



Assessing the transmission dynamics of measles in Japan, 2016



Hiroshi Nishiura^{a,b,*}, Kenji Mizumoto^{a,b}, Yusuke Asai^{a,b}

^a Graduate School of Medicine, Hokkaido University, Kita 15 Jo Nishi 7 Chome, Kita-ku, Sapporo-shi, Hokkaido 060-8638, Japan

^b CREST, Japan Science and Technology Agency, Honcho 4-1-8, Kawaguchi, Saitama 332-0012, Japan

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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%),

* Corresponding author at: Graduate School of Medicine, Hokkaido University, Kita 15 Jo Nishi 7 Chome, Kita-ku, Sapporo-shi, Hokkaido 060-8638, Japan.

E-mail addresses: nishiurah@med.hokudai.ac.jp, nishiurah@med.hokudai.ac.jp (H. Nishiura).

(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 overdispersed if $k < 1$ and Poisson distributed if $k \rightarrow \infty$. 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 non-parametric 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

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

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 $1 - \pi$. 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

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