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学　位　論　文

Towards an assessment framework for herd immunity against vaccine preventable diseases

(ワクチン予防可能疾患の集団免疫度に関する評価体系の提案)

2020 年 3 月

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List of publications and presentations

Part of the research has been published as listed below:

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2. Kinoshita R, Nishiura H. Assessing age-dependent susceptibility to measles in Japan. Vaccine. 2017;35(25):3309-3317.

3. Kinoshita R, Shimizu K, Nishiura H. Measles control in a measles-eliminated country, Japan. Travel Med Infect Dis. 2018;25:8-9.

4. Saito MM, Ejima K, Kinoshita R, Nishiura H. Assessing the Effectiveness and Cost-Benefit of Test-and-Vaccinate Policy for Supplementary Vaccination against Rubella with Limited Doses. Int J Environ Res Public Health. 2018;15(4).

5. Shimizu K, Kinoshita R, Yoshii K, Akhmetzhanov AR, Jung SM, Lee H, Nishiura H. An investigation of a measles outbreak in Japan and Taiwan, China, March-May 2018. Western Pac Surveill Response J 2018;9(3).

6. Akhmetzhanov AR, Lee H, Jung SM, Kinoshita R, Shimizu K, Yoshii K, Nishiura H. Real time forecasting of measles using generation-dependent mathematical model in Japan, 2018. PLoS Curr. 2018 Oct 15;10.

7. Nishiura H, Kayano T, Kinoshita R. Overcoming the difficulty of achieving elimination status for measles and rubella due to imported infections: Estimation of the reproduction number R for measles and rubella. Travel Med Infect Dis. 2019 Jul - Aug;30:137-138.

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2. Kinoshita R, Nishiura H. A seroepidemiological analysis of susceptible population against rubella in Japan. Innovative Mathematical Modeling for the Analysis of Infectious Disease Data (IMAID), Hokkaido University Research Center for Zoonosis Control, October 2015 (Oral)

3. Kinoshita R, Nishiura H. Mathematical epidemiology of the rubella epidemic in Japan. Theory of Biomathematics and Its Applications-Mathematical and experimental approach to clarify patterns in transition process-, Kyoto University Research Institute for Mathematical Sciences (RIMS), November 2015 (Oral)

4. Kinoshita R, Nishiura H. A seroepidemiological assessment of susceptible population against rubella in Japan. EPIDEMICS5, Clearwater Florida USA, December 2015 (Poster)

5. Kinoshita R, Nishiura H. A seroepidemiological assessment towards herd immunity attainment of rubella in Japan. Conference on Mathematical Modeling and Control of Communicable Diseases, Fundação Getulio Vargas, Rio de Janeiro Brazil, January 2016 (Oral)

6. Kinoshita R, Nishiura H. Optimizing vaccination program against rubella in Japan. Annual meeting of The Japanese Society for Mathematical Biology (JSMB), Kyushu University, September 2016 (Oral)

7. Kinoshita R, Nishiura H. Modeling herd immunity level of measles in Japan. Innovative Mathematical Modeling for the Analysis of Infectious Disease Data (IMAID), Kobe University, October 2016 (Oral)

8. Kinoshita R, Nishiura H. Assessing the herd immunity level of measles in Japan using mathematical models. The 27th Annual Scientific Meeting of The Japan Epidemiological Association, The Bellclassic Kofu, January 2017 (Oral)

9. Nishiura H*, Kinoshita R. Analyzing the trend of infectious disease death in Japan. The 69th Annual Meeting of the Population Association of Japan, Tohoku University, June 2017 (Oral)

10. Kinoshita R, Nishiura H. Quantifying the age-dependent susceptibility of measles in Japan. EPIDEMICS6, Sitges, Spain, November 2017 (Poster)

11. Kinoshita R, Nishiura H. Trends in infectious disease mortality in Japan, 1946-2015. The Fifth International Conference on Computational and Mathematical Population Dynamics (CMPD5), Florida, USA, May 2019 (Oral)

12. Kinoshita R, Takahashi S, Metcalf CJE, Nishiura H, Grenfell BT. Disentangling the long-term epidemic dynamics of measles in Japan. 17th Annual Meeting on Ecology and Evolution of Infectious Disease (EEID2019), Princeton University, USA, June 2019 (Poster)

13. Kinoshita R, Takahashi S, Metcalf CJE, Nishiura H, Grenfell BT. Epidemic dynamics of measles in Japan, 1949-1984. EPIDEMICS7, South Carolina, USA, December 2019. (Poster)

Abstract

【Background】

In Japan, routine immunization against rubella and measles has been implemented since 1976 and 1978 respectively. For rubella, Japan initially targeted women aged from 12 to 15 years as vaccines, aiming to individually protect women who were at risk of having a fetus with congenital rubella infection, which may lead to congenital rubella syndrome (CRS). From 1995, the vaccination policy shifted, targeting both genders aged after reaching the age of 1, to elevate and maintain herd immunity. For measles, routine vaccination was introduced in 1978, targeting both genders. Only a single dose of attenuated monovalent vaccine was implemented until the second dose regimen initiated against birth cohorts born in and after 1990. Both rubella and measles have yet to be under full control in the country due to insufficient herd immunity, and chains of transmission are frequently observed in the present day. A fundamental path to accurately control vaccine preventable diseases is to evaluate the herd immunity level or to estimate the reproduction number, *R*. The present dissertation consists of two case studies that assess herd immunity levels of rubella (chapter 1) and measles (chapter 2), respectively, in Japan.

【Methods】

Chapter 1 (Rubella): Seroepidemiological data, vaccination coverage data, and demographic statistics were utilized to estimate the proportion susceptible against rubella in the country. Seroconversion was defined as an HI titer ≥32. Susceptible pockets were identified by spotting various types of cohort (e.g. birth cohorts) below the herd immunity threshold (1-1/R_0). The herd immunity threshold for rubella was 83.6% assuming that the R_0 of rubella is 6.1. The age-standardized seronegative proportion, and the absolute number of live births at risk of developing CRS was calculated as a function of time to assess herd immunity against rubella at the population level.

Chapter 2 (Measles): Seroepidemiological data of unvaccinated individuals, vaccination coverage data, and demographic statistics were utilized to estimate to quantify the age-dependent immune fraction against measles in the country. Baseline cutoff value for seroconversion of PA titers was defined as 1:128 (Yoden index = 0.965), and 1:256 (Yoden index = 0.950) was also examined as an alternative. The herd immunity threshold for measles was 90-95% assuming that the R_0 of measles is 10-20. Immunity acquired by natural infection and vaccination was separately inferable by utilizing seroepidemiological data of unvaccinated individuals, and vaccination coverage data. The second dose was interpreted in two different scenarios, i.e., booster and random shots. The effective reproduction number (R_e), the average number of secondary cases generated by a single infected individual, and the age at infection were explored using the age-dependent transmission model and the next generation matrix.

【Results】

Chapter 1 (Rubella): Due to heterogeneities in the susceptible fraction across age and gender, transmission chains of rubella is continuing, fueled by insufficient herd immunity among adult male. Susceptible pockets were identified in adult male for rubella, because the male cohorts remained unimmunized by the present day. Notable susceptible pockets were identified by graphing the seroprevalence by birth years, which found cohorts born from 1974 to 1978 and 1989 to 1993 at low seroprevalence levels below 83.6% (herd immunity threshold). A minor susceptible pocket in those born from 1989 to 1993 was observed in the female population. In 1982, the median (and IQR) age of reported cases was 7 (2.5–7.0) years, among both males and females. The median (25–75th centiles) age in 2014 was elevated to 32.0 (17.0–42.0) years among males and 27.0 (7.0–37.0) years among females. While the seronegative proportions in 1983 were 45.7% (95% CI 32.5% to 58.9%) and 35.6% (95% CI 31.2% to 40.0%) among males and females, respectively, the proportions decreased in 2013 to 18.3% (95% CI 16.8% to 19.8%) and 15.6% (95% CI 10.0% to 21.2%). The number of susceptible live births in 1983 was calculated as 171 875, which was reduced to 23 697 in 2013.

Chapter 2 (Measles): Due to insufficient immunization among working-age adults, transmission chains of measles is maintained in the country even after the verification of local elimination of measles in 2015. If the second dose completely acted as a booster, a proportion immune above 90% would be achieved only among those aged 5 years or less in 2016. Alternatively, if the second dose was randomly distributed, a proportion immune over 90% would be achieved among those aged under 25 years. In 2016, adopting R_0 to be the minimum value of 10 and following scenario 1, R_v was estimated to be 1.50 and 1.57 for cutoff values of 1:128 and 1:256, respectively. Similarly, following scenario 2, R_v was estimated as 1.50 and 1.52, respectively, using the abovementioned cutoff values. If the latest vaccination policy were to continue to 2025, R_v would be 1.50 and 1.39 for scenarios 1 and 2, respectively, assuming R_0 is 10. The R_0 was estimated well above 1 from 2016 to 2025 for all assumed values of R_0. In 1983, the median (and interquartile) age of notified measles cases was 3.0 (3.0–3.0) years; in 2016, the median (25–75th centiles) age had increased to 27.0 (17.0–32.0) years.

【Discussion】

The present dissertation assessed the herd immunity against rubella and measles in Japan. Age and gender dependent risk groups can be identified by analyzing serological surveillance and vaccination coverage data and using mathematical models. Mass vaccination lessens the force of infection and may lead to an elevated age at infection; therefore, it is essential to attain sufficient vaccination coverage to achieve herd immunity especially for rubella, in order to prevent infections among pregnant women. Identifying the susceptible population is beneficial to plan supplementary immunization programs for attaining the local elimination.

【Conclusion】

The present dissertation comprehensively demonstrated an elevated age at infection with rubella and measles, and the presence of susceptible pockets, especially among adults. Although the large oscillating outbreaks may be over, the country will be prone to rubella and measles outbreaks following importations of the diseases. I believe that my series of studies

have successfully shown that supplementary immunization can be objectively planned to construct herd immunity against rubella and measles in Japan.

List of Abbreviations

CRS	Congenital rubella syndrome
CDC	United States Centers for Disease Control and Prevention
HI	Hemagglutination inhibition
M&RI's	Measles and Rubella Initiative's
MIAC	Ministry of Internal Affairs and Communications
NESVPD	National Epidemiological Surveillance of Vaccine Preventable Disease
NESID	National Epidemiological Surveillance for Infectious Diseases
R_0	Basic reproduction number
R_e, R_v	Effective reproduction number
PA	Particle agglutination
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Introduction

In 1980, smallpox was declared to have been eradicated by the World Health Organization (WHO). While the introduction of routine mass vaccination has contributed to the reduction of morbidity and mortality against numerous diseases, smallpox has been only the disease that was totally eradicated to present by vaccination. The present dissertation analyzes why rubella and measles continues to maintain its public threat, in the case of Japan.

In 2012, the Measles and Rubella Initiatives's (M&RI's), a consortium led by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the United States Centers for Disease Control and Prevention (CDC), the United Nations Foundation, and the American Red Cross, set a goal to achieve measles and rubella elimination in at least five WHO regions by the end of 2020. Currently in Japan, both transmission chains of rubella and measles are yet observed in the country due to importation of infected travelers from various other countries. In a country close to achieving elimination like Japan, it is important to understand the proportion susceptible by age and gender to identify where and how much vaccination needs to be implemented to elevate and maintain sufficient herd immunity.

To monitor the immunity at the population level, seroepidemiological surveillance has been implemented in Japan since 1971 against rubella, and 1978 against measles. Utilizing seroepidemiological surveillance data is effective to understand the population immunity, since it can directly measure the proportion immune, while vaccination coverage can only measure vaccine induced immunity. By calibrating seroepidemiological data and vaccination coverage data, we can evaluate the herd immunity level and calculate the effective reproduction number (R_e). While the current WHO criteria of local elimination of measles and rubella is to interrupt continuous chains for more than 12 months, verifying $R_e < 1$ will precisely confirm the interruption of the disease to have sufficient herd immunity. Here we

analyze the seroepidemiology of rubella (Chapter 1) and measles (Chapter 2) in Japan and estimate R_e to evaluate whether herd immunity has been enough in the country.

Chapter 1 Assessing herd immunity against rubella in Japan

Introduction

Although rubella is a vaccine-preventable disease (Best, 2007; Lambert et al., 2015), Japan has yet to be successful in bringing this disease under full control. When rubella vaccination was introduced in 1976, Japan initially focused on women aged from 12–15 years as vaccinees, aiming to individually protect women who were at risk of having a fetus with congenital rubella infection, which may lead to congenital rubella syndrome (CRS) (Duszak, 2009; Sugishita et al., 2013). In 1995, the vaccination policy shifted, targeting both genders aged from 12–90 months (typically from 12–36 months) to elevate and maintain herd immunity. Although Japan is considered to be on its way to establishing sufficient herd immunity through vaccination, the country has recently experienced two major rubella epidemics, in 2004 and 2012–14, involving 4,248 and 12,614 reported rubella cases, respectively, and yielding 45 CRS cases in the most recent epidemic (National Institute of Infectious Diseases (NIID) Japan; Tuberculosis and Infectious Diseases Control Division (TIDCD), 1982–2014). Despite the implementation of supplementary vaccination after the 2004 epidemic, which was conducted not only among women of childbearing age but also among their family members, the most recent epidemic was not prevented and involved a large number of adult cases (Minakami et al., 2014; Yamada et al., 2014).

The age at infection with rubella virus is elevated by vaccination, but if the vaccination coverage is insufficient to prevent major epidemics, the insufficient vaccination program could be responsible for a tragic increase in the number of CRS cases due to an increased risk of infection among pregnant women (Panagiotopoulos et al., 1999). Thus, once a country decides to aim to eliminate rubella, it is critical to ensure a high level of population immunity, among both males and females (Tanaka-Taya et al., 2013). The potential consequence of the 1995 change in the Japanese vaccination policy may be that different birth cohorts have

different levels of immunity against rubella (National Institute of Infectious Diseases (NIID) Japan; Tuberculosis and Infectious Diseases Control Division (TIDCD), 1982–2014; Ujiie et al., 2014). In fact, there were two notable characteristics of the rubella cases from the 2012–14 epidemic: (i) 72% of the cases were adults (Yamada et al., 2014) and (ii) the cases were concentrated in 20–39-year-old males (68%) (Tanaka-Taya et al., 2013). An explicit assessment of the herd immunity is crucial for planning future ways to control the spread of this disease (Ang et al., 2010; Castillo-Solórzano et al., 2011a; Castillo-Solórzano et al., 2011b; Chua et al., 2015; Khandaker et al., 2014; Smits et al., 2014; Vynnycky et al., 2003). The present study aimed to statistically analyze the transmission dynamics of rubella in Japan, with a particular emphasis on the most recent major epidemic from 2012–14, and to assess the population level immunity over age and time.

Materials and Methods

Epidemiological data

To elucidate the epidemiological dynamics of rubella in Japan, we analyzed three pieces of information: (i) reported cases of rubella and CRS, (ii) seroepidemiological data, and (iii) vaccination coverage. The seroepidemiological data and vaccination coverage were investigated to assess herd immunity (Chua et al., 2015; Cutts and Vynnycky, 1999; Ohkusa et al., 2014). The rubella and CRS data rest on the reporting of cases to the National Epidemiological Surveillance for Infectious Diseases (NESID), which were collected according to the Communicable Disease Prevention Law until 1998 and according to the Infectious Disease Control Law thereafter (National Institute of Infectious Diseases (NIID) Japan, 2014; Tuberculosis and Infectious Diseases Control Division (TIDCD), 1982–2014). From 1982–2007, a sentinel surveillance of rubella cases was conducted, which received notifications from approximately 3,000 sentinel pediatric clinics (Tanaka-Taya et al., 2013). Reporting of CRS cases first started in 1999; in 2008, a revision was made to the surveillance,

requiring all diagnosed rubella and CRS cases to be reported (Sugishita et al., 2013; Tanaka-Taya et al., 2013).

The seroepidemiological data were derived from the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD)(2005-2015). This serial cross-sectional serological survey, quantifying hemagglutination inhibition (HI) titers, has been implemented every year from July to September, non-randomly selecting the geographical area from which it draws its subjects. The serum was collected by region from more than 5,400 participants of all ages, recruiting participants from those who visited a prefectural medical facility or public health center (Nabae et al., 2014). The present study takes into consideration the survey data from every five years since 1983 to investigate the longitudinal trend of age at rubella infection, standardized seronegative proportion, and the number of live births that were born to seronegative mothers and considered to be at risk of CRS.

The vaccination coverage data were retrieved from the immunization records of the Ministry of Health, Labour and Welfare. Vaccination coverage was calculated as the ratio of the annual number of vaccinations to the population size of an age-group that newly entered the subject age-group of vaccination, and this was overlaid with data from the reported rubella cases.

Statistical Analysis

Time- and age-dependent epidemiological dynamics of confirmed rubella cases from 1982–2014 were examined along with the changes in the vaccination coverage over this time period. Additionally, the reported rubella and CRS cases from 2012–14 were examined to understand the comparative magnitude of the recent epidemic. The age- and gender-specificity of the recent epidemic were also examined.

Using serial cross-sectional seroepidemiological survey data from 2003, 2008, and 2013, the distributions of HI titer by age and gender were examined. Owing to the small sample size for each age, discrete age grouping was carried out over every 5 years. For this reason, the seroprevalence were compared not only by the age and time but also by birth year cohort. Seroconversion, following the convention in Japan (corresponding to results of ≥7.3 IU/ml from enzyme-linked immunosorbent assays), was defined an HI titer ≥32 (Nishiura et al., 2015). The basic reproduction number, R_0, acknowledged as the average number of secondary cases generated by a single primary case, was estimated at 6.1 for rubella using an age-structured realistic model (Kanaan and Farrington, 2005). The herd immunity threshold against rubella was calculated by $1-(1/R_0)$, and came out to 83.6% (Kanaan and Farrington, 2005). While we set the baseline levels of seropositivity and herd immunity by using the threshold described above, a sensitivity analysis was carried out using alternative values, i.e., a conventionally accepted cut-off value of HI titer ≥8 and a seroprevalence of 94.0%, as adopted elsewhere (Plans, 2013; Plans-Rubió, 2012). Adhering to published studies on herd immunity assessment, we have also analyzed the true prevalence with the assumption that the sensitivity and specificity of the serological testing were each 97% (Plans, 2013; Plans-Rubió, 2012).

The time-dependent elevation of age at rubella infection was examined using the reported case data. The age distribution of reported cases from 1982–2014 was analyzed. A χ^2 trend test was implemented to detect if there was an elevation in the age at infection from 1982–2014.

Evaluation metrics

To assess herd immunity at the population level, we employed two evaluation metrics. These metrics focused on the seroprevalence data (and did not use vaccination coverage) because a substantial fraction of immune individuals, especially adults, acquired their immunity through

a natural infection rather than through vaccination. First, we calculated the age-standardized seroprevalence, $m_{1,g}(t)$, at calendar time t and in gender g (g = 0 for females or 1 for males), as

$$m_{1,g}(t) = \sum_{a=0}^{\infty} \Big(1 - p_{a,g}(t)\Big) n_{a,g}(t),$$

where $p_{a,g}(t)$ is the observed seropositive proportion and $n_{a,g}(t)$ is the relative population size at time t and gender g of those aged a years. This metric is interpreted as the age-standardized seronegative proportion. The data for n_a were obtained from the Statistic Bureau of the Ministry of Internal Affairs and Communications (MIAC) . Second, to assess the risk of CRS in relation to herd immunity, the absolute number of live births at risk of developing CRS was calculated in relation to time using the age-specific annual number of live births, $b_a(t)$, and the age-specific seronegative proportion in the corresponding age-group:

$$m_2(t) = \sum_{a=a_L}^{a_U} \Big(1 - p_{a,0}(t)\Big) b_a(t),$$

where a_L and a_U represent the lower and upper childbearing ages of mothers, respectively.

All of the data that we used were secondary in nature, and all individuals were de-identified in advance of the study (Ministry of Health). For this reason, the present study was exempted from requiring ethical approval by the Institutional Review Board.

Data sharing policy

The summary of secondary datasets that were analyzed in the present study can be shared by the corresponding author upon request.

Results

Figure 1 shows the reported rubella cases and the vaccination coverage from 1982–2014. Damped oscillation was observed for decades, and the magnitude of the most recent epidemic from 2012–14 appeared to be smaller than those in 1980s and 90s. The absolute number of confirmed cases during the major epidemics was: 410,786 in 1987; 223,758 in 1992; 47,599 in 1997; 4,248 in 2004; and 10,675 in 2013. Whereas the vaccination coverage in the 1980s was around 70%, the coverage under the routine immunization program that began in 1995 to raise herd immunity has been maintained well above 90%. During the most recent epidemic from 2012–14 (Figure 2), there were 12,614 confirmed rubella cases and 45 reported CRS cases. The peak in CRS cases took place in the second week of 2014 with n = 4 reported CRS events, which was 33 weeks after the peak of the reported rubella cases in 21st week of 2013. The time-lag of 33 weeks is consistent with our conventional understanding that the exposure leading to CRS occurs during the first trimester of pregnancy. The average age at infection in 2013 was 34.4 years old for males and 24.0 years old for females (Figure 3). In the 2012–14 epidemic, 77% of the cases were male.

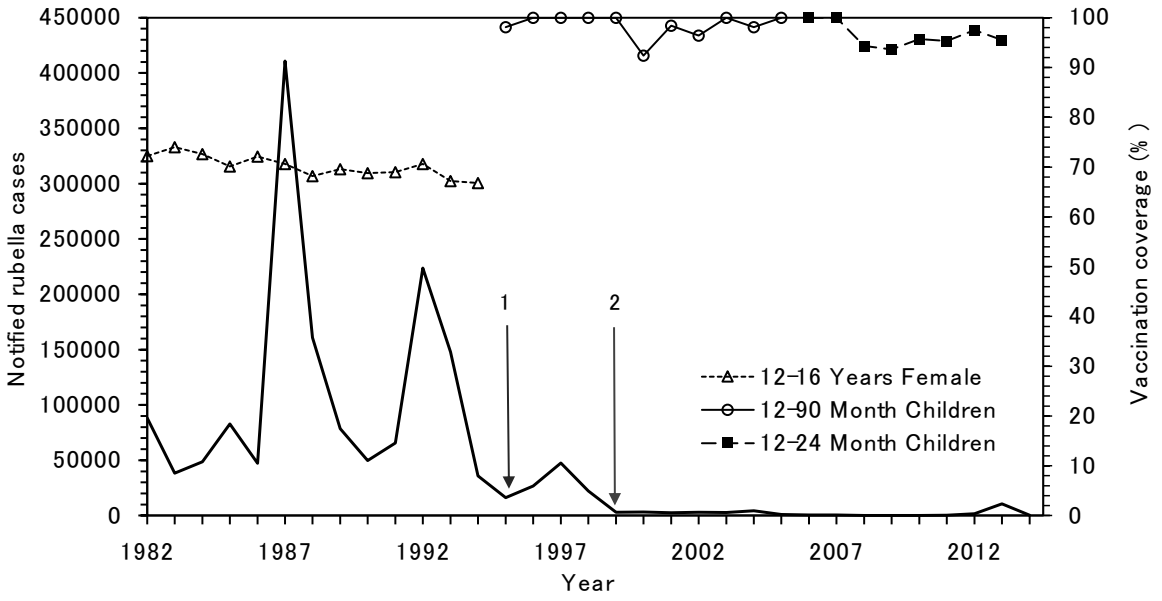

Figure 1. Longitudinal trend in rubella cases and the vaccination coverage in Japan. The solid line represents the rubella cases reported to the NESID from 1982–2014. In 1994 (labeled point 1), the law was revised to shift the focus from individual protection of adolescent females to mass vaccination among infants. In 1999 (labeled point 2), the Communicable Disease Law with sentinel surveillance was replaced by the Infectious Disease Control Law. In 2008, the Infectious Disease Law was revised, requiring the reporting of all diagnosed rubella cases. The dashed line represents the rubella vaccination coverage (first dose) from 1977–2013. The shapes of the data points on this line correspond to the change in target of the vaccination program, from targeting 12–16-year-old females, to 12–90-month-old children (typically 12–36-month-old children), to 12–24-month-old children. Some vaccination coverage in the government statistics exceeded 100% because the coverage was calculated as the ratio of the annual number of vaccinations to the population size of the age-group that newly entered the vaccination-eligible age group.

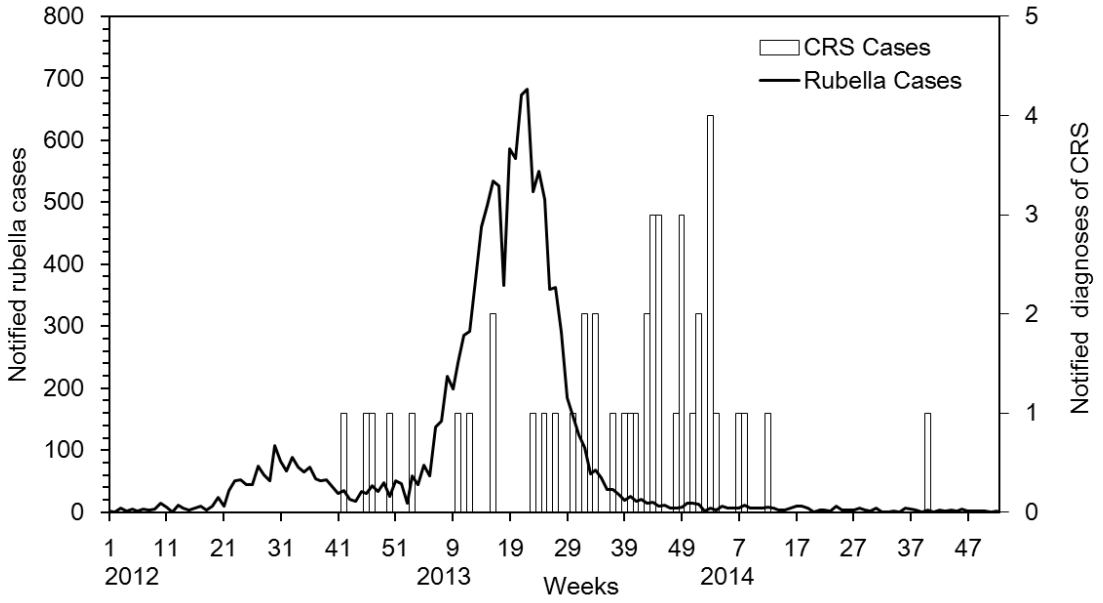

Figure 2. Trend in cases of rubella and congenital rubella syndrome in Japan, 2012-14. The bold solid line indicates the number of reported rubella cases by week (left vertical axis). The bars indicate the number of reported diagnoses of CRS from Jan 2012–Oct 2014 (right vertical axis).

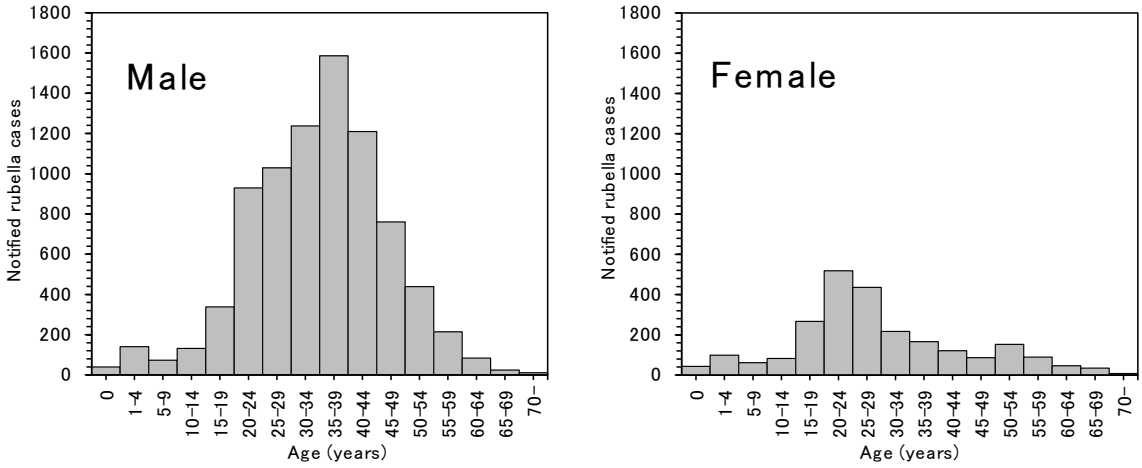

Figure 3. Age distribution of reported rubella cases in 2013 by sex in Japan.

Overall, the seropositive proportion among adults increased over time from 2003–13, except for those aged from 20-24 and 45-49 years among males, and 20-29, 35-39 and 50-54 years among females (Figure 2). In 2013, the seropositive proportion among men was mostly below the pre-specified herd immunity threshold, with the lowest values of 68.0% and 70.0% among those aged from 35–39 and 20–24 years, respectively (Figure 4A). Among females (Figure 4B), the seroprevalence in the majority of the age groups was greater than the herd immunity threshold in 2013, but in those aged 20–24 years, the seropositive proportion was only 78.3%. Notable susceptible pockets were identified by graphing the seroprevalence by birth years, which found cohorts born from 1974–78 and 1989–93 at low seroprevalence levels (Figure 4C). A minor susceptible pocket in those born from 1989-93 was observed in the female population (Figure 4D). If we adopt 94.0% as the herd immunity threshold, all age groups of both sexes are considered to be susceptible to a rubella epidemic. Although the qualitative age-dependent patterns were not drastically different from those shown in Figure 4 when we adopted HI $\geq$ 8 as the cut-off value (Figure 5A, 5B, 5C and 5D), having 94.0% to be considered as the herd immunity threshold, the susceptible pocket among adult males widens, leading those aged from 30-34 years to be vulnerable in 2013. Additionally, when we adopted the cut-off value of HI $\geq$ 8 along with a 94.0% herd immunity threshold for the birth year cohort, only the adult male population of those born later than 1979–83, or all males aged 30 years or older in 2013, appeared to be vulnerable (Figure 5A and 5C). If we adopt 83.6% as the threshold with cut-off value of HI $\geq$ 8, male adult population except for those aged from 35-39 and 45-49 years were considered as substantially immune in 2013, while seroprevalence among adult females predominantly appeared to be above the threshold. Even when we accounted for the sensitivity and specificity of serological testing, the findings were similar to those directly obtained from the observed seroprevalence data (Figure 6A, 6B, 6C and 6D).

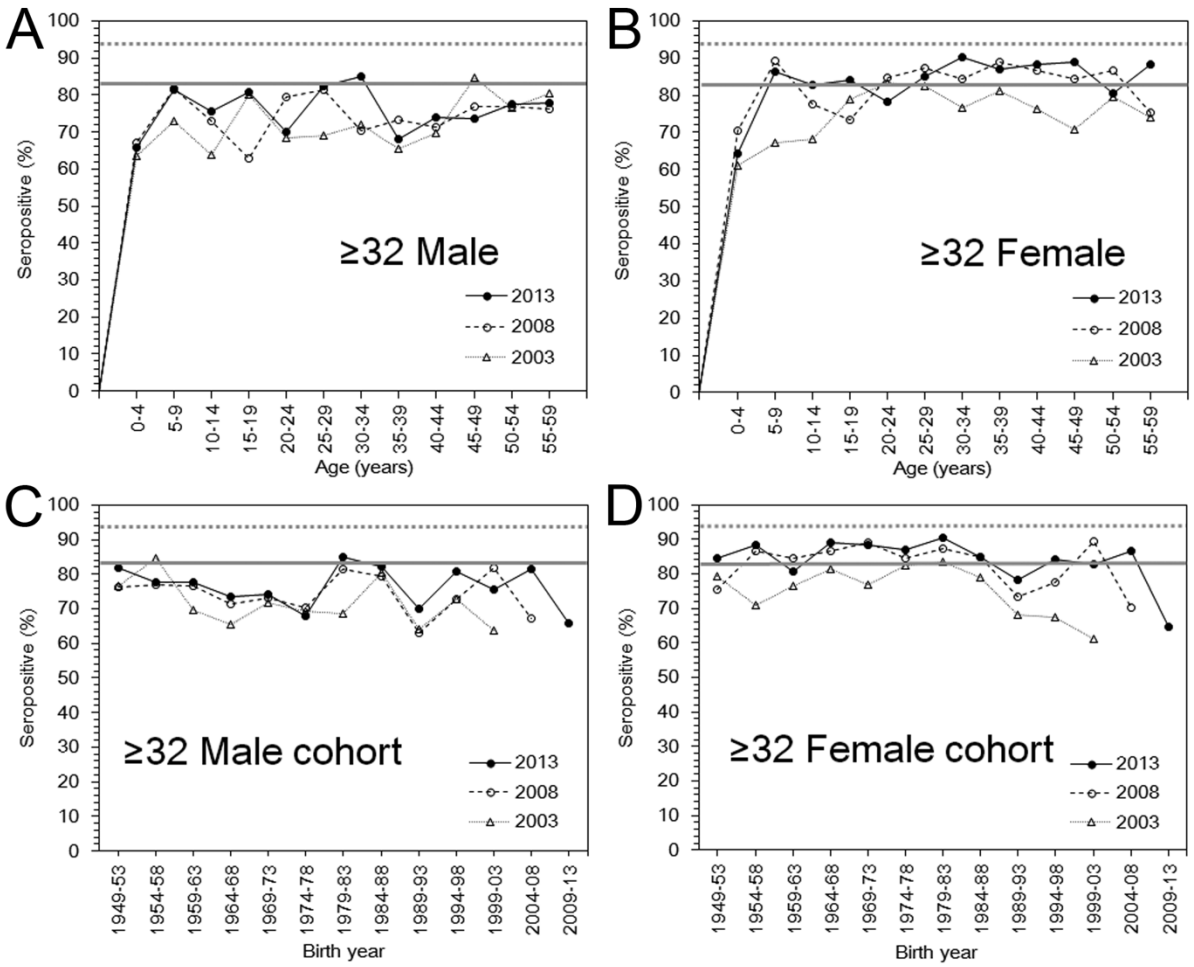

Figure 4. Age-specific rubella-seropositive proportions in Japan from 2003–13, applying HI titers ≥ 32 as a cut-off. Figures (A-B) shows the age-specific proportion of men (A) and women (B) seropositive for rubella antibodies in Japan based on the seroepidemiological data from 2003, 2008, and 2013. The seropositive proportion is shown as a function of age. A HI titer ≥32 was used as the cut-off for deciding if seroconversion had occurred. The horizontal grey bold line indicates a herd immunity threshold of 83.6%, derived from the standard formula: 1−(1/basic reproduction number). A major epidemic should be prevented in populations with serpositivity above this line. The horizontal grey dotted line indicates an alternative herd immunity threshold of 94.0%, derived from the same formula with different dynamic assumptions [31,32]. Figures C−D show the rubella-seropositive proportions among males (C) and females (D) by birth cohort, from 1949–2013.

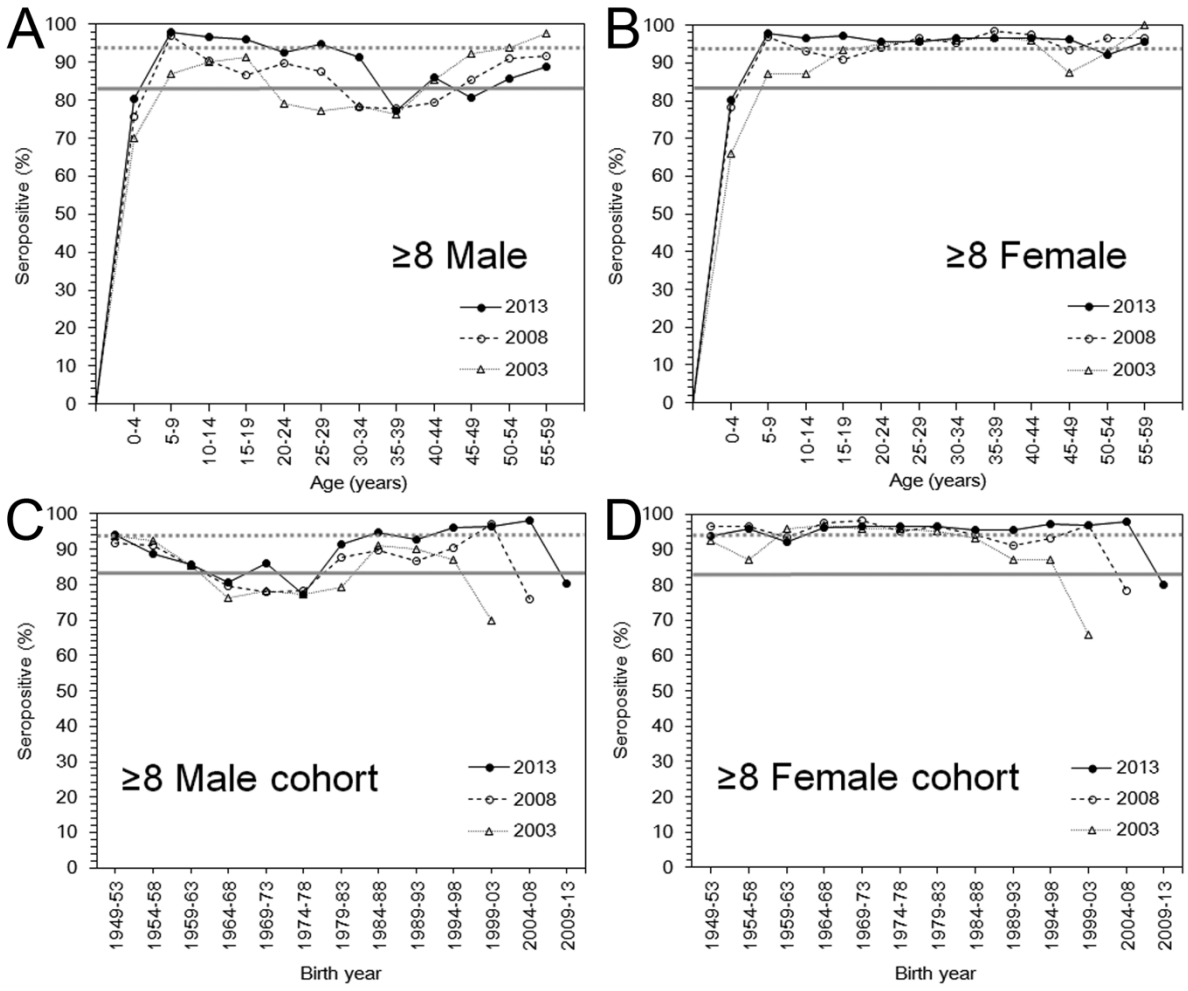

Figure 5. Age-specific rubella-seropositive proportion from 2003–13, applying HI titer ≥ 8 as a cut-off. (A–B) The age-specific proportion of men (A) and women (B) seropositive for rubella antibodies in Japan based on the seroepidemiological data from 2003, 2008, and 2013. The seropositive proportion is shown as a function of age. A HI titer ≥8 was used as the cut-off for deciding if seroconversion had occurred. The horizontal grey bold line indicates a herd immunity threshold of 83.6%, derived from the standard formula: 1−(1/basic reproduction number). A major epidemic should be prevented in populations with serpositivity above this line. The horizontal grey dotted line indicates an alternative herd immunity threshold of 94.0%, derived from the same formula with different dynamic assumptions [31,32]. Figures C−D show the rubella-seropositive proportions among males (C) and females (D) by birth cohort, from 1949–2013.

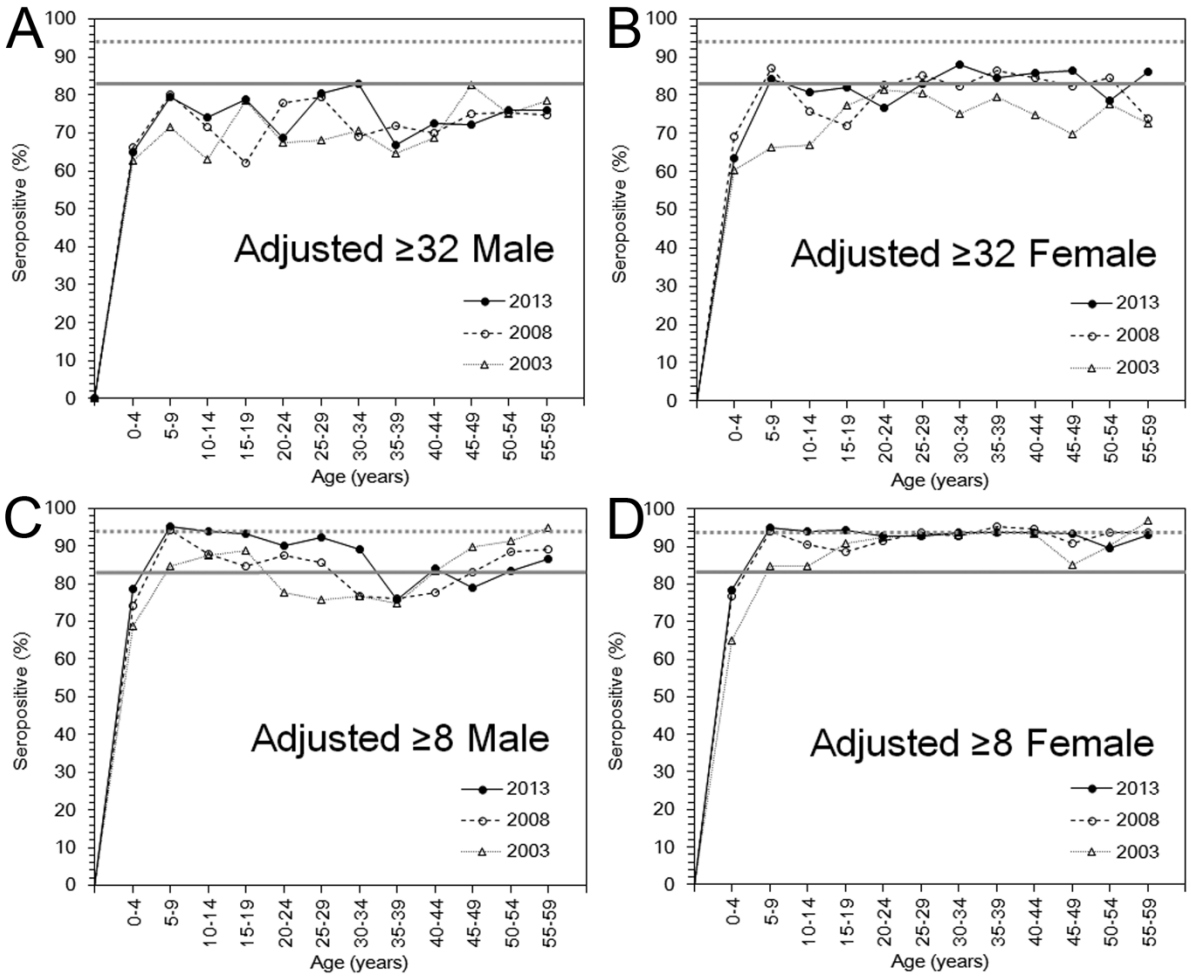

Figure 6. Critical age-specific rubella-seropositive proportion from 2003–13. The critical age-specific rubella-seropositive proportion among males (A, C) and females (B, D) in Japan using seroepidemiological data from 2003, 2008, and 2013. The positive proportion of each sample is shown as a function of age. HI titers ≥32 (A–B) or ≥8 (C–D) were used as the cut-off values for deciding if seroconversion has occured. The critical seropositive proportion was obtained by adjusting the seropositive proportion, assuming 97.0% sensitivity and 97.0% specificity[26,27], calculated as $P_c=I_cSe+(1-I_c)(1-Sp)$, with Ic being the protected individuals, and Se and Sp representing the sensitivity and specificity, respectively. The horizontal grey bold line indicates a herd immunity threshold of 83.6%, derived from the standard formula: 1−(1/basic reproduction number). A major epidemic should be prevented in populations with serpositivity above this line. The horizontal grey dotted line indicates an alternative herd immunity threshold of 94.0%, derived from the same formula with different dynamic assumptions [31,32

The time-series of ages for cases from 1982–2014 is shown by gender in Figure 3. In 1982, the median (and interquartile range) age of reported cases was 7.0 (2.5–7.0) years old, among both males (Figure 7A) and females (Figure 7B). The median (25–75th percentiles) age in 2014 was elevated to 32.0 (17.0–42.0) years old among males and 27.0 (7.0–37.0) years old among females. From 1982–2014, there was a significant time-dependent increase in the age at infection among both males and females ($p \leq 0.001$), although mandatory reporting of all rubella cases only started in 2008 and cases thereafter might look more aged than before reporting was required by law. Nevertheless, even restricting ourselves to the time from 2008–14, the trend test also indicates a significant time-dependent increase in the age at rubella infection among males ($p \leq 0.01$). However, the increase in age at infection among females failed to reach statistical significance ($p = 0.06$).

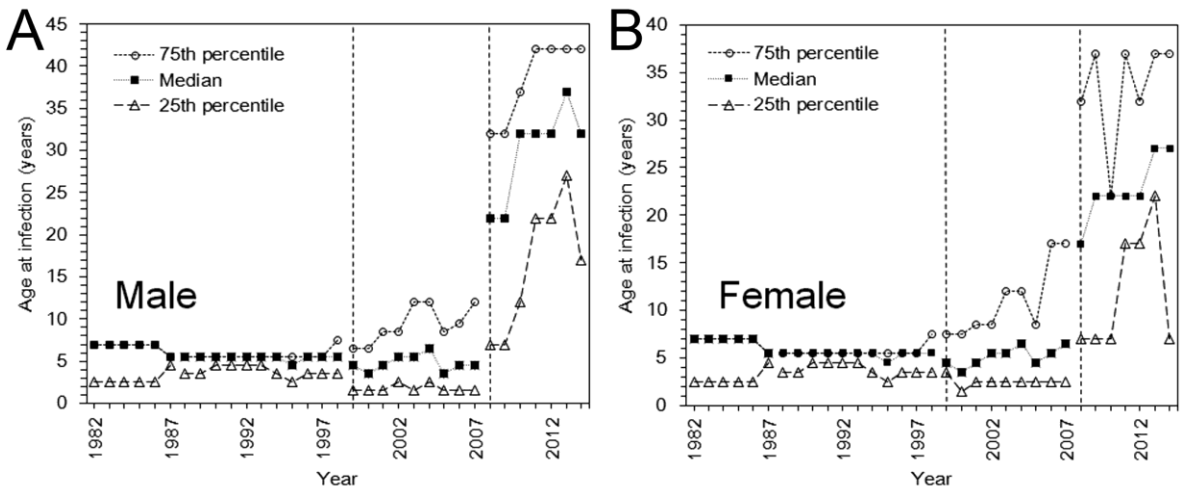

Figure 7. Age at infection with rubella in Japan, 1982–2014. (A−B) Age at rubella infection in Japan among male cases (A) and female cases (B). The dotted line with circles represents the 75th percentile of the age distribution of cases, the small dotted line with filled squares indicates the median, and the large dotted line with triangles represents the 25th percentile. The data is not continuous because the discrete age categories of cases in the reporting system was not consistent throughout the time period. For this reason, the lines are divided when there was a change in reporting practice. Moreover, 75th percentile points overlapped with the median, especially in the early years of observation. The vertical dotted line in 1999 corresponds to when the infectious disease law was introduced. After the vertical dotted line in 2008, surveillance was drastically revised to enforce the reporting of all cases, including the reporting of cases among adults aged 20 years and older.

To allow an explicit comparison between the herd immunity threshold and the observed representative value of the seropositive fraction, the age-standardized seronegative proportion m_1 was calculated as a function of time from 1983–2013 (Figure 8). The results show that the estimate of m_1 steadily dropped in both males and females from 1983–2013 (Figure 8). While the seronegative proportions in 1983 were 45.7% (95% confidence interval (CI): 32.5–58.9%) and 35.6% (95% CI: 31.2–40.0%) among males and females, respectively, the proportions decreased in 2013 to 18.3% (95% CI: 16.8–19.8%) and 15.6% (95% CI: 10.0–21.2%), respectively. When the seropositive proportion was compared against the theoretical herd immunity seropositive threshold calculated using $R_0 = 6.1$ (83.6%), the estimate among males was still below the herd immunity threshold and that among females was only slightly above the threshold value. Figure 9 shows the number of live births at risk for CRS from 1983–2013. The number of susceptible live births in 1983 was calculated as 17,1875, which was reduced to 23,697 in 2013. The slope of the decline in Figure 9 was sharper than that among females in Figure 8 because the decrease in Figure 9 reflects not only the immunized fraction but also the trend in the decline of the absolute number of births per year.

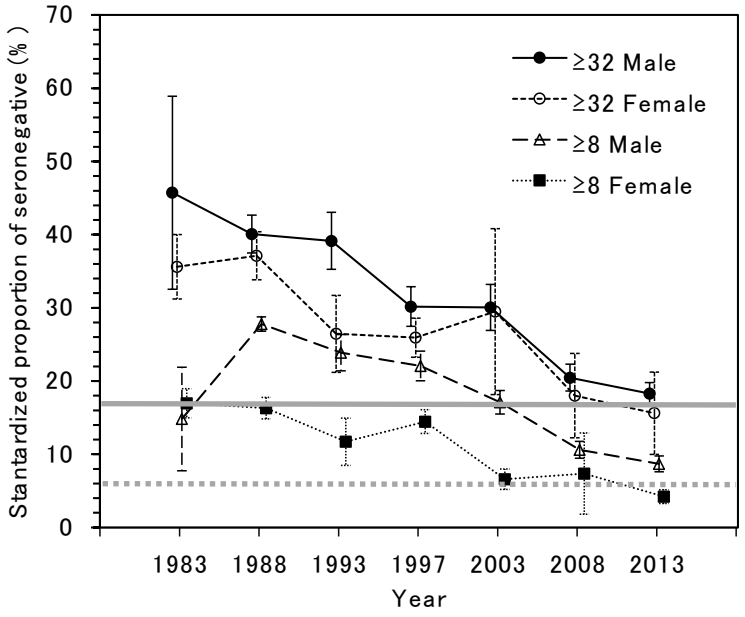

Figure 8. Time-dependence in the standardized rubella-seronegative proportion in Japan, 1983–2013, by sex and seroconversion definition. The trend is plotted separately by sex for two different seroconversion definitions: HI titer >32 and HI titer >8 (see legend). Values were adjusted using the age- and gender-specific population sizes[25]. The error bars show the 95% confidence intervals derived from the normal approximation to the binomial distribution. Samples with HI titers ≥ 8 or ≥ 32 were considered to be seroconverted. The horizontal bold and dotted grey lines indicate herd immunity thresholds of 83.6% and 94.0%, respectively[31,32], which were calculated by $1-(1/R_0)$. A major epidemic should be prevented when seronegative proportions are below this line.

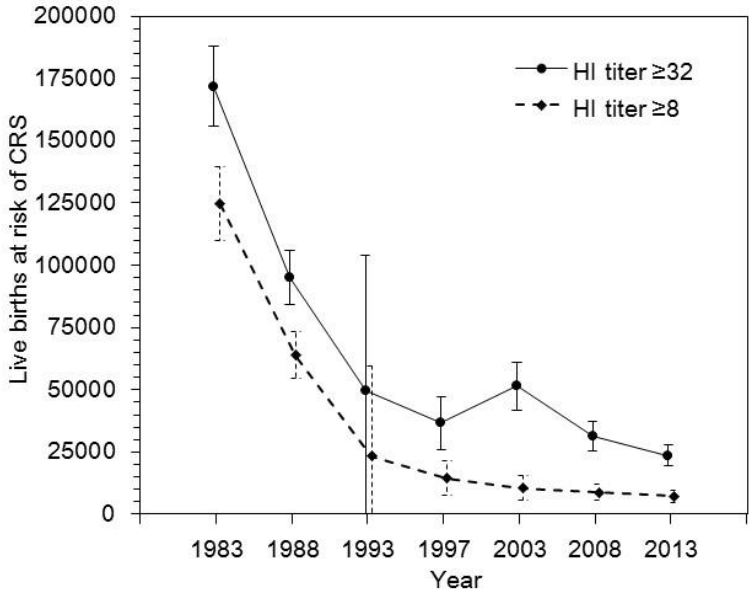

Figure 9. Number of live births at risk of CRS in Japan, 1983-2013. The number of live births at risk for developing CRS. The number of live births at risk was calculated from 1983-2013; the age-specific annual number of live births was multiplied by the age-specific seronegative proportion in the corresponding age-group and the product was summed over age to yield a standardized proportion. Since the statistics for the number of live births by age of mothers were not available for every corresponding year, the data from the closest year available were used [26]. The error bars show the 95% confidence intervals derived from the normal approximation to the binomial distribution.

Discussion

The present study assessed the herd immunity against rubella in Japan, characterizing the special epidemiological features that led Japan to experience the 2012–14 rubella epidemic. We identified susceptible pockets, especially among adult male cohorts, which were an important factor that helped the epidemic to take off. Making rubella control more difficult, there has been an elevation in the average age at infection. Although the absolute number of rubella cases was smaller in the 2012–14 rubella epidemic than in earlier epidemics (Figure 1A), the occurrence of this epidemic was fueled by insufficient herd immunity. The unfortunate tragedy that was identified in Greece in the 1990s (Panagiotopoulos et al., 1999) has been repeatedly experienced by present day Japan. While a recently published study focused on estimating the impact on the age-specific rubella seroprevalence of the most recent epidemic in Japan from 2012–14 (Nishiura et al., 2015), the present study has comprehensively assessed the herd immunity in Japan through the analysis of longitudinal seroepidemiological data, which allowed us to compare between the age-standardized seropositive proportion and the theoretical herd immunity threshold, and moreover, an elevated age at infection over time was confirmed based on an analysis of reported case data.

Mass vaccination lessens the force of infection and may lead to an elevated age at infection; therefore, it is essential to attain a sufficient vaccination coverage to achieve herd immunity to prevent complications, such as infections among pregnant women (Massad et al., 1994; Nokes et al., 1986). In addition to the elevated age of rubella cases, the present study has shown that Japan has unvaccinated cohorts that were effectively left susceptible until their 30s and 40s, perhaps contributing to an increased opportunity for women of childbearing age to be infected. The epidemic in Japan has indicated that a major rubella epidemic can occur with adult patients making up the majority of cases. Given the limited immunizing effect of the 2012–14 epidemic (Nishiura et al., 2015), our findings call for a supplementary vaccination among those remaining susceptible.

Considering these findings, an important conclusion from the present study is that public health policymakers must make sure that susceptible pockets are not left when switching the vaccination policy from an individual-centered prevention program to one aiming to achieve herd immunity or when introducing a new mass vaccination program. Seroepidemiological studies can help to monitor susceptible fractions over time and age, so that susceptible pockets will not remain in the population. Identifying susceptible groups and optimizing prioritized birth cohorts will be the subject of our future study.

A few limitations of this study should be noted. First, we adopted 1:8 and 1:32 HI titers to define the seropositive cases, but employing these cut-off values might not accurately capture all of the susceptible individuals. To minimize the effect of this limitation, we have implemented sensitivity analyses using two different cut-off values and two different herd immunity threshold levels. Second, we did not explore any geospatial dynamics, although the major rubella epidemics mostly occurred in urban settings (Sugishita et al., 2014). The spatio-temporal analysis of rubella epidemics is one of our ongoing research subjects. Third, our analysis of age at infection among reported cases was biased by the selection of sentinel medical facilities, and thus, the estimated ages might be biased, especially those prior to 2008. Nevertheless, the elevation of age at infection among male population was observed even when we focused on the years from 2008 onward.

In conclusion, the present study comprehensively demonstrated an elevated age at infection with rubella and the presence of susceptible pockets, especially among adult males, as two important factors that have characterized the rubella epidemic in Japan from 2012–14. Even though the large epidemic might be over, it is important to remember that this population remains vulnerable to rubella infection and could lead to further CRS cases unless supplementary vaccination is conducted.

Acknowledgements

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Chapter 2 Assessing age-dependent susceptibility to measles in Japan

Introduction

Measles is a highly contagious disease caused by measles virus. The infection is clinically characterized by prodromal symptoms of fever, cough, coryza, and conjunctivitis, following an incubation period of 11–12 days (Klinkenberg and Nishiura, 2011); subsequently Koplik's spots and rash are observed. Before routine mass vaccination, measles was expected to naturally occur during childhood. Mass vaccination made noteworthy progress toward reducing the disease burden (Mina et al., 2015), but measles maintains high transmissibility with its capacity for aerosol transmission (Moss and Griffin, 2012). Additionally, imported cases of measles can lead to outbreaks in a population with insufficient herd immunity. Published studies have shown that an epidemic can occur if 10% or more of the population is susceptible (Gay, 2004; Moss and Griffin, 2012).

In Japan, routine immunization against measles started in 1978, offering only a single dose using attenuated monovalent measles vaccine until 2005. A second dose regimen has been introduced to birth cohorts born in and after 1990 (Okabe, 2007). Since 2006, a bivalent vaccine containing both measles and rubella vaccine has become widespread. Figure 1 shows the time-dependent variations in the subject of measles vaccination along with the age-specific fraction of different vaccination doses in the present day Japan. During the past two decades, the primary vaccination coverage of measles was estimated to be above 90% whereas it was well below 80% before 1994.

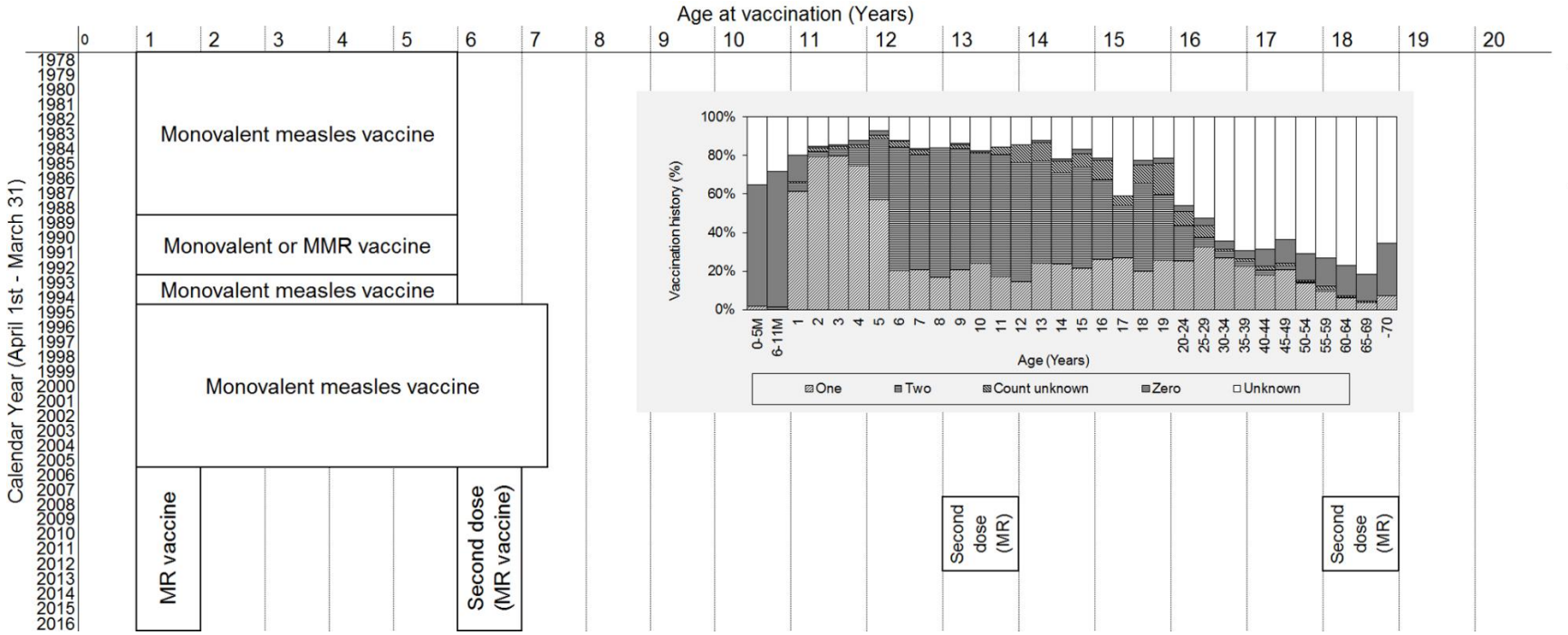

Figure 1. Measles vaccination with varying age of subject as a function of calendar year, Japan. Square area represents age-groups that were subject to measles vaccination in a given year. MMR stands for measles-mumps-rubella vaccine, while MR stands for measles-rubella vaccine. Upper right bar chart shows the age distribution of vaccination coverage stratified by the number of doses as of the end of 2015.

Continued control efforts against measles in Japan have contributed to verified elimination in 2015 by the World Health Organization (Ihara, 2009; Minagawa et al., 2015). However, it has not been long since the coverage exceeded 90% and revaccination was introduced; thus, the population with insufficient coverage poses a potential risk of epidemic. Indeed, Japan experienced multiple outbreaks of measles in 2016 (Watanabe et al., 2017), and the effective reproduction number (R_v)—the average number of secondary cases in a partially vaccinated population—during the outbreak from August to September of 2016 was estimated to be above the value of 1 (Nishiura et al., 2017). An analogous event was also seen in Japan with rubella from 2012–2014, with an older average age at infection and a substantial number of adult cases (Kinoshita and Nishiura, 2016).

Monitoring herd immunity is essential in practice, and seroepidemiological survey and vaccination coverage have been used for evaluating vaccination programs (Boulton et al., 2016; Cutts et al., 2016; Cutts and Hanson, 2016; Cutts et al., 2013; Plans, 2013; Plans-Rubió, 2012). To analyze such datasets, mathematical models of transmission dynamics and susceptibility have been used to quantify susceptibility, so that future vaccination strategies can be elucidated (Bednarczyk et al., 2016; Chen et al., 2012; Gay et al., 1995; Hens et al., 2015; Lessler et al., 2016; Verguet et al., 2015; Wallinga et al., 2003). Here, we aimed to assess the herd immunity against measles in Japan as a function of age and time.

Materials and Methods

To investigate how the immune population is distributed in Japan, we analyzed four pieces of information: (1) the vaccination coverage, (2) seroepidemiological data, (3) notified measles cases to the surveillance system, and (4) population census. To quantify the proportion immune owing to vaccination, published empirical estimates of parameters that govern vaccination failures were retrieved from the literature (Davidkin et al., 2008; Watson et al., 1998; Wood et al., 2009) (see Appendix).

The nationwide dataset of vaccination from 1978 to 2014 was obtained from the immunization record of the Ministry of Health, Labour and Welfare . The statistical data source yields vaccination coverage given as the ratio of the annual total number of vaccinations to the population size of an age group that has just become eligible for vaccination in the corresponding year. Because eligible ages for measles vaccination range across multiple years, the annual total number of vaccinations can exceed the population size in the denominator (e.g., if children aged 1, 2, and 3 years were subject to vaccination campaign in a year, the denominator population reflects the population size of only 1 year olds, and the ratio is greater than 100%). Therefore, the coverage data in the source sometimes exceeded 100% and did not reflect the actual vaccination coverage. We have corrected this problem below.

Over the past years, the targeted monthly age to fully complete primary vaccination has been revised several times. From 1978 to 1994, primary vaccination was scheduled to take place in the first 12 to 72 months of life; in 1995–2005, the targeted age was from 12 to 90 months and from 12 to 24 months in 2006–2017. Although the scheduled age range was larger in the past, the accumulation of vaccination had mostly plateaued by the age of 36 months. Moreover, the age at second dose has also differed over time (2008). To fill the gap caused by an absence of revaccination among people born from 1990 to 1999, Japan initiated a revaccination program among those born from 1990 to 1994 at age 18 years, from 1995 to 1999 at age 13 years, and those born in 2000 and later at age 6 years. Such variations in the second dose occurred among people born from 1990 to 1999; a measles epidemic in 2007 and the surrounding years involved a substantial number of high school students and teenagers, highlighting the need to conduct supplementary vaccination among adolescents (Saitoh and Okabe, 2014). To understand the age-specific frequency of vaccine uptake during the scheduled ages subject to vaccination, a series of cross-sectional surveys on the age-dependent cumulative distribution of vaccination was used (Sakiyama, 2001; Takayama et al., 2008; Takayama et al., 2005; Takayama et al., 2006; Takayama et al., 2015; Takayama et al., 2007a). The cumulative distribution surveys were conducted not as part of a governmental program but as individual research programs, and survey data were available from 1999 to 2013. The age-specific vaccine uptake for the remaining years, including that in the future, was imputed by a linear regression of the age-specific rate of

vaccination with time, assuming that the age-specific vaccine uptake curve follows an exponential distribution.

Seroepidemiological data were retrieved from the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD) (2005-2015), as done previously (Kinoshita and Nishiura, 2016). Figure 7 illustrates the empirical seroprevalence data. The survey rests on a serial cross-sectional serological study that measures particle agglutination (PA) titers against measles in the serum of a total 5,000 healthy voluntary participants per year. Participants were recruited from conveniently selected healthy individuals from whom survey officers obtained informed consent in advance of collecting the blood sample. Although the sampling is allegedly mentioned as random, such solicitation has taken place, for example, among local government officials and their families during ordinary health check-ups including those conducted among school children. Such surveys have been conducted every year from July to September across Japan, non-randomly selecting the geographical area from which it draws its candidates of participant. We retrieved count data of those people with a specific discrete titer category for each age.

Surveillance data of measles were based on case notification to the National Epidemiological Surveillance of Infectious Diseases (NESID) system (1982–2016), collected under the Communicable Diseases Prevention Law until March 1999 and subsequently under the Infectious Disease Law. Sentinel surveillance was conducted from 1982 to 2007, with notification restricted to approximately 3,000 sentinel clinics across Japan. Surveillance data of measles in children (≤18 years old) and adults (≥18 years old) were collected separately and two separate datasets were summed in the following analyses, to assess the increase in the age at infection. In 2008, a revision was made to surveillance requiring all diagnosed measles cases to be notified. The case definition of measles has been cases that clinically satisfy the following triad: (1) measles-specific rashes (i.e., large, flat blotches that often flow into each other), (2) fever and (3) catarrhal conditions including cough, runny nose, and red and runny eyes (conjunctivitis). Confirmatory diagnosis has been made only among a part of notified cases.

Lastly, population census data were obtained from the Statistics Bureau of the Ministry of International Affairs and Communications .

Here we describe how the proportion immune in Japan was estimated as a function of time and age, yielding estimates by birth cohort. We first reconstruct the immune fraction attributable to vaccine-induced immunity by birth cohort, accounting for primary and secondary vaccination failures; subsequently, we incorporate the immune fraction among unvaccinated individuals using seroepidemiological data. Because vaccination uptake takes 36 months, the cumulative distribution of uptake was used. The corresponding probability mass function of vaccine uptake in each birth cohort, denoted by f_n, for ages n=1, 2, and 3 years was calculated using the observed cumulative frequency by ages of 12, 24, and 36 months.

The immune fraction by birth cohort was calculated in the following three steps. First, the immune fraction attributed to primary vaccination was calculated in calendar year *t* among those born in year *y* using our mathematical model (hereafter, referred to as "immune fraction" model; see Appendix). For this calculation, the nationwide counts of vaccination, the probability mass function of vaccine uptake, and age-specific population size based on demographic census were used as inputs. Additionally, the immune fraction model used three parameters, i.e., the proportion of primary vaccination failure, the waning rate of immunity, and the fraction of primary-vaccinated individuals who experience waning, deriving the most plausible values from the literature (Davidkin et al., 2008; Watson et al., 1998; Wood et al., 2009) while examining the sensitivity of our estimates to possible variations in these parameters. Table 1 shows the list of parameters.

Second, we further considered the fraction immune attributable to the second dose. Owing to uncertainty surrounding the vaccination history of recipients, two different scenarios were considered for interpretation of the second dose. Scenario 1 assumes that the second dose acts as booster revaccination—only those receiving primary vaccination would be revaccinated using

the second dose. Scenario 2 assumes that the second dose takes place at random in the targeted cohort, allowing both booster shot and vaccination for the first time to occur. The calculation of immune fraction owing to second dose was carried out using the model (see Appendix). The abovementioned two calculation processes allowed us to classify the population into several categories: (i) people receiving primary vaccination only, (ii) those receiving both primary vaccination and revaccination, (iii) those receiving only the second dose as primary vaccination (scenario 2 only), and (iv) unvaccinated individuals. Immune fraction models yielded how many vaccinated individuals still possessed vaccine-induced immunity.

Third, the immune fraction among unvaccinated individuals owing to natural exposure to measles is calculated using the proportion seropositive to measles based on seroepidemiological survey. We used the proportion immune among unvaccinated individuals at age a in year y, which was multiplied by (iv) above (unvaccinated individuals) to calculate the fraction naturally acquiring immunity to measles. In Japan, PA antibody have been conventionally used for seroepidemiological survey, because this method has been demonstrated to be more sensitive than hemagglutination inhibition (HI) assay and also well correlate with the results from neutralizing antibody assay in the general population [39]. A standard cutoff value for seroconversion of PA titers was determined using the Youden index: analyzing PA distribution, the cutoff value of 1:128 (Yoden index=0.965) was used as baseline, and 1:256 (Yoden index=0.950) was also examined as an alternative (Takayama et al., 2007b). Owing to the limited sample size of unvaccinated individuals, a piecewise constant model of every 5 years was used. The 95% confidence intervals of the proportion were calculated using the exact method. Seroepidemiological data were not used for vaccinated individuals for two reasons: (1) vaccine-induced immunity and naturally acquired immunity were not distinguishable in seroepidemiological data, and (2) we assumed that vaccinated individuals were likely geographically clustered and the opportunities of exposure were far less common than those among unvaccinated individuals owing to an indirect effect.

Lastly, we calculated the effective reproduction number, $R_{v,t}$ in year t. To do so, we employed the published age-dependent contact matrix, C (Ibuka et al., 2016) that is assumed to be proportional to the next generation matrix, $K = \{k_{ij}\}$. The basic reproduction number (R_0) of measles, the average number of secondary cases produced by a single primary case in a fully susceptible population, ranged from 10 to 20 in the literature (Edmunds et al., 2000; Grenfell and Anderson, 1985; Wallinga et al., 2001); we adopted R_0 values of 10, 15, and 20 in our calculations. We normalize the contact matrix C to parameterize the next generation matrix, i.e.,

$$R_0 = \rho(K) = \rho\left(\frac{R_0}{\rho(C)}C\right), \qquad (1)$$

where $\rho(.)$ stands for the largest eigenvalue. Then, the time- and age-specific effective reproduction number was obtained from the next generation matrix under vaccination, K_v, which is described by

$$K_v = \{(1 - x_{y,t})k_{y.}\}, \qquad (2)$$

incorporating that the proportion (1-$x_{a,y,t}$) is immune (and the susceptibility is reduced) in age group y in year t (see Appendix). Subsequently, $R_{v,t}$ is given as $\rho(K_v)$.

Results

Figure 2A and 2B show the proportion immune from vaccination in 2016 and 2030 by applying two different scenarios for the second dose. Because it is assumed that the second dose is randomly distributed in scenario 2, previously unvaccinated individuals are covered by the second dose in this scenario and an abrupt rise in the proportion immune owing to vaccination at 6 years old is observed. In both scenarios, the immune fraction from vaccination drops below 70% at 23 years old, and the proportion immune from vaccination is around 50% for the first few years from the start of routine vaccination in 1978. Figure 2C-2F show the sensitivity of the immune fraction to parameters governing the secondary vaccination failure for scenarios 1 and 2. The impact of varying b and δ on the estimated fraction immune was only marginal.

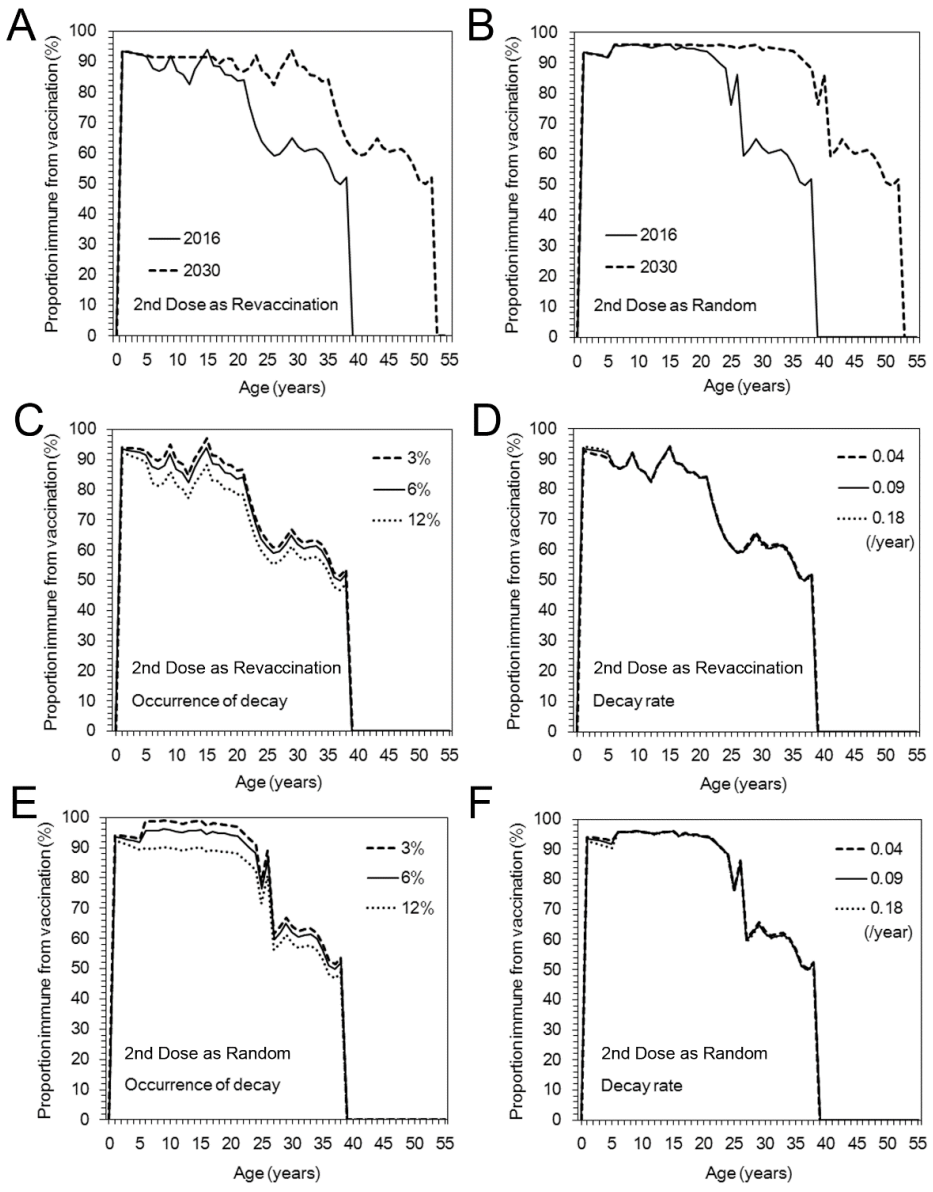

Figure 2. Proportion immune in 2016 and 2030 attributable to vaccination. (A-B) Estimated proportion immune from vaccination in 2016 and 2030, by adopting two different scenarios for the second dose. The projection of 2030 assumed that vaccination coverage and vaccination schedule will remain the same as the latest year over time. (A) shows the results from scenario 1, assuming that the second dose is implemented only against those receiving primary vaccination;(B) shows scenario 2, assuming that the second dose was randomly distributed in the population. (C-D) Sensitivity analysis of the proportion immune to the proportion and rate of waning in scenario 1 (i.e., second dose acts as booster revaccination). In panel C, the parameter b (occurrence of decay) was varied; panel D shows the sensitivity to δ (decay rate), ranging from 1/2 and 2 times the originally adopted values. (E-F) Sensitivity analysis of the proportion immune to the proportion and rate of waning in scenario 2 (i.e., second dose is distributed at random).

Figure 3 combines the proportion immune from vaccination and natural infection. For this estimation, the seroprevalence data among unvaccinated was used (Figure 4). Figure 3A and 3B show the proportion immune in the present year (2016) for two different scenarios, while Figure 3C and 3D illustrate the projected proportion immune in 2030 for these scenarios, assuming that the latest vaccination policy continues to that year. If the second dose completely acted as a booster, a proportion immune above 90% would be achieved only among those aged 5 years or less in 2016. Alternatively, if the second dose was randomly distributed, a proportion immune over 90% would be achieved among those aged under 25 years. The proportion seropositive among unvaccinated individuals is illustrated in Figure 4A–4D. An alternative cutoff value of PA titers (1:256) was considered in Figure 5A–5D, showing that varying the cutoff value in seroepidemiological data had only a marginal impact on the estimated proportion immune.

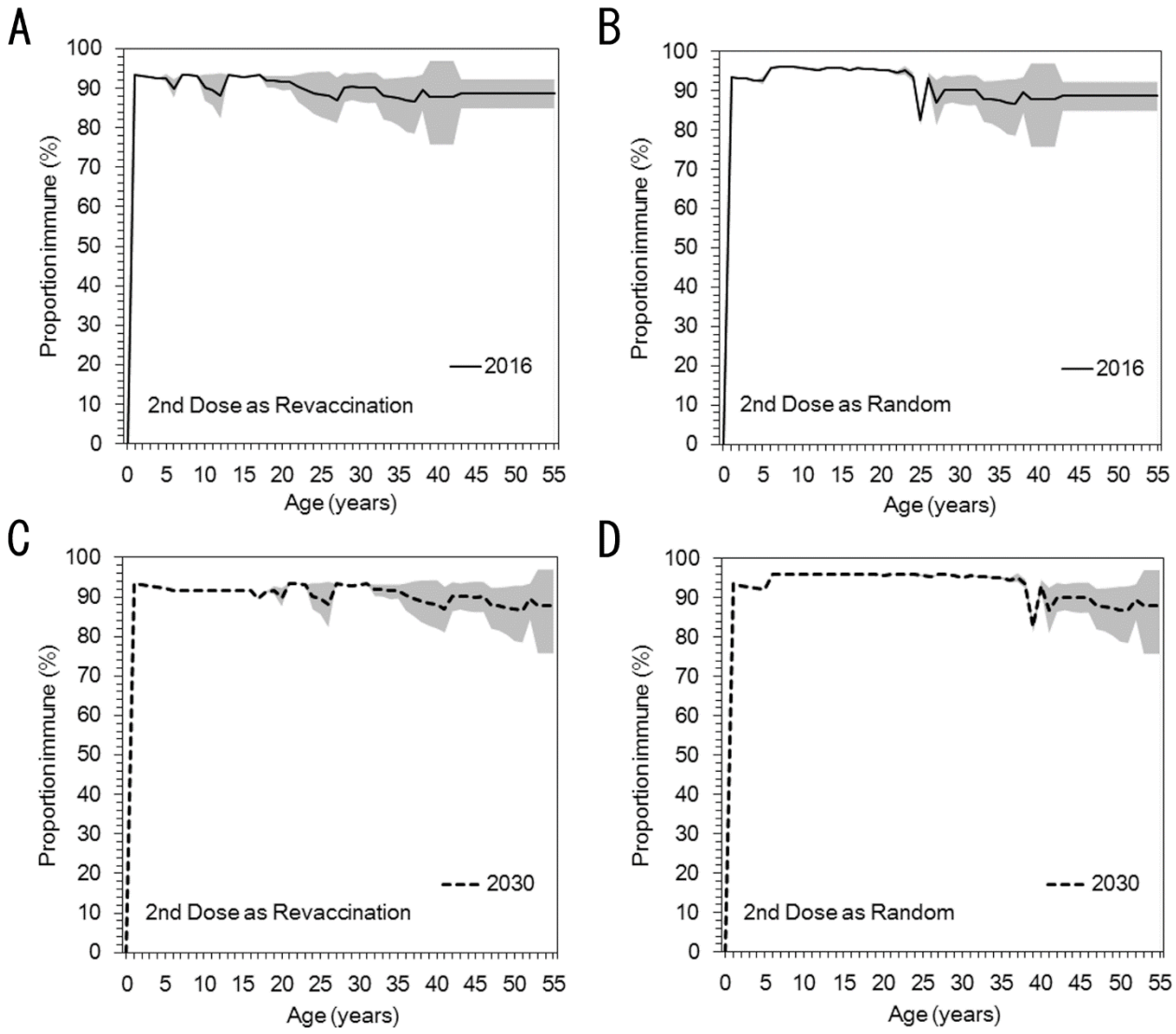

Figure 3. Proportion immune against measles in Japan, 2016 and 2030. (A-D) Estimated proportion immune from vaccination and natural infection by age, using PA titer 1:128 and over as seropositive, and adopting two scenarios for the second dose of vaccination. Shaded area reflects the uncertainty bound for the 95% confidence interval of the seropositive fraction. Panels A and C rest on scenario 1 (i.e., second dose was the booster shot); panels B and D show the results from scenario 2. Panels A and B show the fraction immune in 2016; panels C and D show the estimates in 2030, assuming that the vaccination policy remains the same as the present day (i.e., status quo).

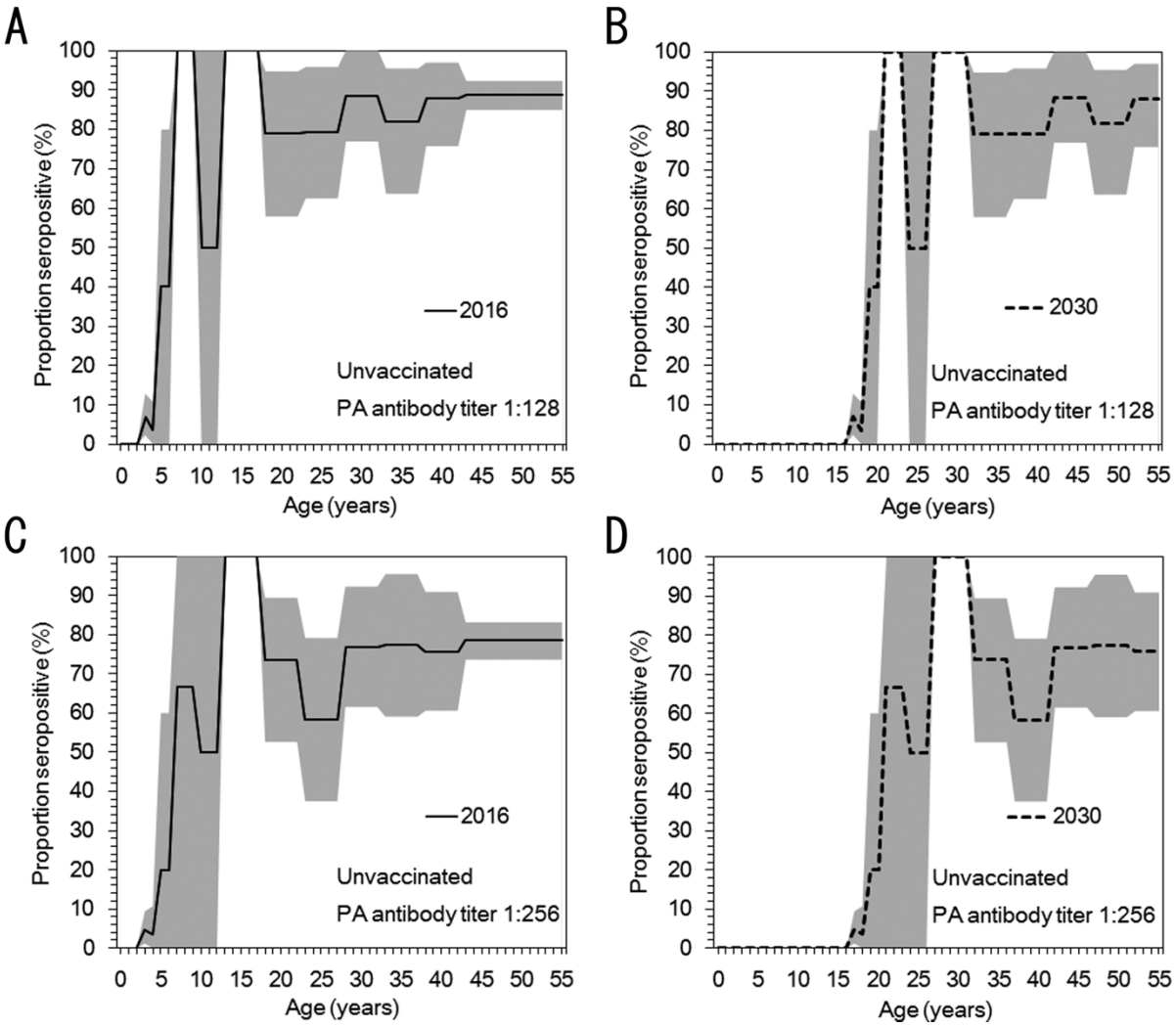

Figure 4. Positive PA antibody titers among unvaccinated individuals by age, using different cutoff values for seropositive. (A-D) The proportion seropositive among unvaccinated individuals in 2013 was quantified using different cutoff values for seropositive and was shifted by corresponding years to the estimated years. Owing to limited data, a step function was assumed and the exact 95% confidence interval (shaded in gray) was calculated using a binomial distribution. (A) Proportion seropositive among unvaccinated individuals in 2013 shifted by corresponding years until 2016, using PA titers 1:128 and over as the cutoff for seropositive. (B) Proportion seropositive among unvaccinated individuals in 2013 shifted by corresponding years until 2030, using PA titers 1:128 and over as the cutoff for seropositive. (C) Proportion seropositive among unvaccinated individuals in 2013 shifted by corresponding years until 2016, using PA titers 1:256 and over as the cutoff for seropositive. (D) Proportion seropositive among unvaccinated individuals in 2013 shifted by corresponding years until 2030, using PA titers 1:256 and over as the cutoff value for seropositive.

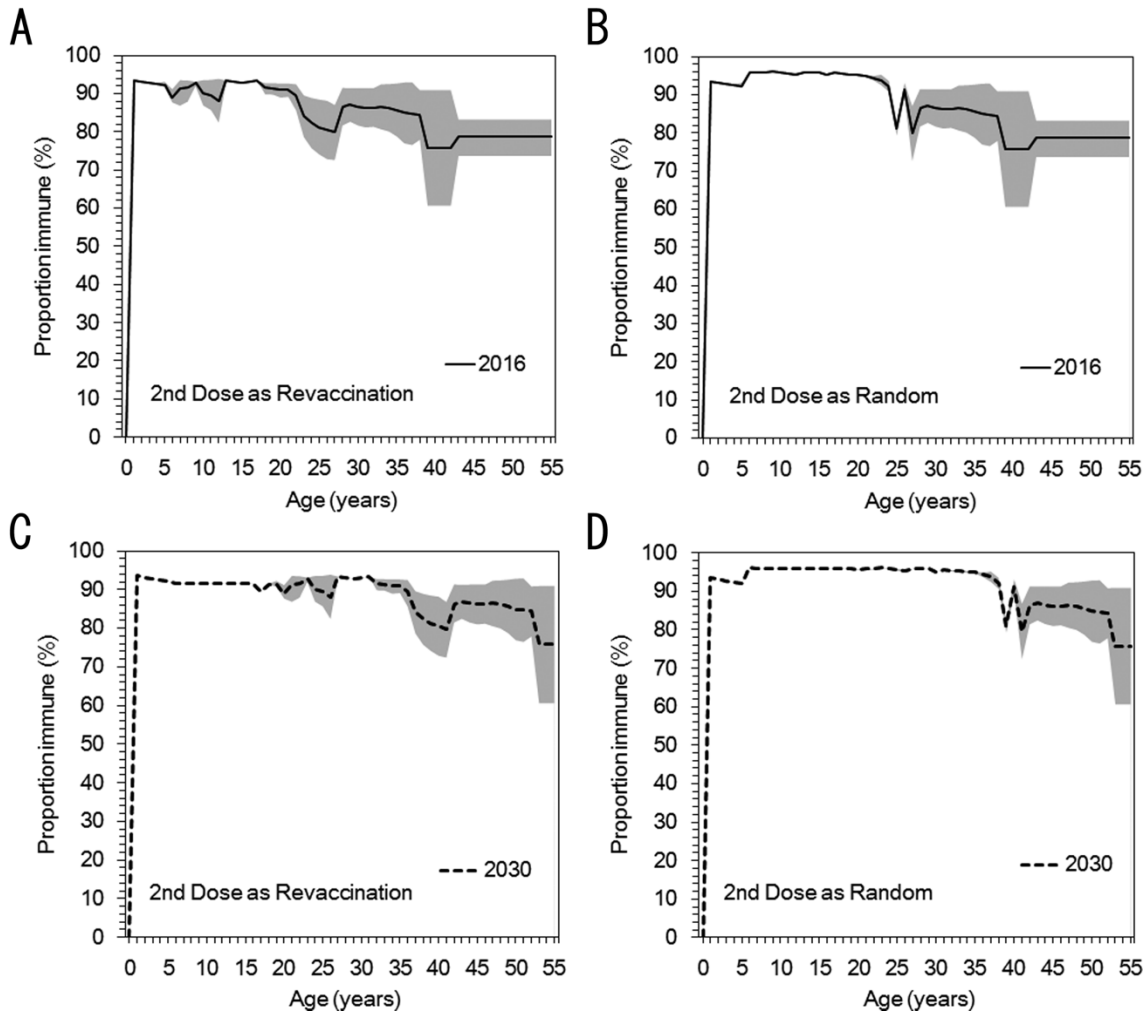

Figure 5. Proportion immune against measles in Japan, 2016 and 2030, using alternative cutoff value of PA titers 1:256 as seropositive. (A-D) Estimation of the proportion immune from vaccination and natural infection by age, using PA titer 1:256 and over as seropositive, and assuming different scenarios for second dose. The shaded area reflects the 95% confidence interval of the serological data. (A) Scenario 1 used to estimate proportion immune in 2016. (B) Scenario 2 used to estimate proportion immune in 2016. (C) Scenario 1 used to estimate proportion immune in 2030. (D) Scenario 2 used to estimate proportion immune in 2030.

Estimated effective reproduction numbers are shown in Figure 6. Assuming that R_0 ranges from 10–20, the estimated immune fraction in Japan was below the herd immunity threshold in 2016, although the estimated proportion immune was above 80% for all ages. In 2016, adopting R_0 to be the minimum value of 10 and following scenario 1, R_v was estimated to be 1.50 and 1.57 for cutoff values of 1:128 and 1:256, respectively. Similarly, following scenario 2, R_v was estimated as 1.50 and 1.52, respectively, using the abovementioned cutoff values. We also calculated the immune fraction using seroprevalence data alone (Figure 7A–7B). Similar values of R_v were also obtained even when we relied on seroepidemiological data (Figure 7C–7D). If the latest vaccination policy were to continue to 2025, R_v would be 1.50 and 1.39 for scenarios 1 and 2, respectively, assuming R_0 is 10 (Figure 4B and 4D). The R_v was estimated well above 1 from 2016 to 2025 for all assumed values of R_0.

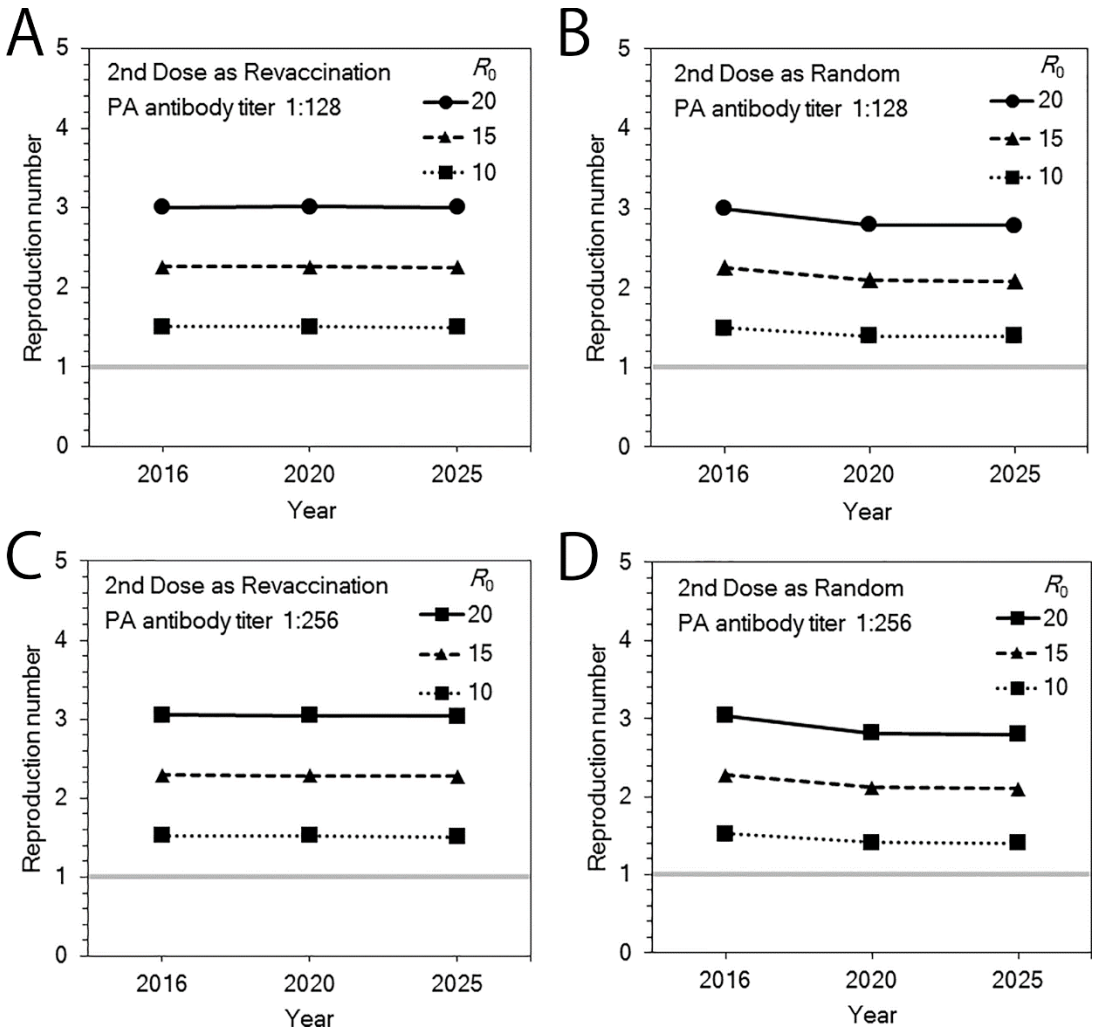

Figure 6. Effective reproduction number of measles in Japan. (A-D) Effective reproduction number of measles in Japan has been estimated using the reconstructed proportion immune in 2016, 2020, and 2025. The basic reproduction number (R0) was assumed as 10, 15, and 20. The horizontal gray line is an indicator at R0 of 1 (below which a major epidemic cannot happen). (A) Scenario 1 using the cutoff of PA titer 1:128 and over. (B) Scenario 2 using the cutoff of PA titer 1:128 and over. (C) Scenario 1 using the cutoff of PA titer 1:256 and over. (D) Scenario 1 using the cutoff of PA titer 1:256 and over.

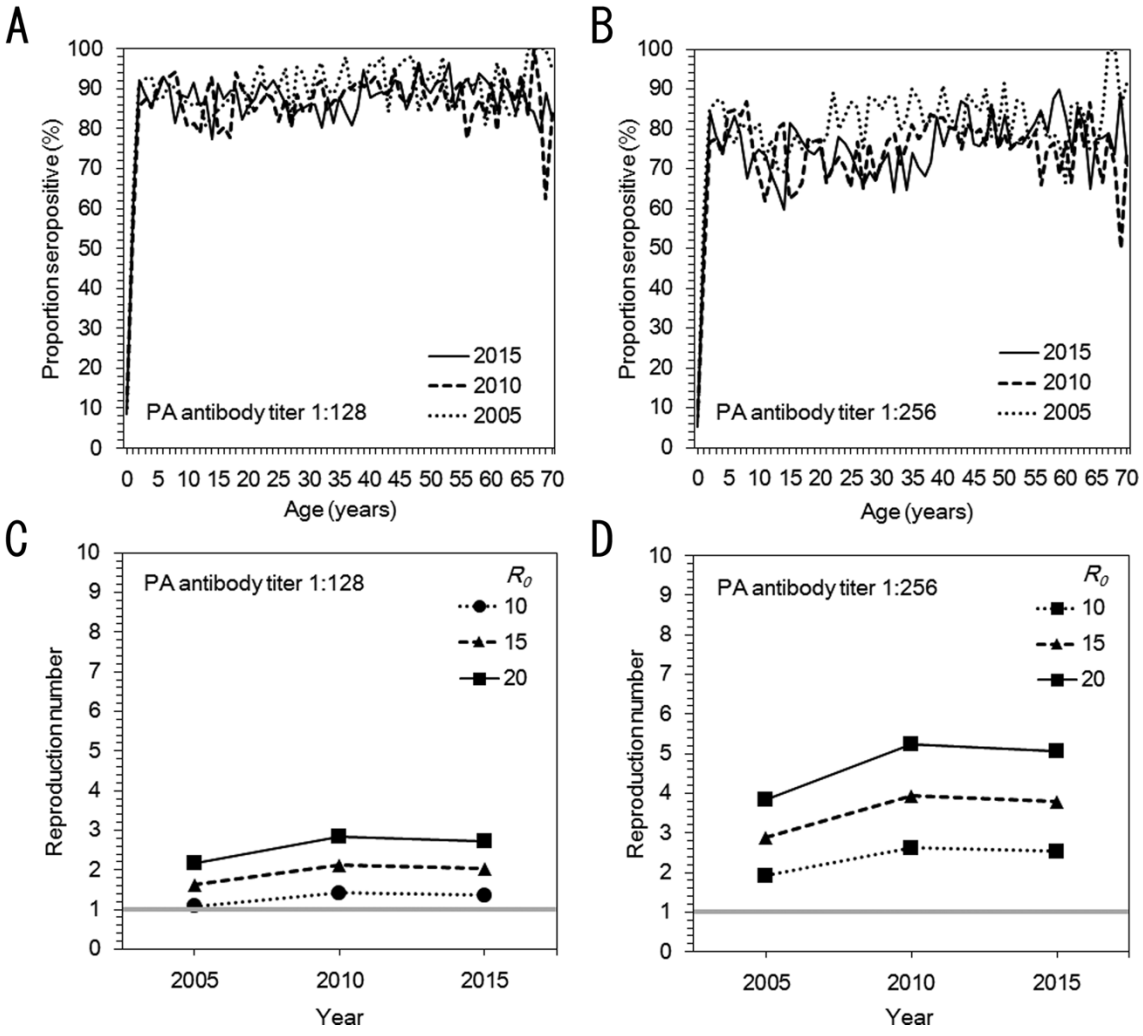

Figure 7. Seroepidemiological analysis of susceptibility and transmission potential, 2005, 2010, 2015. (A-B) Proportion seropositive by age, in 2005, 2010, 2015. The proportion seropositive using PA titers with cutoff values 1:128 (A) and 1:256 (B) and over was plotted by age in the years 2015 (bold line), 2010 (large dotted line), and 2005 (small dotted line). (C-D) The effective reproduction number using serological data only. The effective reproduction number was calculated using PA titers with cutoffs of 1:128 (C) and 1:256 (D) and over. The basic reproduction numbers (R_0) of 10, 15, and 20 were assumed.

To examine the time-varying age of measles cases, a time series of cases' ages from 1983 to 2016 was examined (Figure 8). In 1983, the median (and interquartile) age of notified measles cases was 3.0 (3.0–3.0) years; in 2016, the median (25–75th centiles) age had increased to 27.0 (17.0–32.0) years. The recent 2016 outbreak in Japan by age was overlaid with the modeling result of scenario 1 in Figure 9A. Cases who undertook revaccination accounted for the very small proportion (Figure 9B). This outbreak was fueled by contacts at an international airport among people in their 20s and 30s (Watanabe et al., 2017), and assortative contact among young adults accompanied by insufficient immune fraction could qualitatively explain a part of the observed age distribution of cases in 2016.

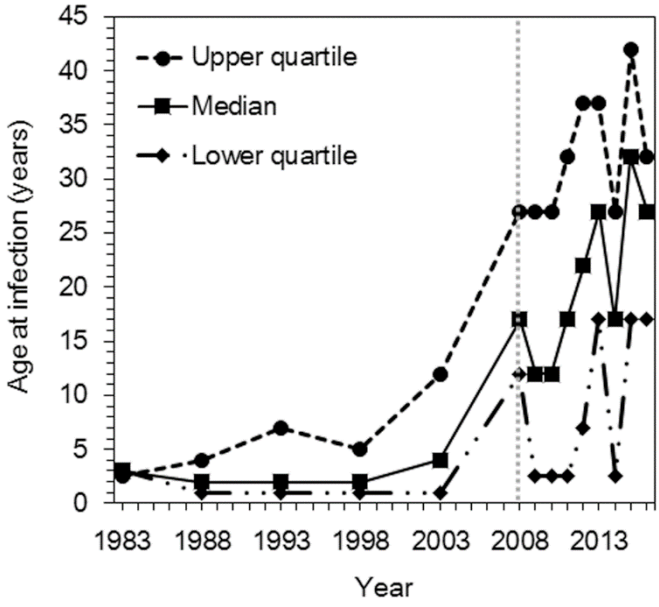

Figure 8. Age at infection with measles in Japan. Age at infection of notified measles cases in Japan from 1983–2016. The dotted line with circles represents the 75th centile of the age distribution of cases, the bold line with squares indicates the median, and the broken line with diamonds represents the 25th centile. The data are not continuous because the discrete age category of cases in the reporting system was not consistent throughout the time period. Before 2008 (vertical dotted gray line), the surveillance of measles was sentinel and was divided into childhood measles (below 18 years old) and adult measles (over 18 years old). In and after 2008 (vertical dotted gray line), the surveillance was drastically revised to enforce the reporting of all cases in one category, regardless of age.

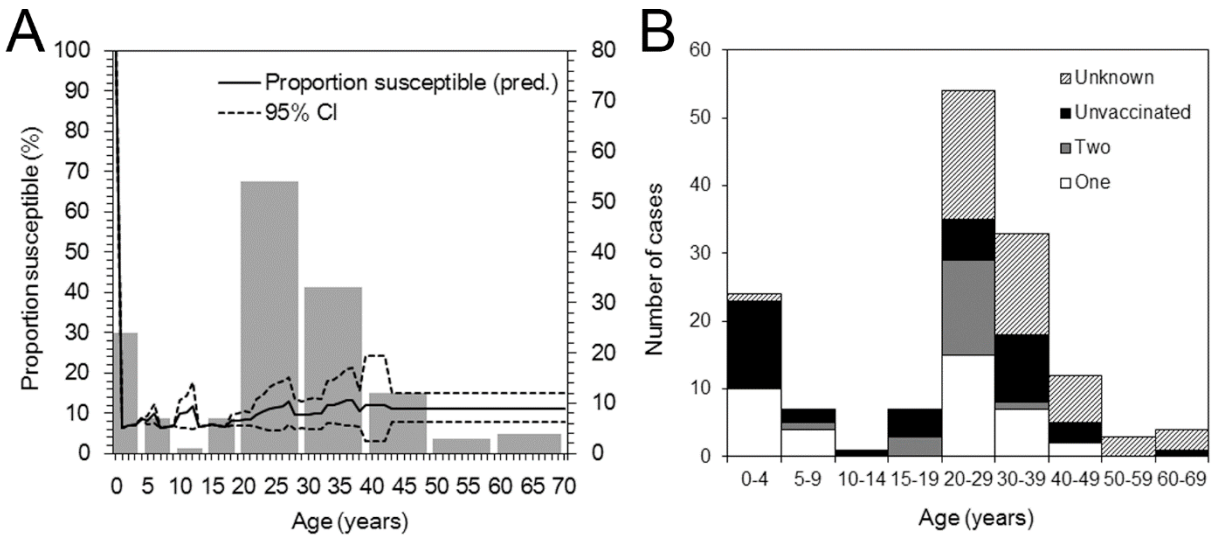

Figure 9. Age distribution of measles cases in 2016, Japan. (A) Proportion susceptible and the age distribution of measles cases during the outbreak in 2016, Japan. The proportion susceptible in scenario 1 was plotted by taking one minus the estimated proportion immune (left vertical axis). The age distribution of cases is measured on the right vertical axis. Since the original data was sorted into age groups, the width of the bars corresponds to cases compiled in the recorded age groups. (B) Age distribution of measles cases by vaccination history.

Discussion

The present study assessed the herd immunity against measles in Japan, using both vaccination and seroepidemiological data. Incorporating the cumulative distribution of vaccine uptake and addressing vaccination failures in the proposed immune fraction model, we first estimated the proportion immune owing to vaccine-induced immunity. By additionally accounting for natural infection among unvaccinated individuals, the total fraction of the population immune was quantified. We have been able to identify that the immune fraction hardly reached 90%–95% and the estimated effective reproduction number appeared to take values above 1 in the present day.

We identified a particularly susceptible cohort with insufficient immunity among those aged from 20 to 49 years in 2016. The fact that this cohort has insufficient herd immunity, in addition to analysis of case data, demonstrated that the age at infection has increased over time in Japan. Mass vaccination reduces the force of infection, and consequently raises the age at infection (Anderson and May, 1985). Moreover, those who missed the chance to be vaccinated can grow older without acquired immunity, allowing the risk of infection to be maintained among older age groups. Age at infection is an important determinant for disease severity; the probability of acute measles death is higher, especially among adults (Fefferman and Naumova, 2015; Miller and Gay, 1997).

Our modeling approach showed that the effective reproduction number of measles in the present year (2016) is above the value of 1. The estimated proportion susceptible by age roughly synchronized with the age distribution of notified cases in 2016. To construct the herd immunity against measles, the proportion immune should be maintained roughly above 90%–95% and that level should ideally be sustained across age groups (Fine et al., 2011). Whereas Japan has been verified to have eliminated endemic measles virus transmission, the country would continue to be vulnerable to measles importation without implementation of supplementary vaccination among susceptible adults. $R_v>1$ indicates that there could be a large scale epidemic if infected individuals are not properly diagnosed and their contact not restricted.

Owing to the highly contagious nature of measles, implementing supplemental vaccination so as to raise the proportion immune to achieve 90%–95% is ideal; however, such a measure can involve a large investment. Moreover, measles vaccination is not mandated in Japan. These factors make the full construction of herd immunity against measles too ambitious. Considering that importation of the virus is likely to continue, expeditiously interrupting continuous transmission while building up herd immunity would be achievable by enhancing contact tracing and case isolation. When advising supplementary vaccination among adults, it is essential to routinely monitor immunity among populations at risk (Farrington et al., 2003; Gay et al., 2004), to allow for fast and effective contact tracing response to minor outbreaks.

An advantage of our approach was that the herd immunity level in Japan was quantified using both vaccination and seroepidemiological data (Plans-Rubió, 2012). Table 2 shows the pros and cons for monitoring the level of herd immunity using either vaccination coverage or seroepidemiological data alone to assess the vaccination program. While relying on either of these data has known drawbacks, we have shown that the immune fraction could be better estimated using both datasets, as has been similarly carried out elsewhere (Gay et al., 1995; Wood et al., 2009). As part of policy evaluation, we believe that the proposed modeling approach could supplement routine monitoring of herd immunity. It is noteworthy that the effect of a second dose of measles vaccine is expected to be greater if the vaccine reaches previously unvaccinated children (i.e. random distribution) than it reaches only children who received a primary vaccination. Theoretically, it is more efficient if vaccination services explore and prioritize previously unvaccinated naïve children to undertake the immunization.

Several limitations must be noted. First, we discarded two important opportunities in the age- and time-dependent dynamics of immune population. Namely, our modeling approach was not able to incorporate naturally acquired immunity and booster events among vaccinated individuals owing to limitations in quantifying natural exposure among them. Incorporating these features likely requires additional pieces of data (e.g., time series of measles cases); validating an

advanced model with these features will be the subject of future studies. Second, geospatial dynamics was not incorporated in the estimation of R_v. While our results may be useful for considering the vaccination policy for the entire Japan, the model has not been extended to evaluation at a local level. If a certain geographic area with very low vaccination coverage (e.g. due to refusal to undertake vaccination (Gastañaduy et al., 2016)) exists, that pocket of susceptibles appears to be at risk of an epidemic, and such hotspot has not been captured by our analysis. Third, our result may be biased by using specific fixed parameters for describing vaccination failures and also by using specific cutoff values of PA antibody titers. Such uncertainty cannot be fully overcome. At a minimum, we examined the sensitivity of estimated fraction immune to variations in associated parameters.

Despite these issues, the present study has thoroughly assessed the herd immunity to measles in Japan, indicating the possibility for measles outbreaks to continue in future decades. It is likely that importation events will continue in the country, which will call for fast and prompt contact tracing. While the goal of 90%–95% proportion immune is very difficult to achieve in any country, we have demonstrated that supplementary vaccination of adults aged 20–49 years could be highly beneficial.

Appendix

The immune fraction owing to primary vaccination for birth year y at present year t was calculated as

$$p_{y,t} = \frac{\sum_{n=1}^{3} V_{y+(n-1)} f_{n,y+n} \alpha_1 \left[b \exp(-\delta(t-(y+n)) + (1-b) \right]}{N_{y,1}}, \qquad \text{(A1)}$$

where V_y is the count of primary vaccinations in year y, and $f_{\mathrm{n,y+n}}$ is the probability mass function of vaccine uptake among those aged n in year $y+n$; α_1 is the success fraction of primary vaccination, i.e., one minus primary vaccination failure, assumed as 0.965 (Watson et al., 1998); b is the proportion to experience waning assumed at 6% (Wood et al., 2009); and δ is the rate at which vaccine-induced immunity wanes, assumed as 0.09/year (Davidkin et al., 2008). The

population size as of the age of 1 year was used as the population size in the denominator $N_{y,1}$ for each cohort born in year *y*, since a non-negligible number of deaths occur during the first year of life. In equation (A1), the summation in the numerator of right-hand side is taken from 1 to 3, because cumulative age distribution of vaccination is plateaued by 3 years old. Parameters that we used are given as a list in Table 1.

We then calculate the immune fraction attributable to the second dose. In scenario 1, there are three possible combinations of vaccination history: (i) the proportion immune from primary vaccination but that did not receive revaccination, (ii) the proportion immune from primary vaccination that were also revaccinated, and (iii) the proportion whose immunity owing to primary vaccination was lost but that were boosted owing to a second dose. These are respectively described as

$$q_{y,t,1} = p_{y,t}\left(1-\frac{S_{y+a}}{\sum_{n=1}^{3} V_{y+(n-1)} f_{n,y+n}}\right), \tag{A2}$$

$$q_{y,t,2} = p_{y,t}\frac{S_{y+a}\alpha_2\left[b\exp\left[-\delta(t-(y+a))+(1-b)\right]\right]}{\sum_{n=1}^{3} V_{y+(n-1)} f_n}, \tag{A3}$$

$$q_{y,t,3} = \frac{\sum_{n=1}^{3} V_{y+(n-1)} f_n\left[1-\alpha_1\left[b\exp(-\delta(t-(y+n))+(1-b)\right]\right]}{N_{y,1}}\frac{S_{y+a}\alpha_2\left[b\exp\left[-\delta(t-(y+a))+(1-b)\right]\right]}{\sum_{n=1}^{3} V_{y+(n-1)} f_n}, \tag{A4}$$

where S_{y+a} is the count of second doses in year *y* and implemented at age *a*; and α_2 is the success rate of revaccination (i.e., 1 minus vaccination failure), assumed as 0.99 (Watson et al., 1998). Other parameters were assumed to be identical to those used during primary vaccination. Consequently, in scenario 1, the total proportion immune among those with birth year *y* in calendar year *t* owing to vaccination is given by,

$$u_{y,t} = \sum_{h=1}^{3} q_{y,t,h}\,. \tag{A5}$$

In scenario 2, we account for a possibility that the vaccine prepared as a second dose acts as a primary vaccination. Under this scenario, there are four different possible combinations of vaccination status, i.e., (i) the proportion immune from primary vaccination that did not receive revaccination, (ii) the proportion immune from primary vaccination and also revaccination, (iii) the proportion whose immunity owing to primary vaccination was lost but were boosted with a second dose, and (iv) the proportion of those that missed primary vaccination and received a second dose for the first time as primary vaccination. These are modeled as

$$r_{y,t,1} = p_{y,t}\left(1-\frac{S_{y+a}}{N_{y,a}}\right), \tag{A6}$$

$$r_{y,t,2} = p_{y,t}\frac{S_{y+a}\alpha_2\left[b\exp\left[-\delta(t-(y+a))+(1-b)\right]\right]}{N_{y,a}}, \tag{A7}$$

$$r_{y,t,3} = \frac{\sum_{n=1}^{3} V_{y+(n-1)} f_n\left[1-\alpha_1\left[b\exp(-\delta(t-(y+n))+(1-b)\right]\right]}{N_{y,1}}\frac{S_{y+a}\alpha_2\left[b\exp\left[-\delta(t-(y+a))+(1-b)\right]\right]}{N_{y,a}}, \tag{A8}$$

$$r_{y,t,4} = \left[1-\frac{\sum_{n=1}^{3} V_{y+(n-1)} f_{n,y+n}\alpha_1}{N_{y,1}}\right]\frac{S_{y+a}\alpha_2\left[b\exp(-\delta(y+a)+(1-b)\right]}{N_{y,a}}. \tag{A9}$$

Parameter values are identical to those used for scenario 1. Note that the denominator in scenario 1 is the population size of primary-vaccinated individuals whereas that in scenario 2 is the population size owing to the random nature of a second dose. The total proportion immune owing to vaccination in scenario 2 is given by

$$w_{y,t} = \sum_{h=1}^{4} r_{y,t,h}\,. \tag{A10}$$

Because those who remained unvaccinated could acquire immunity owing to natural infection, vaccination coverage data cannot fully capture the immune fraction at the population level; thus, we additionally account for immunity owing to natural infection among unvaccinated individuals. The proportion receiving vaccination at least once in scenarios 1 and 2 are respectively given as

$$h_{y,t} = \frac{\sum_{n=1}^{3} V_{y+(n-1)} f_{n,y+n}}{N_{y,1}}, \quad \text{(A11)}$$

$$g_{y,t} = \left(\frac{\sum_{n=1}^{3} V_{y+(n-1)} f_{n,y+n}}{N_{y,1}} + \frac{S_{y+a}}{N_{y,a}} \right) - \left(\frac{\sum_{n=1}^{3} V_{y+(n-1)} f_{n}}{N_{y,1}} \frac{S_{y+a}}{N_{y,a}} \right). \quad \text{(A12)}$$

The seropositive fraction was then incorporated in these scenarios as

$$x_{y,t,booster} = u_{y,t} + (1 - h_{y,t}) m_{a,t}, \quad \text{(A13)}$$

$$x_{y,t,random} = w_{y,t} + (1 - g_{y,t}) m_{a,t}, \quad \text{(A14)}$$

where $m_{a,t}$ represents the proportion seropositive among unvaccinated individuals at age a in year t.

Because the latest seroepidemiological dataset available was derived from a survey in 2013, the proportion seropositive in later years was shifted right to the required number of years, assuming that the acquiring of immunity from natural infection was limited owing to a greatly reduced chance of natural infection (Figure 4A–4D).

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Conclusion

In Japan, continuous effort to elevate vaccination coverage via routine vaccination program has contributed to maintain sufficient population immunity among children. However, a substantial number of adult cohorts have been left without the chance of acquiring immunity, contributing to maintain the risk of rubella and measles outbreak. In the present day, multiple chains of transmission are observed for both rubella and measles in Japan, and cases are concentrated among adults. By assessing herd immunity against rubella and measles by age and gender in Japan, the characteristics of risk groups that are vulnerable to infection were identified, and the extent of the vulnerability was quantified by estimating R_e. In this way, we successfully verified whether supplementary immunization is required to prevent a major epidemic.

For rubella, from 1976 to 1995, only teenage women were routinely vaccinated to prevent CRS. This was the immunization program targeting individual risk populations only, and thus, male born in the corresponding year only had the opportunity to acquire immunity by natural infection. Compared with female, the immune fraction is low, contributing to dominate rubella transmission in Japan among male. Due to insufficient herd immunity, the force of infection has weakened, contributing to increasing mean age at infection over time. While the fraction of infected women was small compared to male, the increase in age at infection allowed infection among women to concentrate in childbearing age. This has contributed to observe 45 diagnosed cases of CRS cases in the 2012-2014 rubella epidemic. Insufficient vaccination may have contributed to increasing the disease burden, and supplementary immunization to fill the susceptible pocket may be beneficial to mitigate the risk of CRS.

For measles, from 1978, routine vaccination has been implemented for both male and female. A second dose regimen has been introduced to only for birth cohorts born in and after 1990. Using vaccination coverage data accounting for primary and secondary vaccination failure, and by calibrating it with seroepidemiological data of unvaccinated individuals, the proportion immune was calculated. Moreover, since the second dose may be delivered at random or to previously

vaccinated individuals, we computed the proportion immune in two different scenarios. We identified that those born before 1990 has a higher risk to measles infection. Since the R_e was above the value of 1, this study has shown that supplementary vaccination is necessary to elevate herd immunity. Furthermore, when we estimate the R_e in 2030 assuming the vaccination strategy is maintained, the R_e is still maintained above the value of 1, indicating the probability of measles epidemic to continue in the future without supplementary immunization.

While the seroepidemiological analysis successfully identified the susceptible pocket by age and gender for measles and rubella, geospatial dynamics has been ignored. Sine both rubella and measles cases were concentrated in the urban area, analyzing the spatial susceptibility and incorporating the risk of importation may improve planning vaccination strategies. The spatiotemporal analysis of susceptibles and locations at risk of epidemic is my ongoing research.

Despite the remained task for future, the present dissertation has identified that both rubella and measles epidemic will continue without the implementation of supplementary vaccination. In 2019, supplementary vaccination against rubella has started for male born in 1962 to 1979, while no more than 10% of the targeted population tested their antibody titer to verify whether vaccination is necessary. As of December 18, 2019, measles notification has reached 742 in the country, which is the highest number of cases in a year since the declaration of local elimination of measles in Japan in 2015. The situation with a shortage of herd immunity is expected to continue in Japan, unless drastic supplementary immunization campaigns are conceived, accounting for the series of studies that went into this dissertation.

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Conflicts of interest

The author declares no conflict of interest.

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