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Assessing the transmission dynamics of measles in Japan, 2016

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ABSTRACT

Objectives: Despite the verification of measles elimination, Japan experienced multiple generations of measles transmission following importation events in 2016. The purpose of the present study was to analyze the transmission dynamics of measles in Japan, 2016, estimating the transmission potential in the partially vaccinated population.
Methods: All diagnosed measles cases were notified to the government, and the present study analyzed two pieces of datasets independently, i.e., the transmission tree of the largest outbreak in Osaka (n = 49) and the final size distribution of all importation events (n = 23 events). Branching process model was employed to estimate the effective reproduction number R_v, and the analysis of transmission tree in Osaka enabled us to account for the timing of introducing contact tracing and case isolation.
Results: Employing a negative binomial distribution for the offspring distribution, the model with time-dependent decline in R_v due to interventions appeared to best fit to the transmission tree data with R_v of 9.20 (95% CI (confidence interval): 2.08, 150.68) and the dispersion parameter 0.32 (95% CI: 0.07, 1.17) before interventions were introduced. The relative transmissibility in the presence of interventions from week 34 was estimated at 0.005. Analyzing the final size distribution, models for subcritical and supercritical processes fitted equally well to the observed data, and the estimated reproduction number from both models did not exclude the possibility that $R_v > 1$.
Conclusions: Our results likely reflect the highly contagious nature of measles, indicating that Japan is at risk of observing multiple generations of measles transmission given imported cases. Considering that importation events may continue in the future, supplementary vaccination of adults needs to be considered.

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1. Introduction

Measles is a highly contagious viral disease caused by the measles virus that belongs to the genus Morbillivirus within the family *Paramyxoviridae*. Once infected, pyrexia starts with three C's (i.e. cough, coryza and conjunctivitis) after an incubation period of 10–12 days (Klinkenberg and Nishiura, 2011). The prodromal period is then followed by the period with specific rash across the body, involving Koplik's spots (tiny white spots) inside the mouth. The virus is known to be transmitted not only by droplet and direct contact but also conveyed via aerosol, and for that reason, the basic reproduction number, R_0, interpreted as the average number of secondary cases generated by a single primary case in an unvaccinated fully susceptible population, has been reported to range from 10 to 20 (Wallinga et al., 2001; Edmunds et al., 2000; Grenfell and Anderson, 1985; Wallinga et al., 2005). Due to the highly contagious nature, the transmission event can happen even in an open space or semi-open environment (e.g. during concert or in a gymnasium) as long as specific acquired immunity is not possessed by exposed individuals.

Japan is a country that has been verified of having eliminated measles. Routine immunization against measles has started since 1978, and revaccination has been conducted for those who were born 1990 and thereafter (Okabe, 2007). A high primary vaccination coverage of over 90% has been achieved in the most recent decade. Because of intensified immunization effort, the incidence has dramatically declined in Japan, e.g. from 11,013 cases in 2008–35 in 2015. A genotype D5 that continuously circulated in the country in the past has not been isolated since the last isolation in May 2010 (Takahashi et al., 2014). Meeting elimination criteria including (i) the incidence below 1.0 per 1 million inhabitants, (ii) maintenance of high vaccination coverage (among newborns over 95%),

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(iii) maintaining virus surveillance and no continued circulation of specific genotype, the elimination was declared in 2015, although the validity and reliability of such criteria have been repeatedly debated among experts (e.g. (Kelly et al., 2009)).

Despite the successful achievement, multiple importation events have occurred in 2016, involving multiple generations of local transmission. Such minor outbreaks offer an opportunity to explicitly assess the transmission dynamics (Gay et al., 2004; Blumberg et al., 2015; Blumberg et al., 2014), enabling researchers to evaluate the past immunization policies and discuss the future control strategies. The purpose of the present study was to analyze the epidemiological dynamics of measles outbreaks in Japan, 2016, estimating the transmission potential in the partially vaccinated population.

2. Methods

2.1. Epidemiological data

All diagnosed measles cases were notified to the government following the Infectious Disease Law in Japan. Notified cases are either clinically or laboratory diagnosed. Clinically diagnosed case satisfies all of triads, i.e., (i) rash, (ii) fever and (iii) cough, coryza and conjunctivitis, and laboratory diagnosed cases represent clinical cases whose virus was identified by laboratory method including polymerase chain reaction (PCR) method or elevated IgM antibody based on paired serum. Modified measles, satisfying at least one of clinical triads plus laboratory diagnosis, are also included as part of measles cases that are notified to the government. Week of diagnosis, gender, age group, prefecture of notification, the estimated place of infection (e.g. domestic or imported), genotype (if any detected) and history of immunization were recorded.

In the present study, we analyzed two pieces of data independently. One was the line list of the largest outbreak in Osaka, which was continuously updated during the outbreak (National Institute of Infectious Diseases, 2016). The outbreak caused by genotype H1 ended in September 2016 and detailed epidemiological descriptions are provided elsewhere (Watanabe et al., 2017). During the outbreak, contact tracing outcome has been reported from the prefecture of Osaka (Osaka Prefecture, 2016) and the transmission tree showing who acquired infection from whom has been available. Another dataset is the final size distribution of measles outbreaks in 2016 including the one in Osaka. Based on the abovementioned surveillance, all importation events of measles resulted in notifications and a total of 23 outbreaks were traced. The outbreak in Osaka involved extensive contact tracing and case isolation which started upon diagnosis of first generation in week 34, 2016, and thus, the timing of interventions was known for the transmission tree data. On the other hand, the final size data were not accompanied by the information of any time-dependent event.

2.2. Mathematical model

To assess the transmission dynamics, we employ a branching process model as was done elsewhere (Gay et al., 2004; Blumberg et al., 2014; Farrington et al., 2003). Since we have two different types of datasets, we estimated the transmission parameters of the branching process models in two different ways.

First, since the transmission tree showing who acquired infection from whom is obtained from the outbreak in Osaka, we estimate the effective reproduction number, R_v, by fitting the model with negative binomially distributed offspring distribution directly to the observed counts of secondary transmission data:

$$f(x;R_v,k)=\frac{\Gamma(x+k)}{\Gamma(x+1)\Gamma(k)}\left(\frac{R_v}{k}\right)^x\left(1+\frac{R_v}{k}\right)^{-(x+k)}. \quad (1)$$

where k is the dispersion parameter, indicating that overdisparsed if $k<1$ and Poisson distributed if $k\to\infty$. Eliminating k by equating it to 1 leads to geometrically distributed offspring distribution. A part of the Osaka outbreak was recognized on 14th August 2016 and additional local transmissions were reported from 27th August 2016, leading to implementing intensified contact tracing and case isolation (i.e., movement restriction of diagnosed individuals). Traced contacts of cases were requested to report their health status to a local health center every day during the quarantine period. The case isolation was conducted in a negative pressure isolation room of designated hospitals and strict precautionary measures for airborne disease were conducted at the hospital. Due to such interventions, it is likely that the transmissibility dropped from around week 34 of 2016, and we assumed in a part of our models a step function to describe this possible time-dependent change:

$$R_v(w)=\begin{cases}R_v \text{ if } w<34\\ \alpha R_v \text{ if } w\geq 34\end{cases}. \quad (2)$$

where w represents the week of illness onset in 2016. In addition to varying R_v as a function of week, we also examined the similar step function for the dispersion parameter k. In summary, we examined five different models, (i) negative binomial (NB) model without any time-dependence, (ii) NB model with time-dependent R_v, (iii) NB model with time-dependent R_v and k, (iv) geometric model without any time-dependence and (v) geometric model with time-dependent R_v. Akaike Information Criterion (AIC) was compared among these models. In the Osaka outbreak, the relationship between vaccination history and secondary transmission event was also explored among notified cases, employing nonparametric Wilcoxon test followed by the post-hoc Steel-Dwass method.

Second, we analyzed the final size data of all observed importation events of measles. Final size data are not accompanied by time-dependent (dynamic) information and we fitted the final size distribution derived from a static branching process model. Since the dataset alone does not inform us the criticality (i.e. if $R_v>1$ or ≤ 1), statistical estimation was performed for each assumption. Assuming that $R_v>1$, we use the final size equation of minor outbreaks for supercritical process as was reported by Nishiura et al. (2012). Let p_y be the probability that the outbreak size is y. We have

$$p_y=\begin{cases}\dfrac{1}{\pi}\left(1+\dfrac{R_v}{k}\right)^{-k} \text{ if } y=1\\ \dfrac{\prod_{j=0}^{y-2}\left(\frac{j}{k}+y\right)}{\pi y!}\left(\dfrac{k}{R_v+k}\right)^{ky}\left(\dfrac{R_v k}{R_v+k}\right)^{y-1} \text{ if } y\geq 2\end{cases}. \quad (3)$$

It should be noted that the distribution is divided by the probability of extinction π, because major epidemic is expected to occur with the probability 1-π. In the case of supercritical process, k was assumed as a known constant, because that assumption allows us to replace π by a simple function of R_v (Nishiura et al., 2012) and the distribution (3) can then be handled as a closed-form likelihood function. Instead of adopting a specific single value for k, we examined the sensitivity of R_v to various values of k, i.e., 1/3, 1/2, 1, 2 and 3 with which π in (3) is eliminated. In the case of $R_v<1$, we do not

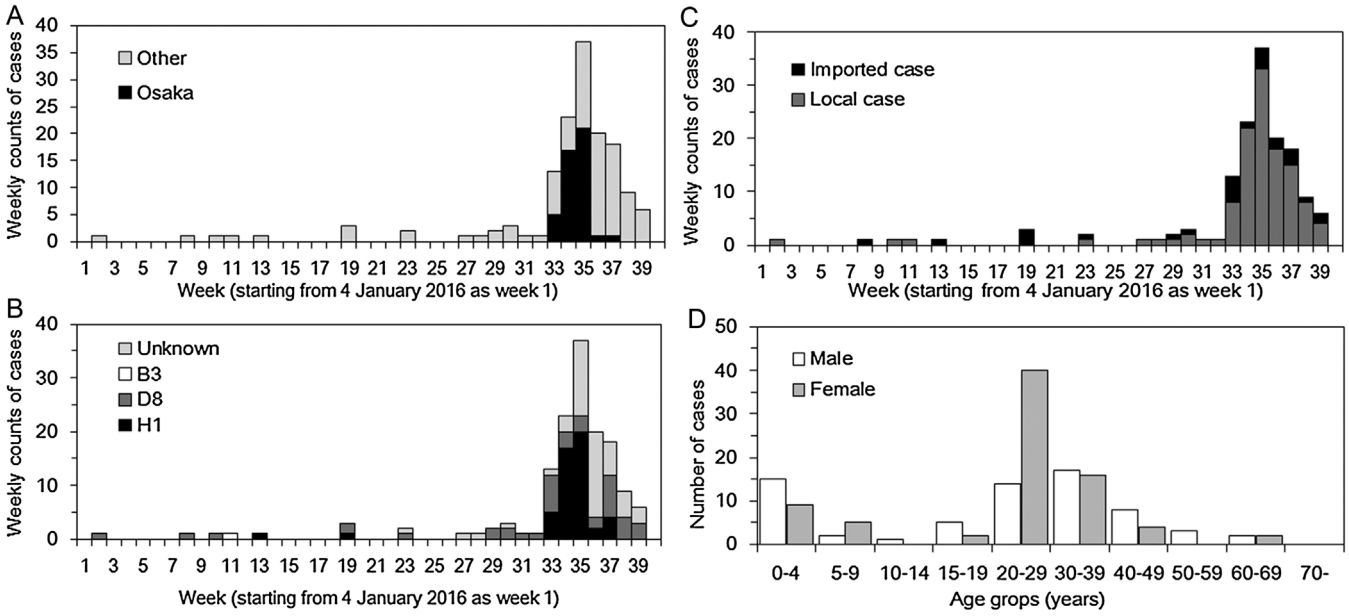


Fig. 1. Epidemiological dynamics of the measles outbreaks, Japan, 2016.
Temporal distribution by isolated-area (A), virus genotype (B) and travel history(C) as well as the age distribution by age groups and gender (D) are shown. A: Reported weekly counts of measles cases, Japan, 2016, stratified by two isolated-regions: Osaka prefecture and other areas. The curve of weekly counts is based on the week of diagnosis. Weekly counts start from 4th January 2016. B: Reported weekly counts of measles cases, Japan, 2016, stratified by virus genotype. C: Imported cases with travel history are separately shown from local cases who were considered to have acquired infection within Japan through the contact with imported or local cases. D: Measles cases categorized by age groups and by gender. White and grey bars correspond to male and female, respectively.

have to normalize the final size distribution by the probability of extinction, π, i.e.,

$$p_y = \begin{cases} \left(1+\frac{R_v}{k}\right)^{-k} & \text{if } y=1 \\ \frac{\prod_{j=0}^{y-2}\left(\frac{j}{k}+y\right)}{y!}\left(\frac{k}{R_v+k}\right)^{ky}\left(\frac{R_v k}{R_v+k}\right)^{y-1} & \text{if } y\geq 2 \end{cases} . \quad (4)$$

In this model (4), R_v and k were jointly estimated (Nishiura et al., 2015). In addition to the joint estimation, we also fixed k using the same values as mentioned above and estimated R_v, so that supercritical and subcritical process models can be analogously compared. Again, AIC was used for model comparison.

For the model optimization and parameter estimation, a maximum likelihood method was employed, using (1), (3) and (4) to be rewritten as the likelihood. The 95% confidence intervals (CI) were computed using the profile likelihood.

3. Results

Fig. 1 shows the temporal dynamics and age-distribution of measles outbreak in Japan, 2016. Evident surge of cases have been seen from around week 30, followed by a sharp increase of cases in Osaka (Fig. 1A) and a genotype H1 has been isolated from that outbreak (Watanabe et al., 2017). There was also a smaller concurrent outbreaks caused by genotype D8 during summer season, 2016 (Fig. 1B). Before the epidemic, notified cases represented imported cases (Fig. 1C). For both male and female, the age distribution exhibits a bimodal pattern, i.e., one peak in pre-vaccination group aged from 0 to 4 years, and the other peak in those aged 20s and 30s.

The transmission tree of the largest outbreak in Osaka, 2016, caused by H1 genotype, is shown in Fig. 2. The index case of this outbreak has unfortunately not been identified, but it is known from contact tracing that the four secondary cases share an exposure history at Kansai International Airport on 31st July 2016 (Watanabe et al., 2017). Two remarkable transmission events occurred from two among the four secondary cases. After exposure in Osaka, one attended a concert in Chiba and a mass gathering event, causing three tertiary cases, and also additional four tertiary cases were caused in the household. The other was a worker at the Airport, diagnosed on 17th August 2016. From 27th August 2016, tertiary

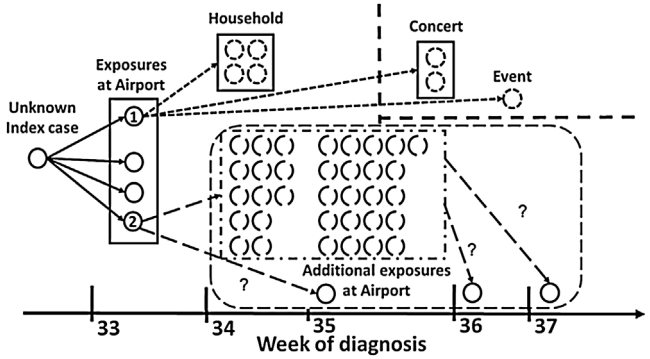


Fig. 2. The transmission tree of the measles outbreak in Osaka, Japan, 2016.
The transmission tree showing who acquired infection from whom was reconstructed by close contact tracing and virus surveillance. The four individuals within the left solid square in week 33 were the first identified measles cases in this outbreak and all of them used Kansai International Airport on 31st July 2016 (Watanabe et al., 2017). The top circle, numbered 1, was the individual who came back from Indonesia and the bottom one, numbered 2, was the airport staff at Kansai International Airport. Four cases in Hyogo, in the top solid square in week 34, were the secondary cases infected by the case 1. The 4 individuals were his/her family members and this is household transmission event. The case 1 visited a concert in Chiba on 14th August and an event in Tokyo on 26th August. Three secondary cases outside Hyogo were also confirmed. Only the contact dates of these three cases are known and they were listed independently on the top right corner. Thirty-four cases were reported in Kansai International Airport area (32 staffs and 2 health care workers) in the week 34 and 35, which are described by the long-dash circles in the dash-dot square. The pathways of infection of the bottom 3 solid circles in week 35, 36 and 37 are possibly connected to the outbreak in Kansai International Airport.

Table 1
Transmission parameters of measles estimated from the transmission tree during an outbreak in Osaka, Japan, 2016.

Offspring distribution	Time dependence in R_v*	Time dependence in k*	R_v (95% CI)	Dispersion parameter (95% CI)	AIC (n*)
Negative binomial	No	No	0.98 (0.23, 13.19)	0.03 (0.01, 0.08)	65.6 (2)
Negative binomial	Yes	No	9.20 (2.08, 150.68)	0.32 (0.07, 1.17)	52.3 (3†)
Negative binomial	Yes	Yes	9.20 (1.94, NC)	0.30 (0.06, 1.13)	53.2 (4‡)
Geometric	No	NA	0.98 (0.66, 1.46)	NA	136.5 (1)
Geometric	Yes	NA	9.20 (4.03, 26.53)	NA	54.0 (2‡)

NC: not calculable. NA: not applicable.
* R_v: Effective reproduction number, k: Dispersion parameter of negative binomial distribution, n: the number of estimated parameters. CI: confidence interval.
† Relative transmissibility in the presence of interventions: 0.005 (95% CI: NC, 0.038). ‡Relative transmissibility in the presence of interventions: 0.005 (95% CI: NC, 0.034). Dispersion parameter during intervention: 91.8 (95% CI: not calculable).
‡ Relative transmissibility in the presence of interventions: 0.005 (95% CI: 0.001, 0.022).

cases started to be diagnosed among airport workers, and extensive contact tracing and case isolation were carried out. Although there are no additional exposed and traced cases other than those shown in Fig. 2, a total of 49 cases (including unidentified index case) have experienced infection.

Employing the branching process model, the reproduction number R_v and dispersion parameter were estimated (Table 1). Models that incorporated time-dependent changes, especially in R_v, were favored than others without time-dependence, and negative binomially distributed offspring distribution with time-dependent R_v yielded the smallest AIC value. Negative binomial distribution was always preferred to geometric distribution, and using the time-dependent R_v resulted in better fit for both offspring distributions. Employing the best fit model, R_v before interventions was estimated at 9.20 (95% CI: 2.08, 150.68) and the dispersion parameter was estimated at 0.32 (95% CI: 0.07, 1.17). The relative transmissibility in the presence of interventions was estimated to be 0.005 (95% CI: NC, 0.038) where NC represents not calculable. Using the best fit model, observed and predicted offspring distributions are compared in Fig. 3A.

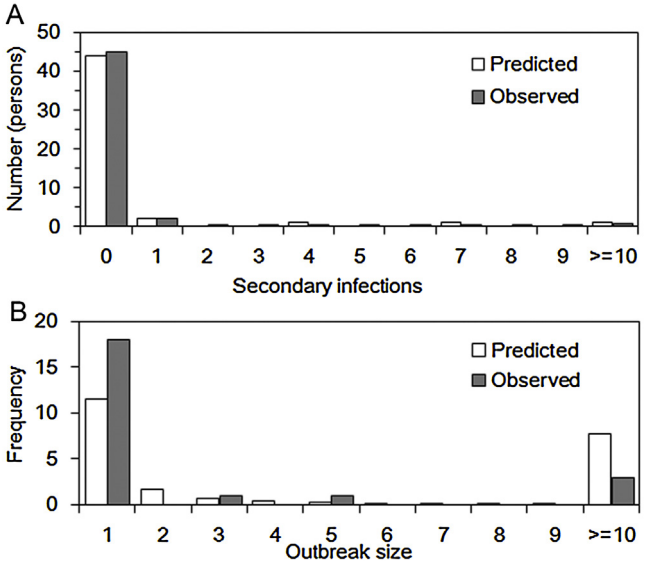


Fig. 3. Distributions of offspring and final size for measles, 2016 in Japan.
A: Distribution of the number of secondary cases produced by each primary case in Osaka, 2016 (n = 49 cases). White and grey bars correspond to predicted and observed counts, respectively. See online supporting materials for the raw data. B: Distribution of the outbreak sizes arose from each imported case (n = 23 outbreaks). White and grey bars correspond to predicted and observed counts, respectively. There were 18 importation events without secondary case, 1 outbreak with a total of 3 cases and 1 outbreak with a total of 5 cases. Final size of outbreaks with 10 or more cases was 13, 18 and 49 cases.

Fig. 4 shows the distribution of secondary cases in Osaka outbreak by vaccination history. Unfortunately, the vaccination history of as many as 14 cases were unknown, and among the remaining 30 cases, 6 were unvaccinated. One way Wilcoxon/Kruskal-Wallis test revealed a significant difference in secondary transmissions among groups ($p = 0.03$), and post-hoc test indicated that the secondary cases arising from unvaccinated individuals (mean = 1.3) are significantly greater than those vaccinated (mean = 0.0, $p = 0.01$).

Table 2 summarizes the estimated transmission parameters from an analysis of final size data of measles. Models for supercritical and subcritical processes were equally fitted well to the observed data. Within the assumed range, a dispersion parameter of $k = 1/3$ yielded the smallest AIC value regardless the criticality, although it might be possible that even smaller dispersion parameter may yield better fit. For both models, the 95% confidence intervals were wide, containing the value of 1, not enabling us to judge the criticality from the final size data alone. Fig. 3B compares the observed and predicted final size distributions of measles using the best fit model (which would be identical between supercritical and subcritical processes). Although the fit with static model has some limit, the qualitative pattern of final size distribution was crudely captured.

4. Discussion

The present study analyzed the transmission dynamics of measles in Japan, investigating the transmission tree data in Osaka

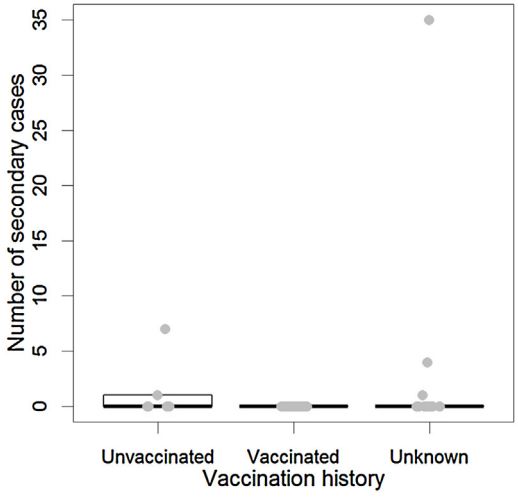


Fig. 4. Number of secondary transmissions by vaccination history.
The box-whisker plots of the reported number of secondary cases stratified by vaccination history, i.e., unvaccinated, vaccinated and unknown. The gray points are the numbers of secondary cases in each cases.

Table 2
Transmission parameters of measles estimated from the final size distribution in Japan, 2016.

Offspring distribution	Criticality	Assumed value of k^*	R_v (95% CI)	AIC (n^*)
Negative binomial	$R_v > 1$	1/3	1.29 (0.85, 2.02)	68.7 (1)
Negative binomial	$R_v > 1$	1/2	1.29 (0.90, 1.87)	70.0 (1)
Geometric	$R_v > 1$	1	1.28 (0.96, 1.71)	72.4 (1)
Negative binomial	$R_v > 1$	2	1.27 (1.00, 1.61)	74.5 (1)
Negative binomial	$R_v > 1$	3	1.26 (NC)	75.5 (1)
Negative binomial	$R_v \leq 1$	NA	0.78 (0.40, 1.81)	69.1 (2[†])
Negative binomial	$R_v \leq 1$	1/3	0.78 (0.53, 1.17)	68.7 (1)
Negative binomial	$R_v \leq 1$	1/2	0.78 (0.56, 1.11)	70.0 (1)
Geometric	$R_v \leq 1$	1	0.78 (0.59, 1.04)	72.4 (1)
Negative binomial	$R_v \leq 1$	2	0.78 (0.60, 1.00)	74.5 (1)
Negative binomial	$R_v \leq 1$	3	0.78 (0.61, 0.99)	75.5 (1)

NC: not calculable. NA: not applicable.
[*] R_v: Effective reproduction number, k: Dispersion parameter of negative binomial distribution, n: the number of estimated parameters. CI: confidence interval.
[†] k was estimated as 0.11 (95% CI: 0.02, 0.65).

as well as the final size distribution across Japan. Analyzing the transmission tree data, the model with $R_v = 9.2$ before interventions along with time-dependent decline in the reproduction number by 99.5% appeared to fit well to the data. Synchronized with the timing of contact tracing effort, the reproduction number was shown to have quickly and abruptly declined. Final size distribution indicated that supercritical and subcritical processes explain the observed distribution equally well. The estimated reproduction numbers from both models contained the value of 1.0 within 95% confidence intervals and did not exclude the possibility that $R_v > 1$. These results indicate that (i) regardless of criticality, Japan is at risk of observing multiple generations of transmission in the absence of extensive contact tracing and case isolation and (ii) control effort in Osaka, 2016 should be commended due to its high effectiveness. Notified cases were mainly seen in pre-vaccination age children and adults aged from 20 to 39 years.

Our findings of $R_v = 9.2$ before interventions in Osaka and failure to rule out the possibility of $R_v > 1$ from final size data likely reflect the highly contagious nature of this disease (Metcalf et al., 2011). In fact, the vaccination coverage in Japan have remained to be below 95% except for newborns during the most recent decade, and the coverage would be inadequate to eliminate local transmission by means of mass vaccination only. With such insufficient coverage, the highly contagious virus could find a cluster of susceptible individuals easily (Mollema et al., 2014). Whereas elimination of measles has been declared in Japan, our study underscores the fact that the country remains susceptible to importations and local chains of transmission can continue for multiple generations. Our initial R_v in Osaka could have been slightly an overestimate if susceptible individuals were clustered (because that could a lead to rapid increase in the number of cases as compared with what is expected from homogeneous model), and the initial transmissibility estimate that we obtained from the largest observed outbreak is of course estimated to be large due to the nature of data generating process. Thus, our findings do not clearly indicate that $R_v > 1$ and exclude the possibility that outbreaks including the one in Osaka were caused by $R_v < 1$. Rather, our findings at least call for a concrete plan to strategically cut the chains of transmission given an importation. Considering that the possibility of $R_v > 1$ is not excluded, it is valuable to strengthen herd immunity by means of supplementary vaccination and revaccinations. It should also be recognized that exposure to imported cases may continue to force contact tracing and case isolation to be frequently implemented, considering that the frequency of importation events is unlikely to wane rapidly in near future.

Our estimate of the relative reproduction number in the presence of contact tracing was very high (e.g. 99.5% reduction). It is not extraordinary high for three reasons. First, the contact tracing of this small outbreak in Osaka involved strict quarantine of healthy exposed individuals, and moreover, the case isolation was conducted at hospital facilities with negative pressure rooms (for precaution of airborne transmission). These countermeasures were extremely intensive. Second, clinical signs and symptoms of measles are relatively apparent among many viral infectious diseases, and that feature must have helped identify cases and bring them under isolation in a short period of time. Third, not only accounting for the effectiveness of case isolation but the estimated reduction likely reflects local depletion of susceptible individuals in the partially vaccinated population. That is, the abrupt decline in R_v may not only reflect the success in interventions but also intrinsic factors. In any case, our finding has captured the pattern of outbreak in which the disease may be highly contagious in the beginning but may be brought under control in a matter of several weeks.

Age distribution has possibly mirrored an insightful immunity distribution of Japanese population against measles. To prevent infection among pre-vaccination infants and children, it is advised to implement the primary vaccination at the earliest possible opportunity. Many adult cases aged from 20 to 39 years imply the effects of waning immunity. Those aged 26 years or older in the present day received only primary vaccination, and as indicated in other studies (Davidkin et al., 2008; Chen et al., 2012), a part of vaccine-induced immunity among them may have already waned over the past time. To assess the herd immunity level more explicitly, our ongoing future study is to reconstruct the age-dependent immunity pattern of the population against measles and design future vaccination strategy.

Several limitations must be noted. First, our theoretical approach was limited to an assumption of homogeneous transmission allowing over-dispersion due to individual heterogeneity. An analysis of larger scale outbreak data may allow us to identify heterogeneity appropriately. Second, while we analyzed individual data, the present study was unable to clarify the immunity status of those who escaped infection. Clarifying the herd immunity and identifying susceptibles would be of utmost importance for the planning of future supplementary vaccination (Lessler et al., 2011; Wood et al., 2015). Third, the analysis of final size distribution ignored the time-dependence including control effort, while our analysis of Osaka data was suggestive of high effectiveness of contact tracing and case isolation. While such analysis has been implemented elsewhere for subcritical cases (Toth et al., 2016), we have seen that the alternative likelihood for supercritical process requires intensive mathematical exercises, and thus, we save the opportunity as future study. Fourth, we have not addressed the possibility that smaller outbreaks have potentially been underascertained. Since the contact of measles is immediately traced upon notification in Japan, it is unlikely that any diagnosed measles

is missed from the data, but it is possible that modified measles cases could have missed a chance of diagnosis at clinical settings. Ascertainment bias could have led to an overestimation of the reproduction number. Lastly, possible genotypic specificity in the transmission was also discarded due to data scarcity.

Despite these limitations, we believe that the present study successfully characterized the transmission dynamics of measles in Japan, demonstrating that the country is at risk of observing multiple generations of transmission given importation of cases. We plan to conduct additional modelling studies to help clarify the direction for future control strategy against this highly contagious disease.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

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Counts of secondary transmissions for each diagnosed case with week of illness onset in Osaka, 2016.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2017.03.005.

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