et al., 2019), which finally compelled the Japanese government to implement a supplementary immunization program for adult males (Ministry of Health, Labour and Welfare, 2019; Ujiie, 2019). As a result of the 2018–2019 epidemic, more than 5,000 confirmed cases were reported to the National Institute of Infectious Diseases, with the majority of cases observed in urban areas and especially among adult male aged 35–64 years, a slightly elevated ages of cases compared with 2012–14 epidemic (Ministry of Health, Labour and Welfare, 2020).

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Such recurrent epidemics are undoubtedly fueled by the introduction of untraced imported cases (Nishiura et al., 2019). Because of the increasing number of foreign visitors, mainly from the Asian continent, the risk of imported infectious diseases, in general, has increased (Yuan and Nishiura, 2018; Yuan et al., 2019). Therefore, Japan is repeating experiments to test herd immunity using various vaccine-preventable imported diseases (e.g., measles), which have mostly resulted in a sporadic or small number of secondary transmissions, but sometimes resulting in a large cluster of cases (Nishiura et al., 2016; Shimizu et al., 2018). The government of Japan aimed to verify the elimination of rubella by 2020, when, before the outbreak of coronavirus disease 2019 (COVID-19), the country was planning to host the Summer Olympic Games (Jindai et al., 2018); ironically, however, without good herd immunity, repeated introductions can cause continued transmission, and welcoming in more visitors increases the risk of an outbreak (Nishiura et al., 2019).

Considering that the population still includes a substantial number of susceptible individuals and has not fully attained sufficient herd immunity levels to eliminate major epidemics, it is vital that a tool is devised to monitor the vulnerable subpopulation on the basis of the further introduction of untraced imported cases. As part of risk assessment practices, the present study aimed to create a risk map of rubella in Japan by geographic location via analyzing seroepidemiological data and accounting for the number

of local foreign visitors. Because the seroepidemiological data were available up to 2016, we aimed to create the risk map for 2017.

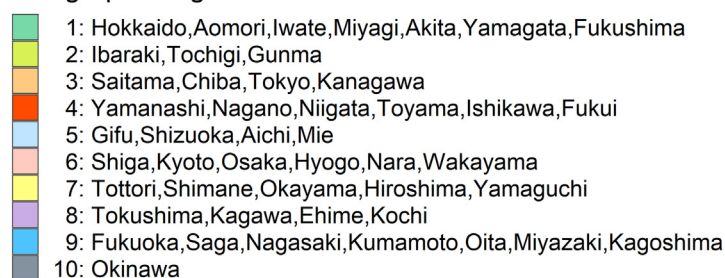
## Materials and Methods

### Epidemiological data

#### Notification data

The annual number of notified rubella cases in 2016 was collected from the National Epidemiological Surveillance of Infectious Diseases (NESID) (National Institute of Infectious Diseases, 2017a, 2017b). Revised from 2008, the government of Japan mandated the notification of all diagnosed rubella cases to be reported following the Infection Control Law. During the early part of the rubella epidemic in Japan from 2012 to 2013, notified rubella cases were mostly reported in and around urban prefectures (Saito et al., 2018), and this was the case even after the 2012–2014 epidemic, perhaps reflecting the large number of travelers to prefectures with larger population sizes. We specifically extracted the annual cumulative number of rubella cases in 2016 because it was a non-epidemic season and could approximate the total number of imported cases during non-epidemic years. In 2016, there were 131 notified cases, of which the majority were notified in urban prefectures (National Institute of Infectious Diseases, 2017a, 2017b).

### Geographic region



**Figure 1.** Geographical regions in Japan.

In the present study, the 47 prefectures of Japan (first level of jurisdiction and administrative division). In the present study, the prefectures were grouped into 10 geographic regions, which are conventional classifications of regions in Japan.

### Population data in Japan

To quantify the age and sex distributions in the population by geographic area, we collected the demographic dataset for 2016 from the Statistics Bureau in Japan (Statistics Bureau, 2017). The population was divided into 15 different age groups: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and  $\geq 70$  years old, and these discrete age groups were similarly used to arrange the published seroepidemiological data (see below).

### Seroepidemiological data

The seroepidemiological data for rubella by age, sex, and prefecture were collected from the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD) from 1995 to 2016 (National Institute of Infectious Diseases, 2017a, 2017b). The NESVPD investigates antibodies raised against rubella in different prefecture populations every year, recruiting approximately 5,000 volunteers via random sampling (as described by the official statement, but strictly speaking, a non-random selection process of the geographical locations from which participants are mostly randomly drawn is used). A hemagglutination inhibition (HI) titer of  $\geq 32$  was used as the cut-off to determine seropositivity, which is a conventionally accepted value in Japan. Because the sampled prefectures in the survey were manually determined out of the total of 47 prefectures and varied every year, we grouped prefectures into 10 geographic regions (Figure 1). As mentioned above, subject ages were grouped as 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and  $\geq 70$  years, thus, the positive proportion in 2016 could be calculated. However, because the original report crudely stratified the age groups as 0, 1, 2–3, 4–6, 7–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, and  $\geq 40$  years, a smooth spline was fitted to the seropositive proportion for 5-year age group analysis, that is, 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, and  $\geq 40$  years as for 2016. Moreover, as we had missing information for the older age groups (i.e.,  $\geq 39$  years), we used the survey data for earlier years (i.e., 1995–2015) to estimate the seropositive fraction by birth cohort and used those estimates as the seropositive fraction for 2016. Unfortunately, despite this, the following data remained missing: people aged between (i) 50–54 and 55–59 years in geographic region 2, (ii) 45–49 and 50–54 years in region 6, and (iii) 60–64, 65–69, and  $\geq 70$  years in all geographic areas; therefore, the imputed data were retrieved from the whole of Japan. Furthermore, because seroepidemiological surveillance was not conducted in region 6 in 2016, we used the results for 2015.

### Foreign travelers

The number of foreign travelers expected to visit each geographic area was extracted from the Consumption Trend Survey for Foreigners Visiting Japan in 2016, which was surveyed by the Japan Tourism Agency, a public agency closely affiliated with the Ministry of Land, Infrastructure, Transport, and Tourism (Japan Tourism Agency, 2017). Additionally, to obtain the specific countries from which the travelers came, the number of annual visitors was retrieved from the Statistics of Visitor Arrivals, which is reported by the Japan National Tourism Organization (Japan National Tourism Organization, 2017). In a published phylogeographic study of rubella in Asia, international human mobility in East and South East Asia was characterized as contributing to the importation of the rubella virus to Japan for strains that had not continuously circulated in Japan (Bozick et al., 2019). For this reason, we focused on incoming travelers from the following eight different countries: China, India, Indonesia, Malaysia, Philippines, Taiwan, Thailand, and Vietnam.

### Area-specific contact matrix

We used epidemiological information from the abovementioned datasets to compile a risk assessment of rubella in Japan, that is, the probability of a major epidemic. To account for different population sizes by age, sex, and geographic area (e.g., the predomination of young adults in urban locations or older people in remote areas), the matrix of contact rates in geographic region  $g$  was adjusted from the contact matrix of the entire of Japan. Let  $z_{ax}^Y$  be the proportion of the population of age  $a$  and sex  $x$  among the total population in area  $Y$  where sex  $x \in \{\text{male}, \text{female}\}$ .  $z_{ax}^Y$  is defined by

$$z_{ax}^Y = \frac{n_{ax}^Y}{n^Y}, \tag{1}$$

where  $Y$  represents the geographic region, which is either the entire of Japan ( $J$ ) or region  $g$  (i.e.,  $g = 1, 2, \dots, 10$ ),  $n^Y$  is the total population in the geographic region  $Y$ , and  $n_{ax}^Y$  is the population size of age group  $a$  and sex  $x$  in region  $Y$ . Assuming that the age- and sex-specific proportions of the population characterizes the differential contact frequency for age and sex in the different geographic regions, the contact matrix in geographic region  $g$  was adjusted from the contact matrix for the entire of Japan as

$$m_{abxy}^g = m_{abxy}^J \frac{z_{ax}^g}{z_{ax}^J}. \tag{2}$$

where  $m_{abxy}^g$  represents the adjusted contact rate between a person of age group  $a$  and sex  $x$ , and another person of age group  $b$  and sex  $y$  in geographic region  $g$ .  $m_{abxy}^J$  is the contact rate of the entire of Japan, as described elsewhere (Munasinghe et al., 2019).

### Computing the effective reproduction number

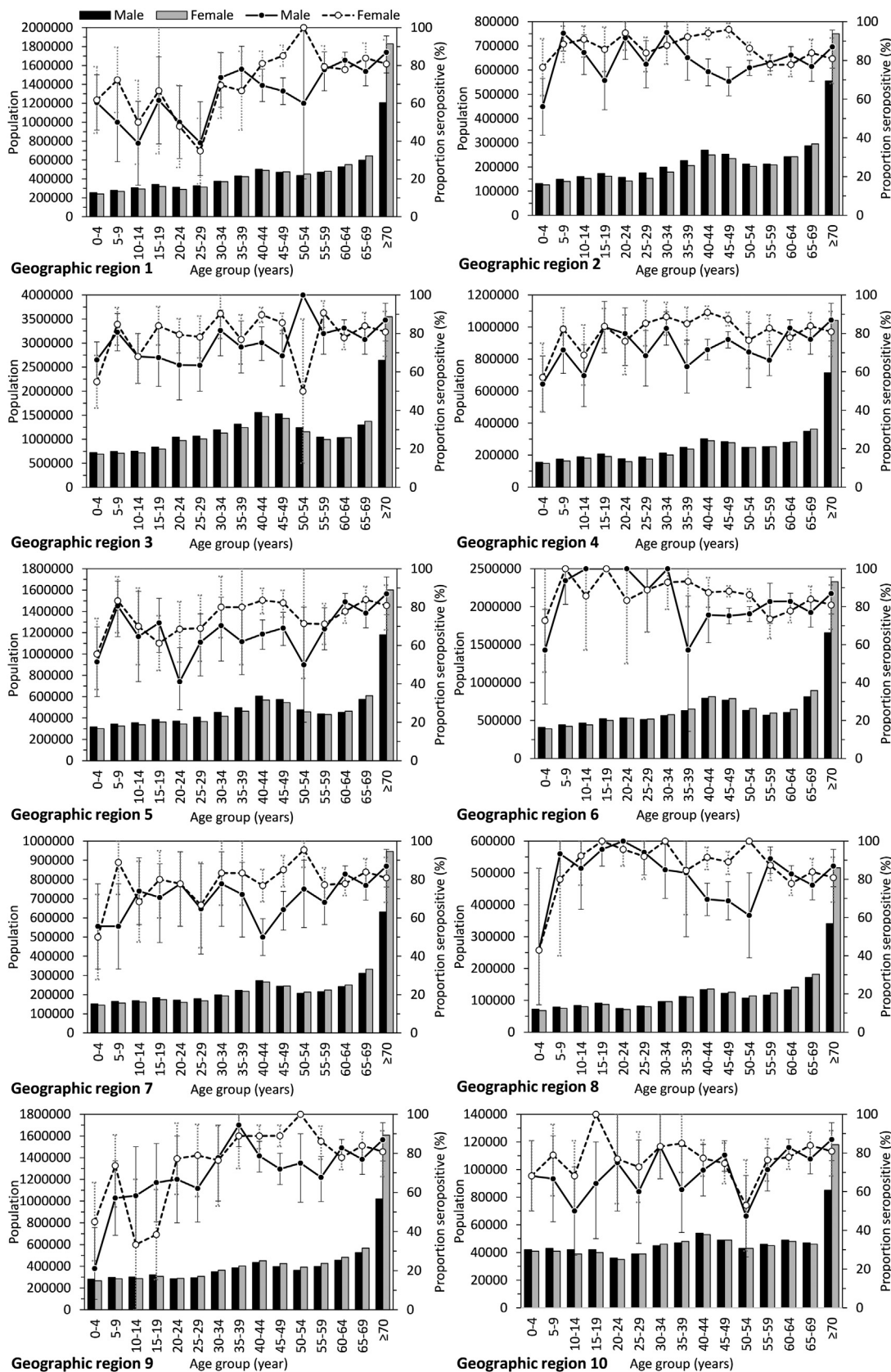
Let  $R_{abxy}^g$  be the reproduction number, that is, the average number of secondary cases in age group  $a$  and sex  $x$  produced by a single primary case of age group  $b$  and sex  $y$  in geographic region  $g$ , which we assumed to be computed as

$$R_{abxy}^g = s_{ax} m_{abxy}^g \frac{(1 - p_{g,a})}{(1 - p_a)}. \tag{3}$$

In equation (3), it was considered that  $R_{abxy}^g$  is an element of the next-generation matrix that consists of three components: (1) the relative susceptibility against rubella in age group  $a$  and sex  $x$  denoted by  $s_{ax}$  as described elsewhere (Kayano et al., 2019), (2) the adjusted contact matrix ( $m_{abxy}^g$ ) in geographic region  $g$  as mentioned above, and (3) the immune fraction in geographic region  $g$ . The original  $R_{abxy}^g$  described in Kayano et al. (2019) was estimated for the entire of Japan, and we accounted for the geographically differing seropositive fractions. That is, we first considered a hypothetical case for the entire of Japan in which everyone was susceptible by dividing previously estimated  $R_{abxy}^g$  by  $(1 - p_a)$ , where  $p_a$  is the seropositive proportion in age group  $a$  for the entire of Japan. Subsequently, we multiplied it to give  $(1 - p_{g,a})$ , where  $p_{g,a}$  is the seropositive proportion in age group  $a$  in geographic region. Finally, the effective reproduction number in the subgroup of area  $g$  denoted by  $R_g^g$  is derived as the largest eigenvalue of the next-generation matrix  $\{R_{abxy}^g\}$ .

### Probability of a major epidemic

Considering the stochastic branching process with a geometrically distributed offspring distribution, the



**Figure 2.** Geographically heterogeneous seroprevalence data for rubella and population size by age and sex in Japan, 2016. The bar chart (measured on the left vertical axis) represents the population size in 2016. The black and gray bars represent males and females, respectively. The line graph (measured on the right vertical axis) indicates the seropositive proportion by age and sex. Regional seroprevalence of rubella in Japan was calculated using seroepidemiological data collected by NESVPD (National Institute of Infectious Diseases, 2017a, 2017b). HI titer  $\geq 32$  was used as a cut-off value to define seropositive individuals. The black filled circle and white filled circle represent the proportions of seropositive males and females, respectively. The solid error bar and dashed error bar represent the 95% confidence interval (CI) of males and females, respectively. The 95% CI was calculated from the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile values from binomial distribution.

probability generating function for the number of secondary cases,  $N$  is

$$G_N(s) = \frac{1}{1 + R(1 - s)},$$

where  $R$  is the reproduction number and  $s$  is the dummy variable (Brauer et al., 2008). If  $R > 1$ , the risk of a major epidemic,  $1 - \pi$ , is calculated by  $\pi = \frac{1}{1 + R(1 - \pi)}$  with exact solution  $\pi = \frac{1}{R}$ . Using this relationship, and assuming that each imported case causes an epidemic independently, the probability of major epidemic  $p_g$  in geographic region  $g$  was given by

$$p_g = 1 - \left(\frac{1}{R_g^e}\right)^{I_g}, \tag{4}$$

where  $I_g$  is the number of “untraced” imported rubella cases in geographic region  $g$  (Dibble et al., 2016). Because of the absence of data on the number of untraced imported cases,  $I_g$  was hypothetically set in two different ways. First, we assumed and examined a small number of untraced cases as being 1 or 5 cases. Second, accounting for the actual number of foreign travelers in geographic region,  $I_g$  was modeled as

$$I_g = \frac{\delta T_g}{w}, \tag{5}$$

where  $T_g$  is the total number of travelers from abovementioned countries to geographic region  $g$  in Japan, which was calculated as  $T_g = \rho_g C$ , where  $\rho_g$  is the fraction of visitors in geographic region  $g$  to all respondents to the questionnaire survey conducted by Japan Tourism Agency, and  $C$  is the annual cumulative number of foreign travelers in Japan. Let  $\delta_g$  represent the fraction of rubella cases of the total volume of travelers in region  $g$  defined as  $\frac{c_g}{T_g}$ , where  $c_g$  represents rubella cases in region  $g$ , then  $\delta$  is the median value of  $\delta_g$  among all geographic regions  $g$ . The factor  $1/w$  represents the untraced fraction of imported cases. In the instance of equation (5), the median value across different regions divided by  $w = 5$  was arbitrarily chosen to potentially approximate the untraced number

of imported cases ( $w = 5$  is arbitrary and is only used for the exposition of the abovementioned method).

The 95% confidence interval (CI) of the effective reproduction number was computed, employing a parametric bootstrap method. For the computation, we sampled each set of parameters from a multivariate normal distribution with the variance-covariance matrix that was quantified during the maximum likelihood estimation. Because the relative susceptibility, as estimated in Kayano et al. (2019), involves uncertainty, a total of 1000 sets of parametric bootstrap samples were generated from the distribution, and then the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile values of the resampled distribution were calculated as the 95% CI. For the entire process of abovementioned coding, statistical package R (ver 4.0.2) was used and the code is available as the online supplementary text. The original seroepidemiological datasets are accessible from NESVPD website (<https://www.niid.go.jp/niid/ja/yosoku-index.html>).

*Ethical considerations*

The datasets used are publicly available and were retrieved from the results of previously conducted surveys (Japan Tourism Agency, 2017; Japan National Tourism Organization, 2017; National Institute of Infectious Diseases, 2017a, 2017b; Statistics Bureau, 2017). The datasets did not contain any information associated with individual identity. Therefore, ethical approval was not required for the present study.

**Results**

Figure 2 shows the age-specific seropositive proportions for rubella by geographic region, along with demographic age distribution by sex. The seroepidemiological status and population pyramid greatly varied by geographic region. A drop in the seropositive proportion among males aged 30–59 was frequently identified, which is consistent with the past vaccination policy (Kinoshita and Nishiura, 2016). However, because of the scarcity of

**Table 1**  
Estimated risk profiles for rubella by geographic region in Japan.

Geographic region	$R_g^e$ (95% CI <sup>a</sup> )	Probability of major epidemic ( $p_g^{(1)}$ )		Untraced cases ( $I_g$ ) per year	Number of foreign travelers per year ( $T_g$ )	Probability of major epidemic ( $p_g^{(2)}$ )
		$I_g = 1$ case	$I_g = 5$ cases			
1	2.30 (2.20, 2.41)	0.56	0.98			
2	1.12(1.07, 1.20)	0.11	0.43	1	353,550	0.11
3	1.91 (1.83, 2.00)	0.47	0.96	10	11,486,915	1.00
4	1.54 (1.48, 1.60)	0.35	0.88	2	2,049,140	0.57
5	2.48 (2.37, 2.60)	0.60	0.99	3	2,992,866	0.93
6	1.13(1.07, 1.19)	0.12	0.46	9	10,782,840	0.67
7	1.80 (1.73, 1.87)	0.44	0.95	1	302,339	0.44
8	1.01 (0.96, 1.06)	0.01	0.05	1	230,545	0.01
9	2.23 (1.81, 2.65)	0.55	0.98	2	1,456,191	0.80
10	1.95 (1.88, 2.03)	0.48	0.96	1	898,217	0.48

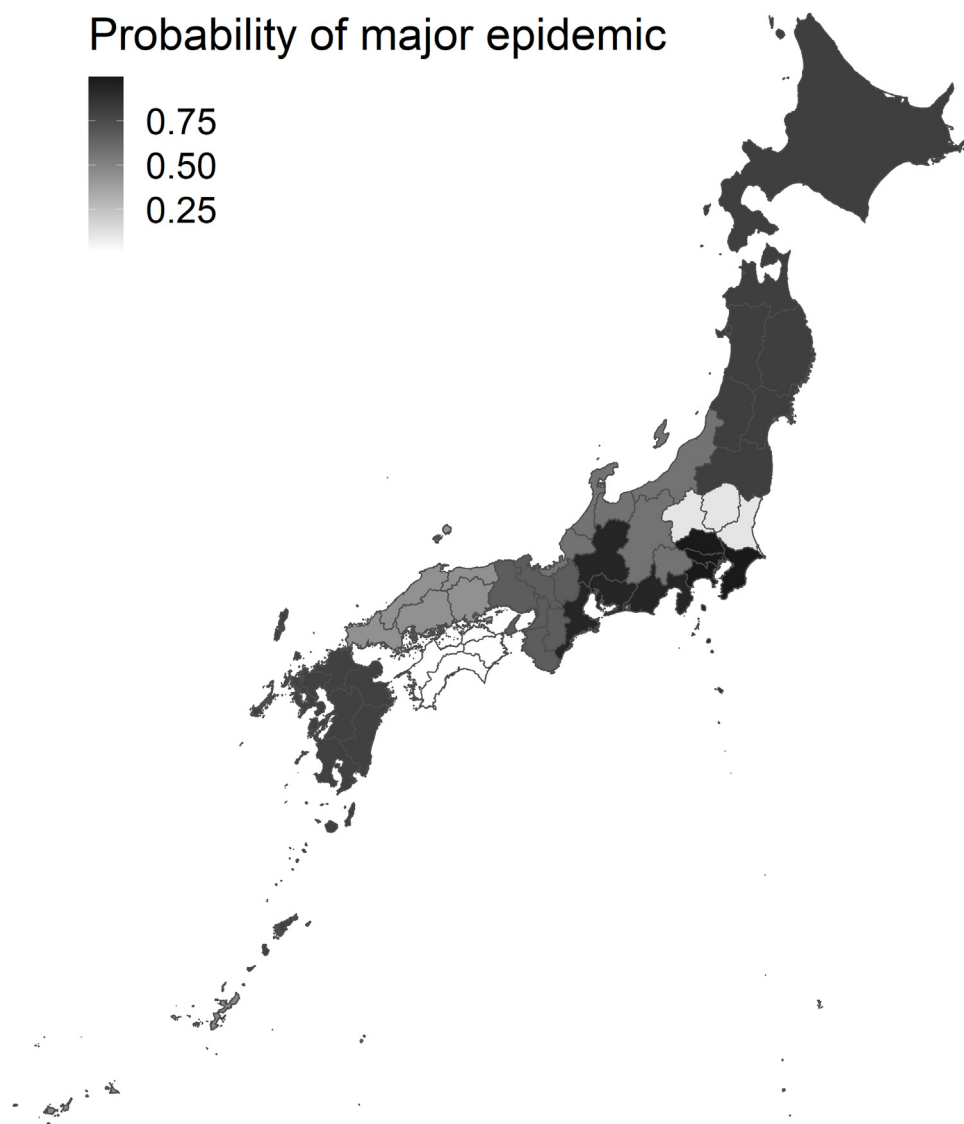
$R_g^e$  is the effective reproduction number in geographic region  $g$  and CI<sup>a</sup> stands for the confidence interval.  $p_g^{(1)}$  is the probability of major epidemic defined as  $p_g^{(1)} = 1 - \left(\frac{1}{R_g^e}\right)^{I_g}$ , assuming that  $I_g$  is sufficiently small (i.e.,  $I_g = 1, 5$ ).  $p_g^{(2)}$  is the probability of major epidemic defined as  $p_g^{(2)} = 1 - \left(\frac{1}{R_g^e}\right)^{I_g}$  given untraced cases ( $I_g$ ) calculated accounting for different numbers of foreign travelers by geographic region  $g$ .  $T_g$  is the total number of foreign travelers in geographic region  $g$ .

serological samples denoted by age and sex, sampling error was unavoidable (e.g., there were only three and eight samples from males and females, respectively, collected among people aged 50–54 years in geographic region 3). Region 3 contains Tokyo and has the largest population size, followed by region 6 containing Osaka and region 5 containing Aichi. The qualitative shapes of the population pyramids among adult males were similar among regions, while a slightly greater proportion of elderly people were observed in areas other than the abovementioned regions (e.g., regions 1 and 7).

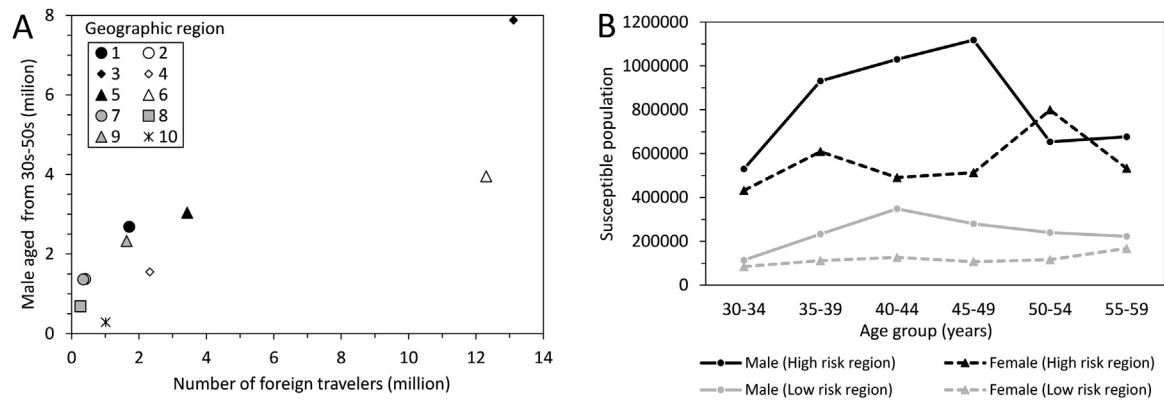
The effective reproduction number and corresponding probability of a major epidemic given a certain number of untraced cases were computed by geographic region and shown in Table 1. The reproduction numbers were higher in regions 1, 5, and 9, estimated to be 2.30, 2.48, and 2.23, respectively, compared with other areas, while the lowest effective reproduction number was expected in region 8 and estimated at 1.01 (95% CI: 0.96, 1.06). Furthermore, given the hypothetically assumed one and five untraced imported cases, the highest probabilities of a major epidemic were estimated to be 0.60 and 0.99, respectively, in geographic region 5. The occurrence of a major epidemic was considered to be unlikely,

because there were only up to five untraced cases in region 8, where the probability was estimated to be 0.05. The abovementioned estimates are conditional arguments given an assumed number of untraced cases and in reality, it is essential to compute the unconditional risk of a major epidemic while accounting for the likely number of untraced importations per geographic region. To do so, the risk of the importation of rubella cases among foreign visitors in 2016 was calculated, and the risk per traveler was not highly variable by geographic region. However, it must be noted that the total number of travelers was greater in regions with megacities: regions 1, 3, 5, 6, and 9 (Table 1). Incorporating these estimates, the risk of a major epidemic was calculated, and as a result, regions 3 and 5 showed the highest and second-highest risks of a major rubella epidemic. Figure 3 graphically shows the geographical distribution of the unconditional probability of a major epidemic. Geographic regions 1, 3, 5, 6, and 9 yielded higher probabilities than others, while the less populated, aged regions, such as regions 2 and 8, had smaller risks.

Figure 4 illustrates the contribution of people aged from 30 to 59 to a rubella epidemic. Figure 4A shows that the geographic regions with large populations of males aged from 30 to 59 were



**Figure 3.** Probability of major epidemic given untraced rubella cases by geographic region. The gradient illustrates the different probabilities of a major rubella epidemic in 10 geographic regions in Japan. The assumed number of untraced cases was computed as proportional to the number of foreign travelers in each geographic region.



**Figure 4.** Relationships between travel volume and susceptible population aged from 30 to 59 in Japan. (A) Scatter plot of population size of 30–59-year-old males in Japan against the number of foreign travelers by geographic region. (B) Susceptible population of 30–59-year-olds was calculated by sex in high- and low-risk regions. Geographic regions with relatively higher probabilities of a major outbreak were identified as regions 1, 3, 5, 6, and 9, and geographic regions with relatively low probabilities of major outbreaks were identified as regions 2 and 8. Seroepidemiological samples were aggregated for high- and low-risk groups, and HI titer  $\geq 32$  was used as a cut-off to determine the positive antibody titer. The proportions of the population seronegative according to age and sex were used to calculate the susceptible population in high- and low-risk geographic regions by sex.

more likely to have a greater number of foreign visitors than other regions, and a significant positive correlation was identified between the two variables (Spearman's  $\rho = 0.89$ ,  $p < 0.01$ ). In Figure 4B, the susceptible population sizes of people aged 30–59 were compared between two groups of geographic regions, one containing the five regions with highest conditional risks of a major epidemic (i.e., regions 1, 3, 5, 6, and 9) and the other the remaining regions. The high-risk regions included higher numbers of the susceptible population in their 30 s, 40 s, and 50 s, especially males. Although the correlation is inevitable due to our modeling method with demography, our exercise mechanistically shows that urban cities with substantial number of males aged 30 s, 40 s and 50 s were at a higher risk of a major epidemic, which would probably involve those age cohorts most affected by the epidemics in 2012–2014 and 2018–2019.

## Discussion

The present study investigated the risk of a rubella epidemic by geographic region in Japan. On the basis of the spatial datasets of age-specific seroepidemiological surveys and the number of foreign travelers, the effective reproduction number was computed with data from 10 different geographic regions (Figure 1), using the nationwide estimate of the age- and sex-dependent next-generation matrix parameterized and quantified in a previous study (Kayano et al., 2019). The populations of susceptible adult males were concentrated in urban regions (Figure 4B), and those regions also had a greater number of foreign travelers (Figure 4A), which contributes to a synergized effect resulting in a greater risk of exposure to untraced cases of rubella. Subsequently, the probability of a major epidemic was calculated. The estimated risk of a major epidemic was high in areas with capital cities (Sapporo/Sendai, Tokyo, Nagoya, Osaka, and Fukuoka), while areas with a higher proportion of elderly people yielded smaller effective reproduction numbers, as well as lower numbers of foreign travelers; thus, they had a lower probability of a major epidemic. To our knowledge, the present study is the first to have comprehensively used geographically dependent seroepidemiological survey data and traveler volumes to conduct risk assessments of rubella epidemics.

It is important to note that the present study has shown that the probability of major epidemics by geographic region can be computed by referring to three major pieces of information: (i) the population pyramid, (ii) susceptibility measured by

seroepidemiological investigation, and (iii) volume of foreign travelers. Factors (i) and (ii) contribute to the geographic variation in susceptibility and therefore, the effective reproduction number; while factor (iii) is the key to computing the unconditional probability of a major epidemic. We have shown that, for each of these three points, urban areas with a substantial volume of susceptible adults and travelers were at the greatest risk of a rubella epidemic than the less populated or aged regions. For instance, our study revealed that region 5, which contains Aichi, had the highest effective reproduction number at 2.48, and region 8 (Shikoku island, which is considerably aged compared with the five urbanized regions) yielded the lowest value at 1.01. Similar seroepidemiological evaluations have also been conducted elsewhere (Pebody et al., 2000; Kafatos et al., 2015; Abrams et al., 2016). Additionally, accounting for the number of travelers, the highest probability of a major epidemic in our hypothetical scenario was estimated to be 1.00 in region 3, which includes Tokyo, and the lowest probability was estimated to be 0.01 in region 8. Remarkably, the calculated risks are consistent with the actual predomination of rubella cases seen in urban prefectures in both the 2013–2015 and 2018–2019 epidemics, when the majority of cases were concentrated in the abovementioned capital cities (Kinoshita & Nishiura, 2016; Saito et al., 2018).

We have explicitly shown that the effective reproduction number does not coincide with the unconditional probability of a major epidemic. Although the effective reproduction number is inversely related to the conditional probability of an epidemic after the introduction of one case (Beraud et al., 2018), our finding was obtained due to variable number of introductions by geographic area. In our case study, region 5 had the highest effective reproduction number, but region 3 had the highest probability of a major epidemic. The effective reproduction number was used to mirror the geographical heterogeneity of susceptibility, while the unconditional probability of a major epidemic additionally accounted for the geographic dependence on the number of rubella introductions from other countries. Furthermore, we have empirically shown that susceptible adult males aged from 30 to 59 are predominantly found in urban areas, and this greater concentration coincides with a higher volume of foreign travelers. These mechanisms may explain the pattern of rubella outbreaks in urban areas.

Without elevated herd immunity and as a result of the increasing number of foreign visitors (Japan Tourism Agency, 2017; Japan National Tourism Organization, 2017), Japan will

experience an increased risk of infectious disease outbreaks (Kanbayashi et al., 2018; Komabayashi et al., 2018). Therefore, it is vital to develop risk assessment systems at greater geographic resolutions. To improve risk assessment practices, it is critical to emphasize that capturing geographic heterogeneity is highly dependent on the sampling technique of the seroepidemiological surveillance scheme, which is regarded as essential for assessing herd immunity worldwide (Metcalf et al., 2016). Because the serological conditions for rubella and demographic population dynamics differ greatly by geographic region, heterogeneous susceptibility and heterogeneous epidemic risk monitoring should be explored for various settings (Béraud et al., 2018; Metcalf et al., 2010; Wesolowski et al., 2016; Winter et al., 2018).

This study had four limitations. First, our risk assessment required the information of  $1/w$ , that is, the fraction of untraced cases out of the total of imported cases, which is not directly observable. A statistical estimation of  $1/w$  from multiple importation events may be required to attain an objective quantitative risk assessment. For similar reasons, the present study simplified the issue to account for importations from eight selected Asian countries, which cover only 50% of all foreign travelers (Japan Tourism Agency, 2017). Thus, it should be noted that our estimates are conservative. Second, we employed the 10 conventional geographic regions of Japan, but having finer detailed seroepidemiological surveillance data would have better addressed sampling errors and allowed for the more precise identification of geographic areas at risk of a major epidemic. Third, we adjusted the age-dependent population size to compute the region-specific next-generation matrix, but the validity of calculating the proportional redistribution of contacts using equation (2) is subject to debate. The formal kinetics of varying the contact matrix with population change should be explored in greater detail, and instead of elucidating the complex mechanisms, the present study simply incorporated the impact of variable demographic age distribution on the risk of an epidemic. Fourth, our evaluation did not include the expected number of CRS cases (Metcalf et al., 2010; Wesolowski et al., 2016). We hypothesized that urban cities with greater numbers of women of childbearing age would have a greater risk of CRS and thus a higher disease burden than remote areas.

While the method has the potential for refinement, we believe that the present study successfully generated a geographical risk map for rubella epidemics in Japan. The probability of a major epidemic was estimated to be higher in urban regions because of the high concentrations of susceptible young adult males and substantial numbers of foreign travelers. Our study indicated that, should a future rubella epidemic occur, it will be seen in areas with large cities, such as Sapporo/Sendai, Tokyo, Nagoya, Osaka, and Fukuoka.

### Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgments

H.N. received funding from the Health and Labour Sciences Research Grant (19HA1003,20CA2024, and 20HA2007); Japan Agency for Medical Research and Development (AMED; 19fk0108104 and JP20fk0108140); the Japan Society for the Promotion of Science (JSPS) KAKENHI [grant numbers, H.N.: 17H04701; H.L.: 19K19343; R.K.: 18J21587]; the Inamori Foundation; and the Japan Science and Technology Agency (JST) CREST

program [grant number: JPMJCR1413]. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Suzanne Leech, Ph.D., from Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing a draft of this manuscript.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.09.1458>.

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