

Research Paper

Real-time Investigation of Measles Epidemics with Estimate of Vaccine Efficacy

Keisuke Ejima¹, Ryosuke Omori², Kazuyuki Aihara^{1,3}, Hiroshi Nishiura^{2,4} ✉

1. Department of Mathematical Informatics, Graduate School of Information Science and Technology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan;
2. School of Public Health, The University of Hong Kong, Level 6, Core F, Cyberport 3, Pokfulam, Hong Kong;
3. Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan;
4. PRESTO, Japan Science and Technology Agency, Saitama, Japan.

✉ Corresponding author: Hiroshi Nishiura, School of Public Health, The University of Hong Kong, Level 6, Core F, Cyberport 3, 100 Cyberport Road, Pokfulam, Hong Kong. Tel: +852 3906 2010, Fax: +852 3520 1945, Email: nishiura@hku.hk.

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Abstract

As part of measles elimination effort, evaluation of the vaccination program and real-time assessment of the epidemic dynamics constitute two important tasks to improve and strengthen the control. The present study aimed to develop an epidemiological modeling method which can be applied to estimating the vaccine efficacy at an individual level while conducting the timely investigation of the epidemic. The multivariate renewal process model was employed to describe the temporal evolution of infection by vaccination history, jointly estimating the time-dependent reproduction number and the vaccine efficacy. Analyzing the enhanced surveillance data of measles in Aichi prefecture, Japan from 2007-08, the vaccine efficacy was estimated at 96.7% (95% confidence interval: 95.8, 97.4). Using an age structured model, the vaccine efficacy among those aged from 5-19 years was shown to be smaller than that among those from 0-4 years. The age-dependent vaccine efficacy estimate informs the age-groups to be targeted for revaccination. Because the estimation method can rest on readily available epidemiological data, the proposed model has a potential to be integrated with routine surveillance.

Key words: vaccination, epidemiology, measles, mathematical model, vaccine efficacy.

Introduction

Although the World Health Organization (WHO) and its member states across the world have aimed to eliminate measles, the elimination has been so far fully successful only in the North American region. As the transmission potential of measles is extremely high with the estimated basic reproduction number of the order of 6-45 [1-4], i.e. the average number of secondary cases generated by a single primary case in a fully susceptible population being 6-45, it is necessary to maintain very high vaccination coverage to eliminate the infection by means of mass

vaccination. In industrialized countries, all children are subject to routine immunization mostly by the age of 18 months using either MR (measles and rubella) or MMR (measles, mumps and rubella) vaccine. Moreover, to boost the vaccine-induced immunity, children aged from 4-5 years receive the second dose, and depending on each individual country's policy, additional doses/revaccinations are scheduled.

Understanding the vaccine efficacy at an individual level is essential to assess the vaccination program. Although the vaccine efficacy against measles is

believed to be high (e.g. >95%) [5], in practice even vaccinated individuals may be susceptible if the vaccination failure occurred or if their vaccine-induced immunity waned [6]. If the evaluation can be made based on readily available epidemiological datasets in real-time, disease control policy making will be able to reflect the results of such analysis. For instance, if we can detect the signature of a potential major epidemic in near future [7] or if we can identify specific sub-populations that are less protected than others [8], the epidemiological modeling study could improve real-time policy making, e.g. identifying an essential part of the population to be (re-)vaccinated.

To estimate the vaccine efficacy, three distinct study approaches have been taken. First, laboratory measurement (e.g. seroconversion) has been used as a surrogate marker of successful immunization, allowing us to judge the vaccine-induced immunity in a biologically well-defined manner. However, such measurement requires laboratory test samples as well as testing capacity, and perhaps more importantly, makes it difficult to directly attribute the result to actual vaccine-induced protection (e.g. actual causal impact of vaccination against infection) at an individual level [9,10]. Other two approaches thus tackle the issue of assessment using epidemiological data. Since the epidemiological data of directly transmitted infectious diseases involve the technical problem of dependent risk of infection between individuals (i.e. the so-called "dependent happening"), the empirically observed datasets are greatly influenced by the indirect effect of vaccination [11]. Therefore, as the second method, the conditional risks of infection (i.e. conditional on an exposure to an infected individual) in vaccinated and unvaccinated individuals are compared to estimate the conditional direct effect of vaccination while reasonably eliminating the influence of indirect effect. For instance, household secondary attack proportion (SAP) is conventionally used to estimate the efficacy using the conditional risk of infection given a primary case in households. However, collection of household transmission data requires substantial observational effort and moreover, such study needs to ensure uniform susceptibility among household contacts. As the third method, the population data may be analyzed by employing a mathematical model that can be believed to have captured the underlying transmission dynamics. In particular, the final size of an epidemic (i.e. the fraction of the total infected individuals in a population throughout the course of an epidemic) has been used to estimate the efficacy in a highly vaccinated population [1,12,13]. However, there has been little attempt to estimate the vaccine efficacy jointly with the epidemic

dynamics in real-time (e.g. during the course of an epidemic).

The present study aims to propose an epidemiological method which we can employ to estimate the vaccine efficacy of measles while conducting real-time assessment of the epidemic based on readily available epidemiological surveillance datasets. While not requiring us to conduct field investigations to specifically assess the vaccine efficacy, we show that the assessment can be partly achieved by analyzing the counts of cases with vaccination history over time.

Materials and Methods

Epidemiological data

The present study investigates empirical data from Aichi prefecture, around the middle of Japan, which has a mild temperate climate and has long served as an intersection between the cultures of eastern and western Japan. In Japan, children aged from 12-24 months had received a single-dose MMR vaccination from 1988 to 1993. MMR vaccine was replaced by MR vaccine in 1993 due to the reporting of the substantial number of abacterial meningitis cases that were attributed to MMR vaccination, lowering the overall vaccination coverage for a while. In 2006, the country initiated the two-dose vaccination program in which first and second doses are given at the age of 12-24 months and before entering primary schools (i.e. before the age of 6 years), respectively. Despite nationwide vaccination campaigns, the vaccination coverage remained insufficient to prevent the epidemic of measles, and only in recent years, the vaccination coverage of the first dose clearly exceeded 95.0% which is believed as the minimum coverage to eliminate a disease given the basic reproduction number of 20. Due to the presence of the various pockets of susceptible individuals, sporadic minor outbreaks have been seen continuously across Japan. To monitor the outbreaks and strengthen the measles control, the Ministry of Health, Labour and Welfare of Japan has enhanced the measles surveillance which enforced compulsory reporting of all measles cases since 2008. Our study rests on the pilot data of the enhanced surveillance in Aichi prefecture in 2007 and 2008. Aichi prefecture was specifically selected as the subject in the present study, because the prefecture voluntarily launched the enhanced surveillance in collaboration with local medical doctors association and this was among the earliest in Japan.

During the surveillance, the confirmed measles cases were defined as follows: (condition i) the cases who reveal all three specific signs and symptoms (i.e. rash, fever and catarrh including coughing, nasal

discharge and congestion of conjunctiva) with (condition ii) laboratory diagnosis based either on (a) isolation of the virus, (b) isolation of the virus RNA, or (c) serological diagnosis (i.e. seroconversion of IgM antibody using paired sera). Isolation of confirmed cases and contact tracing of all known contacts have been made upon confirmatory diagnosis of each case.

The population size of Aichi prefecture in 2007 was approximately 7.3 million [14]. The enhanced surveillance data included the information regarding the date of illness onset (date of fever and date of rash), age and vaccination history. Hereafter, we consistently use only the date of fever to describe the temporal patterns. In 2007 and 2008, the totals of 212 and 198 confirmed measles cases were reported, respectively. Due to the enhanced surveillance, these numbers correspond to the actual total numbers of measles diagnoses in Aichi prefecture. Counting from 1st January in each year, the epidemic in these years revealed a single peak around Days 150 and 125, respectively. A part of the confirmed cases did not remember their own vaccination history in the past against measles. In 2007, there were 57 vaccinated and 87 unvaccinated cases that clearly remembered the vaccination history, while 68 cases did not remember vaccination history. In 2008, there were 50 vaccinated and 86 unvaccinated cases with 62 cases without known vaccination history.

Mathematical model I: Homogeneous population

To develop a real-time estimation framework, we first consider a model to describe the transmission dynamics of measles in a homogeneously mixing population. Let p and α be the vaccination coverage and vaccine efficacy, respectively. Usually, the vaccination coverage is known, and in the case of Aichi prefecture, the baseline coverage of the first dose has been estimated at 94.8% [15], while as sensitivity analysis we estimate the vaccine efficacy by varying the coverage from 90.0 to 99.5%. Let k and l represent the vaccination history of an exposed individual and the primary case, respectively, for which 1 stands for vaccinated and 0 otherwise. We consider the renewal process of measles in which the incidence (the number of new cases) of those with vaccination history k on calendar day t , $j_{k,t}$ is described as

$$j_{k,t} = \sum_l \sum_{\tau=1}^{\infty} A_{kl,t,\tau} j_{l,t-\tau}, \dots(1)$$

where $A_{kl,t,\tau}$ describes the rate of causing secondary transmissions per single primary case whose vaccine status is l among susceptible contacts of those with

vaccination history k on day t at infection-age τ (i.e. the time since infection in each primary case). Let U_t represent the vaccine-unrelated frequency of secondary transmissions per single primary case on day t , which is influenced by all factors other than vaccination including intrinsic and extrinsic ones. We assume that the vaccine efficacy reduces susceptibility of vaccinated individuals by $(1-\alpha)$ as was adopted in an earlier study [12] and assume that $A_{kl,t,\tau}$ is separable into the functions of t and τ as follows:

$$\begin{aligned} A_{0l,t,\tau} &= (1-p)U_t g_{\tau}, \\ A_{1l,t,\tau} &= p(1-\alpha)U_t g_{\tau}, \end{aligned} \dots(2)$$

where g_{τ} is the probability mass function of the generation time, i.e. the time from infection in a primary case to infection in the secondary case caused by the primary case, and $A_{kl,t,\tau}$ is thus assumed to be scaled by p , α and U_t . Based on a published statistical study [16], g_{τ} is assumed to be the discrete function that is derived from the continuous, lognormal distribution with the mean and the standard deviation of 12.0 and 3.5 days, respectively. The instantaneous reproduction number, i.e. the average number of secondary cases per single primary case at calendar time t , is calculated as

$$R_t = [(1-p) + p(1-\alpha)]U_t, \dots(3)$$

which is useful to objectively interpret the epidemic curve in real-time, because if the R_t exceeds 1, it clearly indicates increase in infections on day t . The renewal process in (1) is rewritten as

$$j_{0,t} = \frac{(1-p)R_t}{(1-p) + p(1-\alpha)} \sum_{\tau=0}^{\infty} g_{\tau} (j_{0,t-\tau} + j_{1,t-\tau}), \dots(4)$$

for unvaccinated cases, and

$$j_{1,t} = \frac{p(1-\alpha)R_t}{(1-p) + p(1-\alpha)} \sum_{\tau=0}^{\infty} g_{\tau} (j_{0,t-\tau} + j_{1,t-\tau}), \dots(5)$$

for vaccinated cases.

Due to enhanced surveillance, and because measles rarely involves secondary transmissions arising from asymptomatic or subclinical cases, the number of infected cases is assumed to have been fully captured as a function of calendar time. For mathematical convenience, we assume that the incubation period is a constant so that the epidemic curve can be theoretically shifted leftward for a constant period for the purpose of statistical analysis using the above mentioned model. In empirical observation, a part of cases did not remember vaccination history.

Assuming that the past vaccination history is independent of possessing a memory of vaccination history, the probability of knowing vaccination status, q , is assumed to be governed by a binomial sampling process of the cumulative number of cases with known vaccination history among the cumulative total of cases. Let $h_{0,t}$, $h_{1,t}$ and $h_{9,t}$ denote the observed numbers of unvaccinated cases, vaccinated cases and cases who did not remember vaccination status on day t , respectively. We assume that the observed incidence with vaccination history $h_{0,t}$ and $h_{1,t}$ are the

$$L(\mathbf{R}, q, \alpha; \mathbf{Z}) = \left(\frac{\sum_s (h_{0,s} + h_{1,s} + h_{9,s})}{\sum_s h_{9,s}} \right) (1-q)^{\sum_s h_{0,s}} q^{\sum_s (h_{0,s} + h_{1,s})} \times \prod_s \frac{(qE(j_{0,s}; Z_{s-1}))^{h_{0,s}} (qE(j_{1,s}; Z_{s-1}))^{h_{1,s}} \exp\{-q[E(j_{0,s}; Z_{s-1}) + E(j_{1,s}; Z_{s-1})]\}}{h_{0,s}! h_{1,s}!} \dots (6)$$

The maximum likelihood estimates of \mathbf{R} , q , and α are found by minimizing the negative logarithm of (6). The 95% confidence intervals are computed based on profile likelihood. Maximum likelihood estimation was conducted using the statistical package R (<http://www.r-project.org/>) and we used the *plkhci* function from the *Bhat* package.

Mathematical model 2: Heterogeneous population

Although the above-mentioned model is kept simple, the empirical data suggest that the frequency of cases greatly differs by age (Figure 1). Differential frequency of cases by age may be attributable to (i) the differential population structure, (ii) the different contact patterns, (iii) the differential protection conferred by vaccination and so on. Thus we extend the above-mentioned model to age-dependent data so that the epidemiological dynamics is better captured. We take an approximate approach and divide the population into three discrete age-groups. Since the second-dose vaccination is scheduled by the age of 6 years with the available social contact data categorizing the youngest group of children aged from 0-4 years, and because the adult infections may be separated from those in children to clarify the contribution of schools to the epidemic, the age groups are classified as 0-4 years, 5-19 years and 20 years and above, respectively. The relative population sizes of the age group i , n_i are 4.9%, 15.1% and 80.1% in 2007 and 4.8%, 14.8% and 80.4% in 2008, respectively. Let the age-specific incidence of vaccination status k and age group a as $j_{ka,t}$ on day t , the dynamics is described by the multivariate renewal process as follows:

results of Poisson sampling with expected values $qE(j_{0,t}; Z_{t-1})$ and $qE(j_{1,t}; Z_{t-1})$, respectively, where $E(j_{x,t}; Z_{t-1})$ denotes the conditional expected value of the incidence of cases with vaccination history x on day t given the history of observed data (i.e. $h_{0,t}$, $h_{1,t}$ and $h_{9,t}$) from time 0 up to $(t-1)$, denoted by Z_{t-1} . The likelihood function to estimate the reproduction number for each date, \mathbf{R} , and other parameters q and α is written as follows:

$$j_{0a,t} = (1 - p_a) U_t n_a \sum_b \beta_{ab} \sum_{\tau=0}^{\infty} g_{\tau} (j_{0b,t-\tau} + j_{1b,t-\tau}) \dots (7)$$

for unvaccinated cases, and

$$j_{1a,t} = p_a (1 - \alpha_a) U_t n_a \sum_b \beta_{ab} \sum_{\tau=0}^{\infty} g_{\tau} (j_{0b,t-\tau} + j_{1b,t-\tau}) \dots (8)$$

for vaccinated cases. Here $\{\beta_{ij}\}$ is the normalized contact matrix with the eigenvalue 1, describing the age-dependent contact frequency which we retrieve from the published result of social contact survey in the UK [17]. To address differential contact rates across different age-groups, we assume that the age-dependent frequency in Aichi with an adjustment of the age-dependent population size in Japan is the same as that observed in the UK (Table 1). U_t represents the average number of secondary transmissions per single primary case at calendar time t , which is influenced by all factors other than vaccination including intrinsic and extrinsic ones. The instantaneous reproduction number is calculated as the dominant eigenvalue of the 6×6 matrix derived from (7) and (8), the analytical solution of which is not very insightful in our example, and we focus on estimating U_t as a parameter for the heterogeneous model. The age-dependent vaccination coverage p_a is assumed as known, i.e. 97.0, 93.4 and 99.0% for those aged 0-4 years, 5-19 years, and 20 years and above, respectively. The average of those coverage estimates is greater than that for the base-line in the homogeneous setting, because the coverage for adults 99.0% is not realistically tractable due to past natural exposures and booster effect [18]. Namely, among adults we assume

that the above mentioned coverage denotes the fraction immune or seropositive based on serological survey [19].

Let $h_{0a,t}$, $h_{1a,t}$ and $h_{9a,t}$ be the observed incidence of unvaccinated cases, vaccinated cases and the cases did not remember their own vaccination history in age group a on day t . As discussed in the homogeneous

$$L(\mathbf{U}, q, \boldsymbol{\alpha}; \mathbf{Z}) = \left(\frac{\sum_a \sum_s (h_{0a,s} + h_{1a,s} + h_{9a,s})}{\sum_a \sum_s h_{9a,s}} \right) (1-q)^{\sum_a \sum_s h_{9a,s}} q^{\sum_a \sum_s (h_{0a,s} + h_{1a,s})} \times \prod_a \prod_s \frac{(q E(j_{0a,s}; Z_{s-1}))^{h_{0a,s}} (q E(j_{1a,s}; Z_{s-1}))^{h_{1a,s}} \exp\{-q[E(j_{0,s}; Z_{s-1}) + E(j_{1,s}; Z_{s-1})]\}}{h_{0a,s}! h_{1a,s}!}, \dots(9)$$

where \mathbf{Z} represents the history of epidemic data across all age-groups.

Table 1. The matrix describing the within and between age-group frequency of social contact.

Year 2007			
Age	0-4	5-19	20 and above
0-4	0.139	0.113	0.440
5-19	0.037	0.633	0.532
20 and above	0.027	0.100	0.829
Year 2008			
Age	0-4	5-19	20 and above
0-4	0.145	0.118	0.460
5-19	0.038	0.600	0.561
20 and above	0.027	0.103	0.828

The age-groups in the first column represent those of contactee (i.e. those who are exposed to cases), while the age-groups in second and seventh rows represent those of contactor (i.e. the primary cases). The contact is expressed by per unit time (i.e. per day in case of this table), although each element is adjusted due to normalization.

Results

Figure 1 shows the temporal and age-specific distributions of measles cases stratified by vaccination history. The epidemic curves in 2007 and 2008 recorded the highest incidence in weeks 22 and 18, respectively. Since there have been very few cases nearby new-year and year-end days in both years, and due to epidemic in discrete geographic locations, we analyzed each epidemic year separately from the other, while we focused on the data which combined both years when we estimate the vaccine efficacy

case, we assume that the vaccination status of the cases is independent of remembering their own vaccination history, and we also assume that the probability of having the memory, q is independent of age. To estimate \mathbf{U} , q and α_a , we maximize the following likelihood:

(because the vaccine efficacy is not expected to vary greatly by a single year due to limited antigenic diversity of measles and small changes in vaccination status in the population). The mean (and the standard error, SD) and median age of cases (and inter-quartile range) were 18.9 (13.9) and 17.0 (10.0-26.0) years in 2007, respectively. Similarly, the mean and median were 14.2 (12.5) and 13.0 (2.0-24.0) years in 2008, respectively. In both years, the cases were aggregated among children and very few elderly cases were observed. The cases in 2008 appeared to be significantly younger than that in 2007 ($p=0.0003$, t-test). The proportion of cases who remember as vaccinated was 26.9% (95% confidence interval (CI): 20.9, 32.9) and 25.3% (95% CI: 19.2, 31.3), respectively, in 2007 and 2008, which did not significantly differ by year ($p=0.76$, χ^2 test). The proportion of cases who remembered either as vaccinated or unvaccinated was 67.9% (95% CI: 61.6, 74.2) and 68.7% (95% CI: 62.2, 75.1) in 2007 and 2008, respectively, which was again not significantly different by year ($p=0.99$, χ^2 test).

Figures 2 and 3 show the estimated instantaneous reproduction numbers using the homogeneous model in 2007 and 2008, respectively, along with the visual comparisons between the observed and predicted epidemic curves with known vaccination history. The estimated reproduction numbers in early and late epidemic phases were very high, reflecting a mathematical property of the renewal process, i.e., in these time periods, the effective reproduction number tends to be very large due to small number of primary cases, and thus, we omitted the early estimates in Figures 2 and 3. While the majority of the maximum likelihood estimates of R_t fell below unity, the upper 95% confidence interval continuously exceeded 1, perhaps reflecting a small number of cases (i.e. sampling error) and high transmission potential of measles with limited vaccination coverage. Analyzing

both years with assumed common vaccination coverage, the maximum likelihood estimates of the vaccine efficacy, α , was estimated at 96.7% (95% CI: 95.8, 97.4). The proportion of cases with known vaccination history, q , was estimated at 68.3% (95% CI: 65.1, 71.4). Even when we estimated α separately by 2007 and 2008, they were not significantly different: α in 2007 and 2008 was 96.5% (95% CI: 95.2, 97.5) and 96.8% (95% CI: 95.5, 97.8), respectively.

When we employed the age-heterogeneous model, the vaccine efficacy was separately estimated for each age-group. The maximum likelihood estimates of the vaccine efficacy α_1 , α_2 and α_3 for those aged 0-4 years, 5-19 years, and 20 years and above were 97.9% (95% CI: 95.8, 99.0), 93.4% (95% CI: 89.0, 96.1) and 99.6% (95% CI: 99.2, 99.8), respectively. The proportion of cases with known vaccination history, q , was estimated to be 68.1% (95% CI: 65.2, 70.9). As the model captures the time-dependency, the goodness-of-fit and the estimates of the reproduction number did not greatly differ from those shown in Figures 2 and 3 (Results not shown).

Since we cannot directly estimate the exact vaccination coverage among those involved in the contact, the sensitivity analysis was conducted (Figure 4). Within the assumed range of vaccination coverage (90.0%-99.5%), the maximum likelihood estimate of the vaccine efficacy ranged 93.3%-99.7%. The estimated vaccine efficacy increased as the vaccination coverage increased. The reason for positive relationship in Figure 4 is intuitively understood from equations (4) and (5). That is, if we take the ratio of the incidence of unvaccinated to vaccinated, we get

$$\frac{j_{0,t}}{j_{1,t}} = \frac{1-p}{p} \frac{1}{1-\alpha} \quad \dots(10)$$

The left-hand side of equation (10) corresponds to the observed data which is a constant on a single day (given empirical data). If we increase the vaccination coverage p , then $(1-p)/p$ decreases and this necessitates $1/(1-\alpha)$ to increase in equation (10) or forces the vaccine efficacy α to increase.

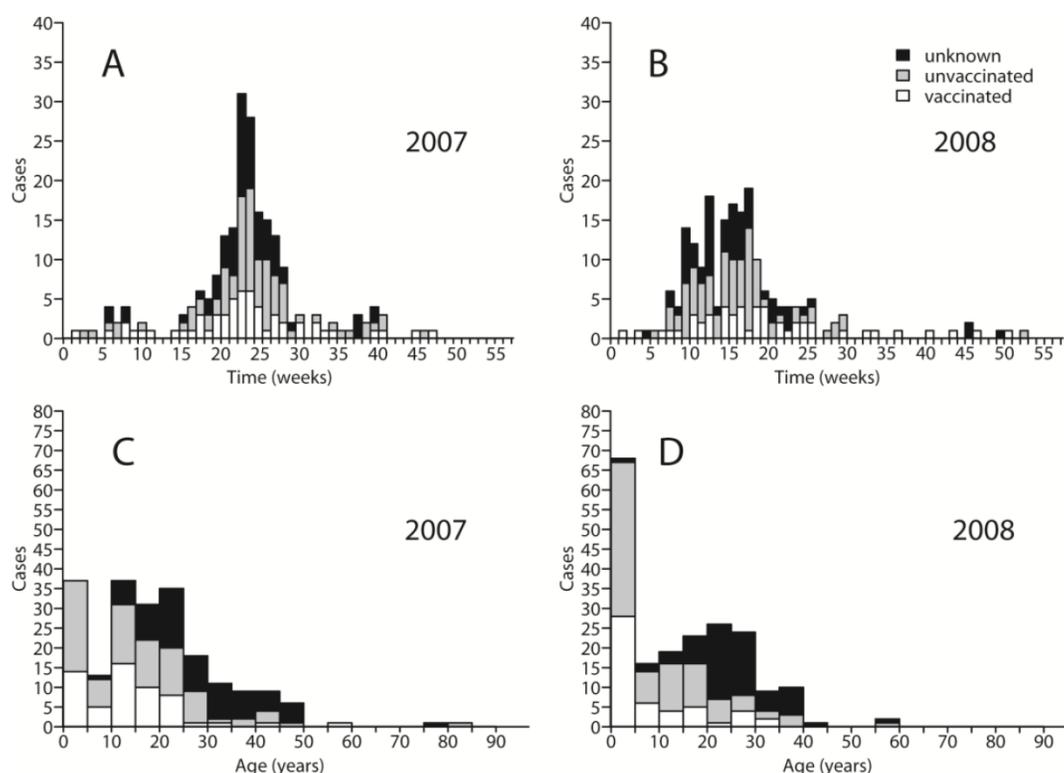


Figure 1. The time and age-specific distributions of the measles outbreak in Aichi prefecture, Japan, from 2007-08. A & B. The temporal distribution of measles cases. The week 1 corresponds to the week that includes 1st January. C & D. The age distribution of measles cases. In all panels, the vaccinated and unvaccinated correspond to the cases who clearly remembered as previously vaccinated and unvaccinated, respectively. Unknown represents the cases who did not remember vaccination history at the time of diagnosis of measles.

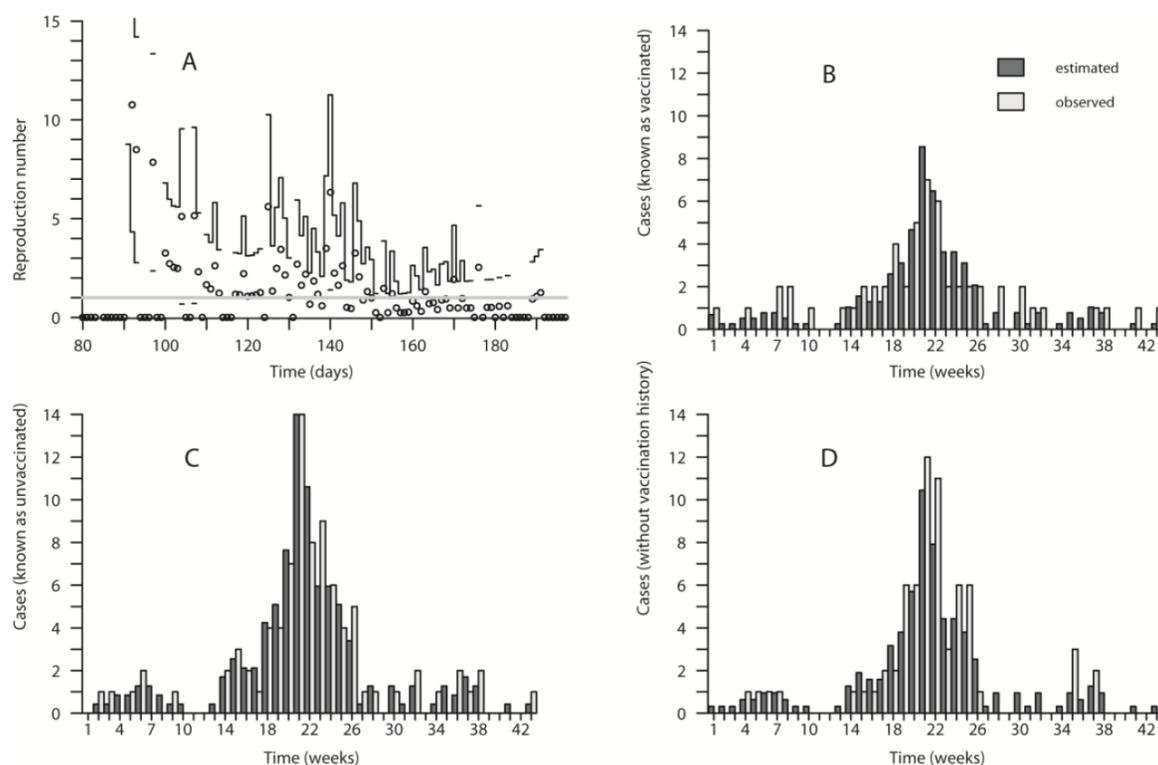


Figure 2. The estimated instantaneous reproduction numbers and visual comparisons between the observed and predicted temporal distributions by known vaccination history in 2007. A. The maximum likelihood estimates (circles) and the upper 95% confidence interval (steps) of the instantaneous reproduction number. The horizontal axis is expressed as the calendar date in which 1st January is set to be 0. The horizontal grey line shows the level at which $R_t = 1$. For mathematical reasons R_t is unrealistically high during the very early and late epidemic phases, and thus, the estimates are omitted from this panel. B, C and D. Comparisons between observed and predicted temporal distributions of cases. B and C compare cases who were known to be vaccinated and unvaccinated, respectively. D shows the cases who did not remember vaccination history at the time of diagnosis of measles. The week 1 corresponds the week that includes 1st January.

Discussion

The present study proposed a simple method to estimate the vaccine efficacy against measles, jointly quantifying the parameters governing the temporal evolution of measles. The method uses only the epidemiological surveillance data with partial information of vaccination history, which can rest on readily available datasets and is not as costly as conducting specialized field study such as that observing household transmissions. To capture the realistic aspect of measles transmission, the extended model accounted for age-dependent heterogeneity [20-22]. Although not significant, the vaccine efficacy among those aged 5-19 years was shown to be smaller than that in children aged below 5 years, which may perhaps reflect the waning immunity among school children [23]. Given Figure 4 and considering that the actual vaccination coverage can be lower than that in literature due to cessation of MMR vaccine in 1993, the assumed coverage of 93.4% may be suggestive of potential overestimation of vaccine efficacy (if the

actual vaccination coverage is lower), but not of underestimation. Therefore, the straightforward policy implication is that one may target school children aged 5-19 for (re-)vaccination to eliminate the pockets of susceptible individuals.

As the proposed method can rest on the readily available data (i.e. routinely collected surveillance data), we believe that the model has a potential to be integrated with the routine surveillance practice of measles across the world. In particular, the proposed method permits the presence of missing data for vaccination history with an assumption of missing completely at random (MCAR), which has not been explicitly dealt with in earlier modeling studies. While various mathematical approaches have been proposed to model the measles epidemic, the present study offered advancement in two different aspects. First, although many studies analyzed the transmission dynamics using mathematical models, the objectives of those studies have been different from the efficacy estimation, and they frequently focused on the estimation of time-dependent notification charac-

teristics [24] or clarification of the kinetics of measles transmission using mathematical model [25]. The present study has shown that the vaccine efficacy is very conveniently estimated, assuming that the depletion of susceptible individuals is negligible. Second, whereas a few other studies estimated the vaccine efficacy, including that based on final size [1,4] and an explicit modeling of epidemic dynamics [26],

the present study is the first to have jointly conducted the vaccine efficacy estimation and the real-time assessment of an epidemic, by estimating the effective reproduction number R_t along with the vaccine efficacy parameter. In other words, our proposed approach not only helps assess vaccine efficacy but permits us to interpret the temporal evolution in an objective manner.

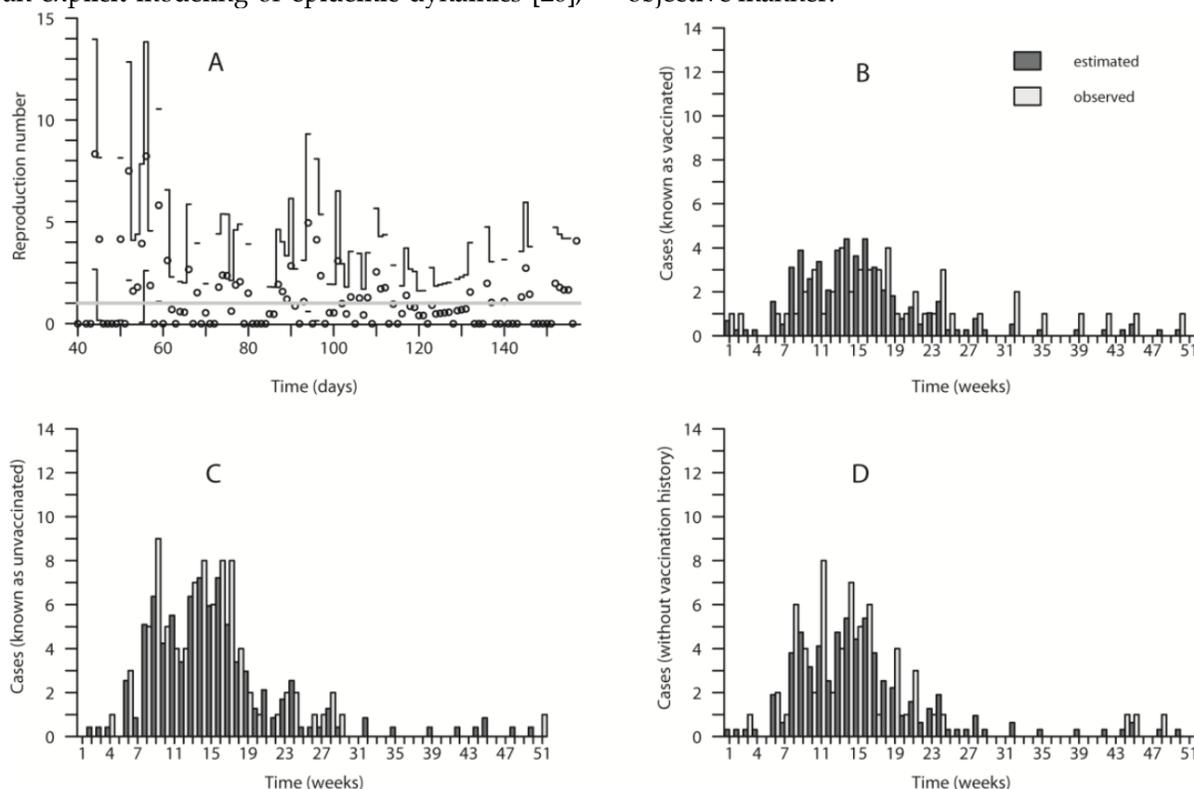
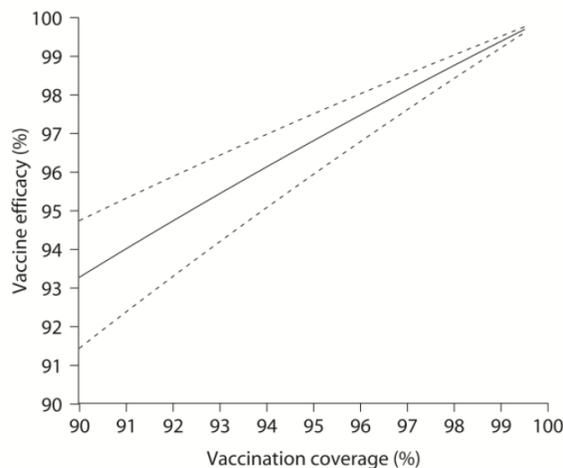


Figure 3. The estimated instantaneous reproduction numbers and visual comparisons between the observed and predicted temporal distributions by known vaccination in 2008. A. The maximum likelihood estimates (circles) and the upper 95% confidence interval (steps) of the instantaneous reproduction number. The horizontal axis is expressed as the calendar date in which 1st January is set to be 0. The horizontal grey line shows the level at which $R_t = 1$. For mathematical reasons R_t is unrealistically high during the very early and late epidemic phases, and thus, the estimates are omitted from this panel. B, C and D. Comparisons between observed and predicted temporal distributions of cases. B and C compare cases who were known to be vaccinated and unvaccinated, respectively. D shows the cases who did not remember vaccination history at the time of diagnosis of measles. The week 1 corresponds the week that includes 1st January.

Figure 4. Sensitivity of vaccine efficacy to the vaccination coverage. Solid line represents the maximum likelihood estimate, while dashed lines are the upper and lower 95% confidence intervals of vaccine efficacy. The 95% confidence intervals were derived from profile likelihood. Although we show the results from homogeneous model, the qualitative patterns of age-heterogeneous model are not different.



However, the following three remarks should be noted as technical limitations. First, we successfully estimated the vaccine efficacy as well as R_t , but we did so assuming that the depletion of susceptible individuals is negligible. We believe that this assumption is reasonable because the number of cases in Aichi remained very small as compared to the population size of unvaccinated individuals who can be theoretically considered as fully susceptible [27], and also because the epidemic data in question were seen in a population which was large enough. However, the model cannot capture detailed heterogeneous transmission such as local depletion of susceptible individuals (e.g. due to formation of a cluster) and thus, the proposed method may not be directly applicable to outbreaks in a very small population. Second, we did not account for detailed revaccination schedules in Japan due to impossibility of precisely tracking the fraction of unvaccinated susceptible individuals as a function of age. The number of doses may have a profound impact on vaccine efficacy, but unfortunately we did not have access to the dose data for each confirmed case. Third, the proposed model assumes a closed population, i.e., without emigration and immigration. However, obviously the observed data must have involved imported cases. From modeling perspectives, the host migration has little impact on the estimate of vaccine efficacy, while it would influence the estimates of R_t [28]. Given the individual case record for the entire country in the future, one can analyze the dynamics, explicitly accounting for the geographic spread of measles across Japan.

Despite such limitations, we believe that the real-time assessment of epidemic dynamics with (age-specific) estimates of vaccine efficacy based on readily available surveillance datasets would be the huge advantage for epidemiological monitoring of measles in any vaccination population. As was seen in age-dependent vaccine efficacy, the proposed method could inform useful vaccination policy to objectively curb the measles epidemic in real-time. If measles vaccination is compulsory, the finding will directly lead to deciding the host for revaccination, and if voluntary, the self- and group-interests may have to be balanced [29-31]. At the very least, we believe that the proposed approach can supplement the existing evaluation methods of vaccine efficacy.

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Competing Interests

The authors have declared that no competing interest exists.

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