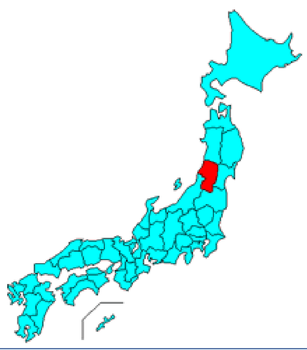

Reconstructing the epidemic dynamics of measles in Yamagata, Japan, 2017

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Background

Measles is a highly infectious disease caused by measles virus, genus Morbillivirus in the family *Paramyxoviridae*. While immunization has successfully reduced local transmissions, imported cases of measles leading to multiple generations of local transmissions have been frequently reported in Japan. In this study, we analyze a measles outbreak in Yamagata prefecture in Japan, 2017, that started with clustering in a driving school. The data provided by the prefecture gives us several links to primary cases while some data on WAIFW* were missing. Thus, we reconstructed the transmission tree for these in the analysis. The aim of this study is to clarify different aspects of information that can be extracted from analyzing epidemic curve only and the transmission network.

Method

Analyzing the same outbreak data, we employ two different methods for interpreting the epidemiological dynamics. Of the total of 60 cases involved in the outbreak, 19 were those with unobserved primary cases. Of the remaining 41 cases, 25 were in the first generation (infected by the index case), and 15 were in the second generation.

(1) Temporal Model (using the incidence data only)

From the abovementioned line list (containing the date of symptom onset, symptoms, and transmission links in 40 cases) as announced by Yamagata city, the epidemic curve, f(t), can be expressed by convolution:

$$f(t_i) = i_1(t_i) + i_2(t_i) + i_3(t_i)$$
$$i_1(t_i; k, \theta, R_0) = R_0 g(t_i)$$
$$i_2(t_i; k, \theta, R_0, R_1) = R_0 R_1 \sum_{j=1}^{i-1} g(t_i - t_j) g(t_j)$$
$$i_3(t_i; k, \theta, R_0, R_1, R_2) = R_0 R_1 R_2 \sum_{j=1}^{i-1} \sum_{h=1}^{j-1} g(t_i - t_j - t_h) g(t_j) g(t_h)$$

where g(t) is serial interval following a gamma distribution and R_0, R_1, and R_2 are the average number of first-, second-, and third-generation cases infected by a single case, respectively.

(2) Network-based Model (using the transmission network data along with place and date of illness onset)

Assuming that the geographic distance dependence is captured by exponential decay function with a decay rate parameter, λ, the likelihood function to estimate the serial interval distribution and λ was written as

$$\mathrm{L}\left(k, \theta, \lambda | t_i - t_{\mathrm{v}(i)}, x_{iv(i)}\right) = \prod_{j \neq i} \prod_{i \in W} \frac{g\left(t_i - t_{\mathrm{v}(i)} | k, \theta\right) \exp\left(-\lambda x_{iv(i)}\right)}{\sum g\left(t_i - t_j | k, \theta\right) \exp\left(-\lambda x_{ij}\right)}$$

We then estimated "the most probable infectors", by picking the person with the highest probability of infecting the person, to reconstruct the transmission tree.

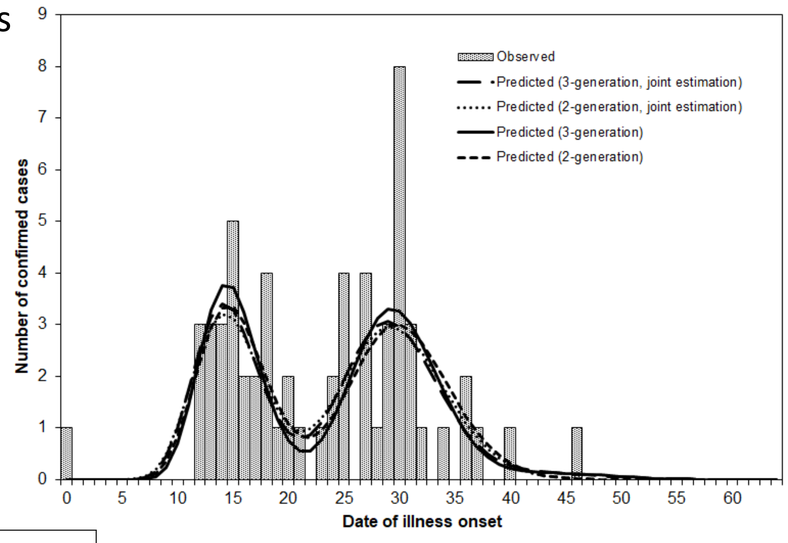
(3) Exploring risk factors of secondary transmission (only using the transmission network data)

Using the transmission tree reconstructed in (2), the symptom data on the line list, and viral shedding status of each case (provided elsewhere**), we performed Wilcoxon's rank sum test to find the risk factors of secondary transmissions.

*WAIFW=Who Acquired Infection From Whom
**Seto, J., et al. Epidemiol Infect, 2018;146(13):1707-1713.

Results (1)

Figure 1. Temporal distribution of measles cases in Yamagata, Japan, 2017. Bars represent observed confirmed cases as a function of the date of illness onset, while continuous lines represent predicted number of cases. A generation-dependent model was employed, and different results with assuming 2 and 3 generations, each with and without joint estimation of the parameters governing the serial interval distribution, are shown.



Model description	R_0	R_1	R_2	k	θ	Mean SI	AIC
3-generation model + joint SI estimation	25.31	1.28	0.04	24.06	0.61	14.76	611.33
2-generation model + joint estimation	25.48	1.32	N/A	21.46	0.70	14.93	611.72
3-generation model (no joint estimation)	25.69	1.24	0.04	29.82	0.50	14.91	403.28
2-generation model (no joint estimation)	25.99	1.27	N/A	23.54	0.65	15.19	404.37

Table 1. The parameter estimates in 3- and 2- generation models, each with and without joint estimation of parameters governing the serial interval distribution. The Akaike information criteria are lower in the 3-generation model than that in the 2-generation model regardless of joint estimations.

Results (2)

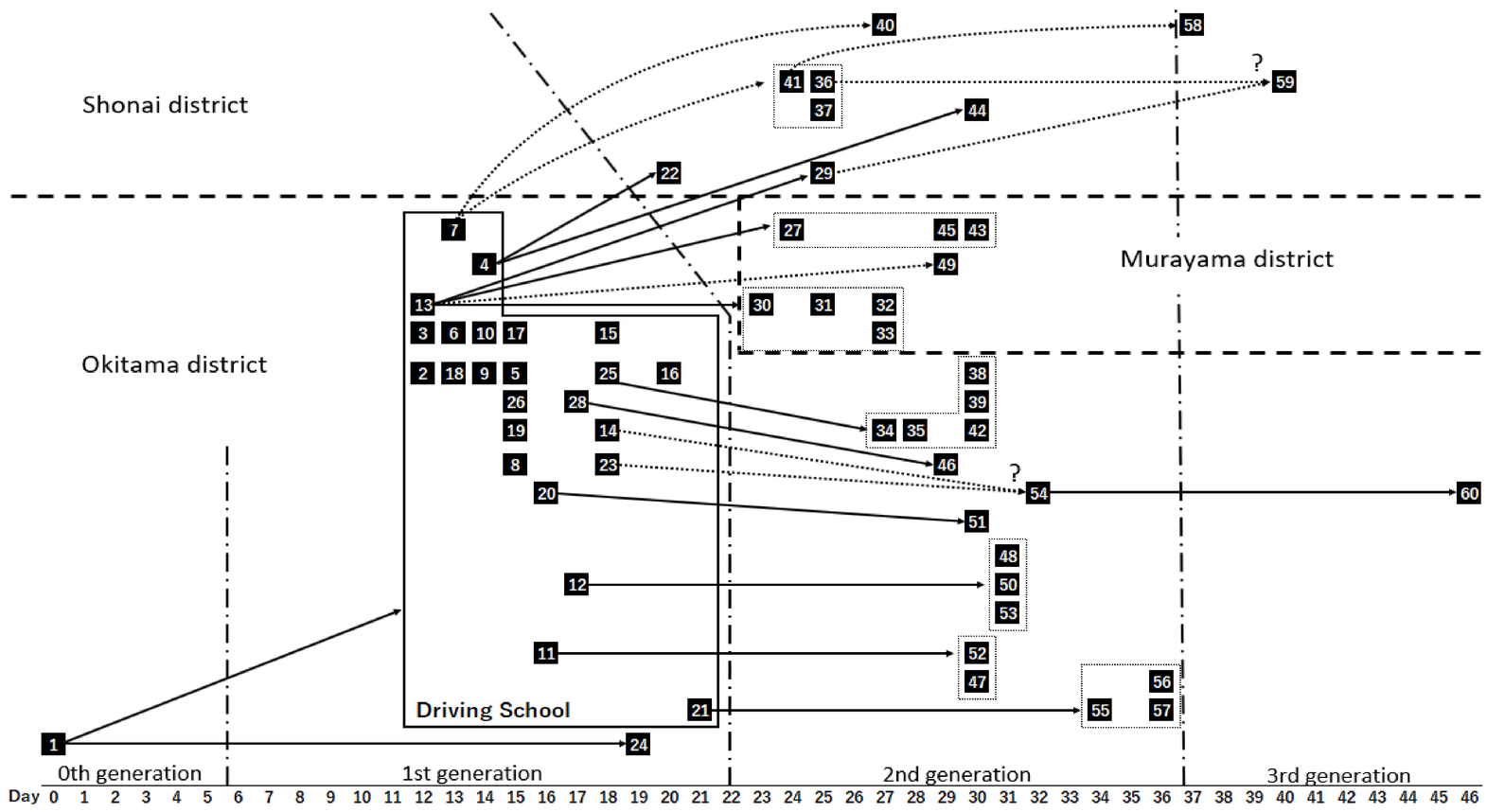


Figure 2. Reconstructed transmission tree of measles in Yamagata, Japan, 2017. Each black square represents an individual confirmed case of measles who is allocated an unique number from 1 (index) to 60 according to the order of notification. If a single primary case was not identified, two or more dotted arrows are drawn for all possible networks with a question mark. Dotted squares of variable sizes represent the grouping of a cluster of cases that were generated from an identical primary case.

Results (3)

# 2ary infections vs. symptom	Medians	P-value (Wilcoxon's test)
Rash	0 vs 0.5	<0.01*
Stomatitis	0 vs 0	0.56
Cough	0 vs 0	1.00
Runny nose	0 vs 0	0.90
Sore throat	0 vs 0	0.67
Conjunctivitis	0 vs 0	0.28
Headache	0 vs 0	1.00
Arthralgia	0 vs 0	0.39
High viral shed	0 vs 8.5	<0.01*
Typical measles	0 vs 0	0.05*

Table 2. Comparing the numbers of secondary infections per person between those with and without each symptom

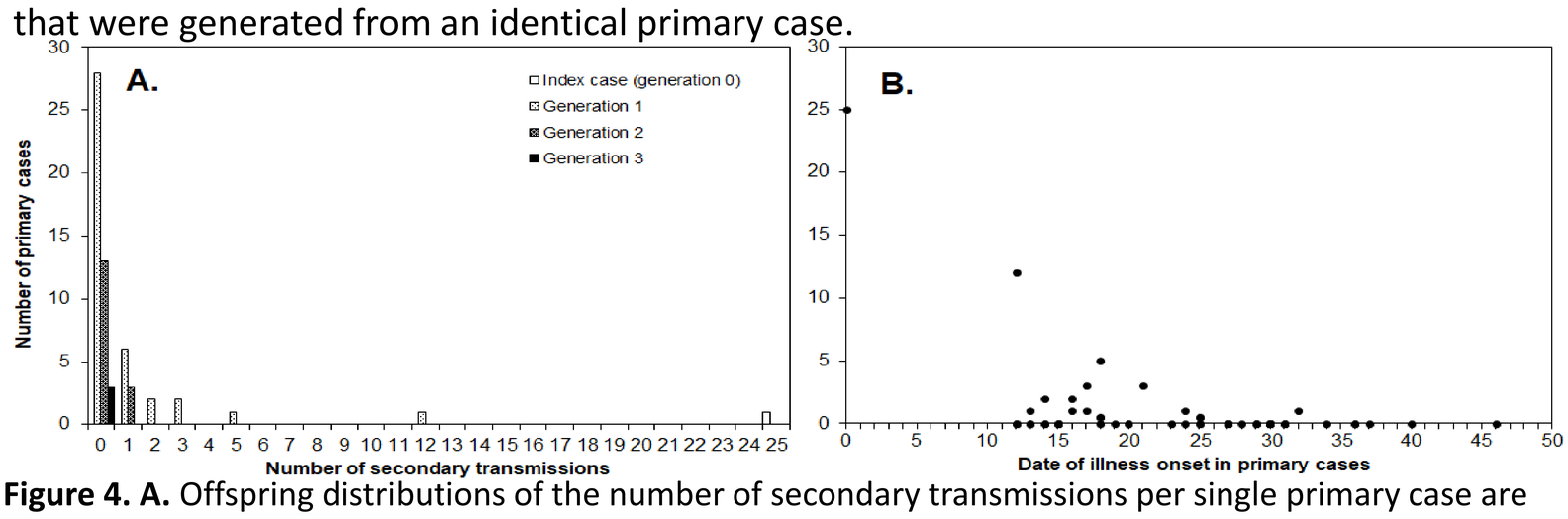


Figure 4. A. Offspring distributions of the number of secondary transmissions per single primary case are shown by generation.
B. Time-dependent variations in the number of secondary transmissions per single primary case. The number of secondary transmissions is shown as a function of the date of illness onset in each primary case.

Conclusion

This study successfully shows two distinct models of transmission dynamics of measles, namely generation-dependent and time-dependent models. The former model theoretically tells us that the outbreak is more likely to consist of 3 generations rather than 2 (i.e. epidemic curve fits better). While it only gives us the mean reproduction number (without variance), the latter model provides us a transmission network from which we can explore the heterogeneity of transmission at an individual level. Therefore, we can see both the mean and variance of secondary transmissions that change over time and generation. In addition, the model helps determine the risk factors for multiple secondary transmissions (i.e. case rash, typical measles, and high viral shedding on throat swab).