International Journal of Infectious Diseases 82 (2019) 1–5

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Predicting congenital rubella syndrome in Japan, 2018–2019

Hyojung Lee[a,b], Taishi Kayano[a,b], Hiroshi Nishiura[a,b,*]

[a] Graduate School of Medicine, Hokkaido University, Kita 15-Jo Nishi 7-Chome, Kita-ku, Sapporo-shi, Hokkaido 060-8638, Japan
[b] CREST, Japan Science and Technology Agency, Honcho 4-1-8, Kawaguchi, Saitama, 332-0012 Japan

ARTICLE INFO

Article history:
Received 27 December 2018
Received in revised form 18 February 2019
Accepted 18 February 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Rubella virus
Statistical model
Forecasting
Outbreak
Epidemiology
Prediction
Japan

ABSTRACT

Objectives: A rubella epidemic has been ongoing in Japan since August 2018. In the present study, we aimed to predict the likely size of a congenital rubella syndrome (CRS) epidemic during 2018–19.
Methods: The expected number of CRS cases was estimated using an integral equation based on age-specific incidence of rubella among adult women, the time delay from gestational age of infection to diagnosis of CRS, and distribution of the mothers' age at delivery. We used epidemic data during 2012–14 to parameterize the model and applied this in the prediction for 2018–19.
Results: In analyzing the 2012–14 epidemic data, the mean delay from the mother's infection to diagnosis was estimated at 24.2 weeks (95% confidence interval (CI): 20.7, 28.1). Applying the parameterized model, together with the more than 480 rubella cases in women in 2018 as well as delayed mother's age at delivery in 2017, we determined that the expected number of CRS cases would be 9.7 (95% CI: 6.5, 12.5) cases. As the epidemic is ongoing, the cumulative number of CRS cases could potentially reach 96.8 (95% CI: 65.3, 125.5) cases, if rubella cases in adult women rose to 10 times the number by week 49 in 2018.
Conclusions: CRS is expected to occur an average of 24 weeks following the mother's infection with rubella virus. Accounting for an increase to 650 cases in women by week 5 in 2019, the expected number of CRS cases during 2018–19 has already exceeded 13 cases, as of week 5 in 2019.

Introduction

Rubella is a vaccine-preventable infectious disease caused by rubella virus. Once infected, a certain proportion of people remain asymptomatic; symptomatic patients develop a rash (exanthem) on the face, spreading to the trunk and limbs, which usually fades after 3 days (Menser et al., 1978). Other symptoms include low-grade fever, lymphadenopathy, and joint pain, among others. The symptoms are mostly self-limiting; however, if pregnant women are infected, the virus can be transmitted to the fetus via the placenta, resulting in congenital rubella syndrome (CRS) (Tang et al., 2003). CRS is the most severe sequela of rubella, involving congenital cardiac, cerebral, ophthalmic, and auditory defects (Duszak, 2009; Lambert et al., 2015). To control rubella, vaccination is required (Zanetta et al., 2003; Wesolowski et al., 2016). As vaccination could elevate the age at infection (Amaku et al., 2003; Berger et al., 2011; Mossong et al., 2008; Tanaka et al., 2017; Saito et al., 2018), controversial routine immunization with low vaccination coverage is known to be accompanied by an increase in CRS (Best et al., 2005; Chua et al., 2015; Panagiotopoulos et al., 1999). To eliminate rubella by means of mass vaccination, high coverage of the entire population is required to attain sufficient herd immunity (Anderson and Grenfell, 1986; Massad et al., 1995; Panagiotopoulos et al., 1999; Cutts et al., 2013).

Since 1993, Japan has adopted a mass vaccination policy with the measles–rubella (MR) vaccine in children. Prior to 1993, only female students in junior high school were subject to vaccination, aiming for individual protection against CRS. Although Japan is on its way to achieving substantial herd immunity to prevent rubella epidemics (Kinoshita and Nishiura, 2016), adult men aged 39–56 years are known to have missed vaccination in childhood, and those aged 28–38 years have only had the opportunity for one vaccination dose. As a consequence, the country remains prone to imported cases and experienced a rubella epidemic during 2012–14 (Mori et al., 2017). Moreover, owing to the absence of an identifiable increase in the proportion of rubella antibody-positive individuals following the 2012–14 epidemic (Nishiura et al., 2015), another epidemic began in August 2018. Because the remaining susceptible people are adult male, and owing to the elevated age at infection over time, cases during both the 2012–14 epidemic and the ongoing 2018 epidemic are most frequently seen in adults (Kinoshita and Nishiura, 2016; National Institute of Infectious

* Corresponding author.
E-mail address: nishiurah@med.hokudai.ac.jp (H. Nishiura).

https://doi.org/10.1016/j.ijid.2019.02.021

Diseases, 2018). Cases have been observed at a higher frequency among men aged 30–59 years and among women aged 20–39 years than in other age groups. As a possible countermeasure to the gap induced by time-dependent vaccination policies, catch-up vaccination of men aged 39–56 years is planned in 2019.

Despite vaccination scheduled for the near future, it is unlikely that the new vaccination program will commence until the new fiscal year in Japan, namely, in April 2019. Thus, the first wave of the ongoing rubella epidemic will occur before interventions can be implemented to elevate herd immunity, which would protect susceptible adult men. Japan manufactures the rubella vaccine domestically; thus, immediate importation of the measles–mumps–rubella (MMR) vaccine, as part of real-time intervention, has not been considered a realistic option. Accordingly, it is critical to anticipate the size of the potential epidemic, especially the cumulative number of CRS cases. A total of 45 confirmed cases of CRS were diagnosed during 2012–14 in Japan. Ironically, this epidemic provided the measurable data needed to precisely anticipate the likely number of CRS cases during the ongoing 2018–19 epidemic.

The purpose of the present study is to predict the extent of CRS in real time in Japan, using a mathematical model, explicitly accounting for the delayed age at delivery and elevated age at infection among pregnant women.

Methods

Epidemiological data

The present study rests on publicly available epidemiological datasets (National Institute of Infectious Diseases, 2014, 2018). In Japan, rubella and CRS are classified as category V diseases according to the Infectious Diseases Law, mandating all physicians to notify diagnosed cases to the government via local health centers. A rubella case is clinically defined as one that satisfies at least one of the following conditions: a generalized rash, fever, or lymphadenopathy. From 2018, all clinically suspected cases are subject to laboratory confirmation by PCR. CRS is defined as a case satisfying at least one of the following: cataract or congenital glaucoma, congenital heart disease, deafness or hearing loss, pigmentary retinopathy, purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent lesion in bone, or jaundice within 24 h of birth. Similar to a rubella diagnosis, clinically suspected cases of CRS are subject to PCR testing for confirmation. To predict CRS cases using rubella case data for 2018–19, we first quantified the dynamics during the 2012–14 epidemic. We collected datasets from both 2012–14 and 2018–19. Rubella case data were stratified by age group and sex. During 2018–19, there have been no reported CRS cases as of 25 December 2018; the collected CRS data were only from 2012 to 2014.

To capture age at delivery among pregnant women in relation to the age distribution of rubella cases among adult women, we also extracted the distribution of mothers' age at live birth from the vital statistics of Japan (Statistics Bureau, 2018). The average distribution of age at delivery from 2012 to 2014 was used to capture the CRS risk during the 2012–14 epidemic; we compensated the 2017 distribution as an approximation in the prediction for 2018–19 (Figure 1A).

For both rubella cases and vital statistics, the empirical data were recorded as discrete age-grouped data, every 5 years. Accordingly, age- and sex-specific rubella cases were divided into nine age groups, i.e., men and women aged <15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, and ≥50 years.

Statistical model

During the 2012–2014 epidemic, a total of 12,614 cases of rubella (including 2922 among female patients) and 45 cases of CRS were confirmed and notified (Figure 1B). The highest weekly number of CRS cases was observed in 32 weeks following the highest weekly incidence of rubella cases. The expected number of CRS cases in week t, c_t, accounting for the gap period between rubella in the mother and incidence of CRS, is described as

$$E(c_t) = p\sum_{\tau=1}^{t-1}\sum_{a=1}^{n_a} i_a(t-\tau)g_\tau b_a, \quad (1)$$

where, p is the scaling parameter, $i_a(t)$ is the incidence of rubella in women of age group a in week t, n_a is the total number of age groups (i.e., $n_a = 9$), g_τ is the probability density of the time from rubella virus infection in the mother to diagnosis of CRS, and b_a is the probability mass function of the mother's age at live birth as a function of age group a. The parameter p is not strictly interpretable, but this single parameter encompasses (i) the probability that a woman is pregnant at a given point in time, (ii) the probability that the pregnant woman is exposed in a particular week (e.g. 16 weeks at high risk of CRS out of 52 weeks per year), (iii) the probability that the virus is transmitted from mother to fetus, (iv) the probability that the infected fetus results in successful delivery (i.e. livebirth), and (v) the probability that the congenital disorders were successfully attributed to rubella infection and finally notified to the government (i.e. ascertainment bias). Similar but differently formulated models of CRS have been described elsewhere (Gao et al., 2013; Ohkusa et al., 2014; Vynnycky et al., 2016; Miyakawa et al. 2014; Cutts and Vynnycky,

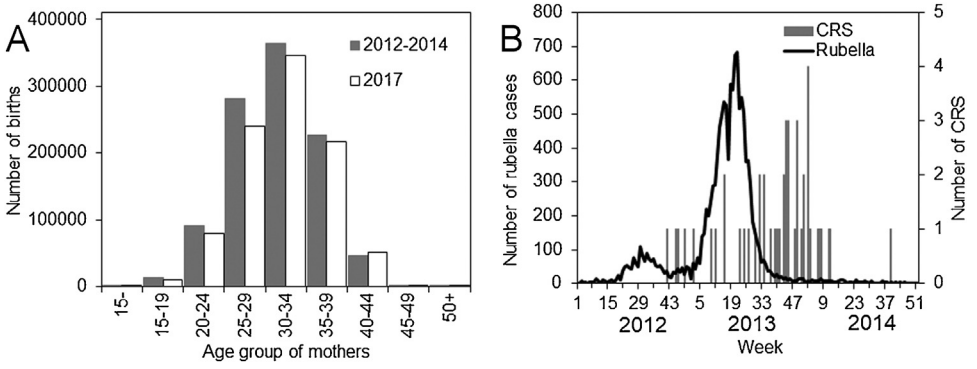

Figure 1. Mothers' age at live birth and temporal distribution of 2012–2014 rubella epidemic in Japan. (A) The distribution of mothers' age at delivery. The corresponding distribution during 2012–14 was the average mothers' age at live birth from 2012 to 2014 (gray). The same distribution in 2017 was used to substitute 2018–19 in the present study (white). (B) Epidemic curves of rubella and congenital rubella syndrome during 2012–14, Japan. The solid line represents rubella cases, and bars indicate congenital rubella syndrome (measured on right vertical axis).

1999). Among these, Miyakawa et al. (2014) calculated the incidence of CRS per 100,000 live births in Vietnam using seroprevalence data. In a similar manner, congenital Zika syndrome with the risk of microcephaly (França et al., 2016) was modeled using the integral equation method (Keegan et al., 2017; Nishiura et al., 2016).

In the present study, g_τ was assumed to follow a gamma distribution with mean μ and standard deviation σ. We assumed that the incidence of CRS (i.e., c_t,) in week t is sufficiently characterized by a zero-inflated Poisson distribution with the probability of extra zeros (denoted π) because there are a substantial number of weeks in which the CRS case count is zero whereas the predicted mean number of CRS cases is non-zero. We used the maximum likelihood method to estimate unknown parameters, $\theta = \{p, \mu, \sigma, \pi\}$ using datasets of (i) rubella and CRS during 2012–14 and (ii) the number of live births during 2012–14 according to mothers' age. Calendar weeks were divided into two groups according to the absence (i.e., $T_0 = \{t; c_t = 0\}$) or presence (i.e., $T_1 = \{t; c_t > 0\}$) of CRS. The likelihood function is

$$L(\theta; \boldsymbol{c}_t) = \prod_{i \in T_0} \left(\pi + (1-\pi)e^{-E(c_i)}\right) \prod_{j \in T_1} (1-\pi) \frac{E(c_j)^{c_j} e^{-E(c_j)}}{c_j!}. \quad (2)$$

The negative logarithm of Eq. (2) was minimized to estimate parameters.

Subsequently, predictions were made for 2018–19 using the datasets of rubella in women and the distribution of mothers' age in 2017. Using the resampled parameter sets (θ^*) for 10,000 times that follow a multivariate normal distribution, which is informed by the maximum likelihood estimate and covariance matrix, and using the zero-inflated Poisson distribution, we computed the predicted number of CRS cases during 2018–29. The 95% prediction intervals were computed by taking the 2.5th and 97.5th percentiles of the simulated value in each future week. We used rubella data up to the latest time point (i.e., week 49 in 2018), with the cumulative number of 486 cases in women. By week 5 in 2019, there has been a cumulative total of 650 cases in women from 2018–19, which we used for discussion to update our estimate.

For sensitivity analysis, the cumulative number of CRS cases during the 2018–19 epidemic was calculated as

$$C = p\kappa \sum_{a=1}^{n_a} I_a b_a, \quad (3)$$

where, C and I_a are the cumulative number of CRS and rubella cases among women in age group a, respectively. The epidemic size from 2018–19 must be greater than what has already been observed by week 49 in 2018, but the exact size would not be known. Thus, we examined several scenarios with different epidemic sizes and varied a parameter κ to scale the number of rubella cases in women compared with what has been observed by week 49 in 2018.

Ethical approval

The present study used publicly available data (National Institute of Infectious Diseases, 2014, 2018; Statistics Bureau, 2018). The datasets had already been fully anonymized and did not include any identity information. Thus, ethical approval was not required for the analysis.

Data sharing policy

Rubella and CRS data are accessible (National Institute of Infectious Diseases, 2014, 2018; Statistics Bureau, 2018). A summary of the secondary datasets that were analyzed in the present study can be shared by the corresponding author upon request.

Results

Figure 2 compares the observed and predicted incidence of CRS during 2012–14. Except for 2 weeks (week 16 in 2013 and week 2 in 2014), all observed cases of CRS were correctly captured within the 95% confidence intervals. Parameter estimates are summarized in Table 1. The cumulative number of CRS cases was estimated at 46.2 (95% CI: 31.2, 59.9) cases, very close to the total of 45 notifications during 2012–14. The mean and standard deviation of the time from rubella virus infection in the mother to CRS in the offspring was 24.2 weeks (95% confidence interval (CI): 20.7, 28.1) and 7.0 weeks (95% CI: 4.1, 11.9), respectively. To scale female rubella cases and CRS, the scaling parameter p was estimated at 0.16 (95% CI: 0.10, 0.24), indicating that the CRS case count was scaled as 0.16 times smaller than that of female rubella cases. The probability of zeros (π) was estimated to be 0.14 (95% CI: 0.01, 0.63), with a wide confidence interval.

Figure 3A shows the predicted CRS incidence from week 1 in 2018 to week 23 in 2020. A total of 486 rubella cases in women were reported by week 49 in 2018. Given the observed count by week 49 in 2018, the rubella incidence among women already peaked at week 41 in 2018; we predict that the peak of CRS will be seen in week 12 of 2019. Figure 3B shows the prediction intervals. Using all observed rubella cases in women by week 49 in 2018, a total of 9.7 CRS reports (95% CI: 6.5, 12.5) are anticipated during 2018–19. Accounting for the increase of rubella cases in women to 650 by week 5, 2019, we anticipate at least a total of 13.0 CRS cases. From week 46 in 2018 to week 4 in 2019, the upper 95% prediction interval is one case of CRS per week; subsequently, there could be up to two CRS notifications per week by week 23 in 2019.

The present prediction should be regarded as the minimum bound because it rests on previously observed rubella incidence. By varying κ values from 1 to 10, Table 2 presents the possible scenarios. If the rubella epidemic begins to grow again in 2019 and the epidemic size of cases among women increases to 10 times that in week 49 of 2018, the cumulative number of CRS reports could be as high as 96.8 (95% CI: 65.3, 125.5) cases.

Discussion

In the present study, we analyzed two recent epidemics of rubella in Japan during 2012–14 and in 2018. We devised an

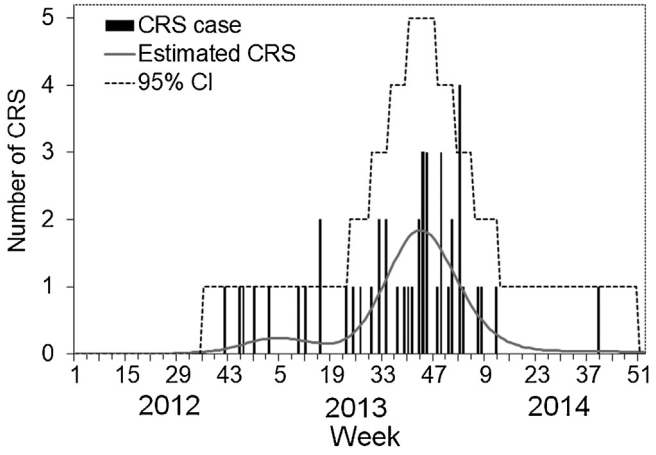

Figure 2. Comparison of observed and predicted congenital rubella syndrome (CRS) cases during 2012–2014.
Black bars represent observed CRS cases during 2012–14. Dashed line indicates the upper 95% prediction interval of CRS and the lower bound is zero. Smooth gray line shows the computed mean number of CRS cases, as predicted from the number of rubella cases in women.

Table 1
Estimated parameter values.

Notation	Description	Mean	95% CI[a]
$p \times 100$	Scaling factor of the CRS adjusted to the calculated total of rubella in females	15.8	10.2, 24.5
μ	Mean time delay from mother's infection to diagnosis (weeks)	24.2	20.7, 28.1
σ	Standard deviation of the time delay from mother's infection to diagnosis (weeks)	7.0	4.1, 11.9
κ	Ratio of the cumulative number of rubella cases in female to the observed cases by week 49, 2018	See Table 2	
$\pi \times 100$	Probability of extra zeros for the zero-inflated Poisson distribution (%)	13.8	1.5, 62.7

[a] Confidence intervals (CIs) computed using the profile likelihood.

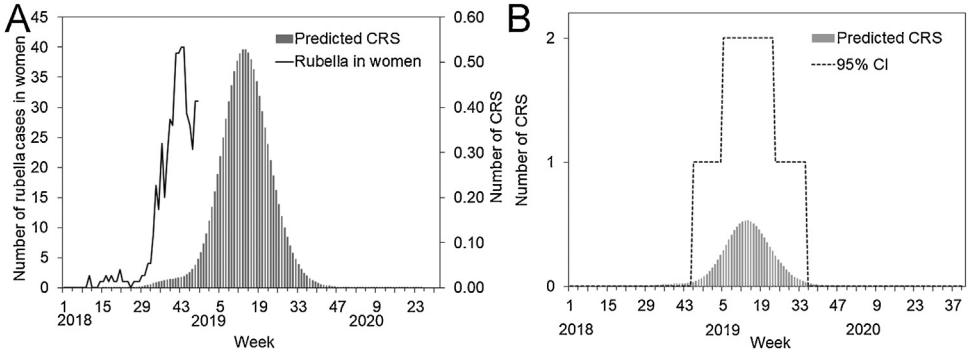

Figure 3. Predicted congenital rubella syndrome epidemic during 2018–19. (A) Observed epidemic curves of rubella and predicted congenital rubella syndrome from 2018–19. Black bars represent predicted CRS cases. (B) Minimum bound of predicted congenital rubella syndrome during 2018–19. Dashed line indicates the upper 95% prediction interval of CRS and the lower bound is zero. Gray bars show the computed mean number of CRS cases, as predicted from the number of rubella cases in women.

Table 2
Predicted cumulative total congenital rubella syndrome cases in Japan, 2018–2019.

κ (Ratio of the cumulative number of rubella cases in female to the observed cases by week 49, 2018)	Cumulative # of congenital rubella syndrome	95% CI[a]
1	9.7	6.5, 12.5
2	19.4	13.1, 25.1
3	29.0	19.6, 37.6
4	38.7	26.1, 50.2
5	48.4	32.7, 62.7
6	58.1	39.2, 75.3
7	67.8	45.7, 87.8
8	77.4	52.2, 100.4
9	87.1	58.8, 112.9
10	96.8	65.3, 125.5

[a] Confidence intervals (CIs) computed using the bootstrap method.

integral equation model to predict CRS incidence owing to rubella in pregnant women, accounting for the time delay from the mother's infection to CRS diagnosis and incorporating the distribution of mothers' age at delivery. Using data of an earlier epidemic during 2012–14, our prediction model was parameterized with the estimation that mean delay from mothers' infection to CRS was 24.2 weeks. Subsequently, the anticipated size of a CRS epidemic during 2018–19 was computed. Given a total of 650 rubella cases in women by week 5 in 2019, there would already be 13.0 cases of CRS to be reported in 2019, and given additional rubella cases in adult women, the expected number of CRS cases is likely to increase (Table 2).

As a key contribution of the present study, we parameterized the CRS model using past epidemic data from 2012 to 2014; even with no observed CRS cases during 2018–19, prediction could be carried out. To predict future CRS cases with no observed CRS cases in the ongoing epidemic, we used an age-specific integral equation modeling approach that accounts for both mothers' chronological age and gestational age. The previous epidemic offered us the opportunity to sufficiently quantify the underlying mechanisms using chronological age and gestational age, allowing reasonable prediction in real time. If the ongoing epidemic is not sufficiently controlled, the cumulative number of CRS cases during 2018–19 is expected to increase. Given that the present rubella epidemic is ongoing, it is of utmost importance to vaccinate either susceptible men to elevate herd immunity or susceptible women who expect to become pregnant. Our model assessment of the size of a CRS epidemic under various vaccination scenarios can be used in health policy decision-making in the future. Different scenarios can be analyzed, depending on the cumulative size of the ongoing rubella among susceptible adult women and also depending on different vaccination scenarios.

Considering the 45 confirmed CRS cases during 2012–14 and 2922 female rubella cases yields a ratio of 45/2922 = 0.0154, a more simplistic ratio-based calculation in 2018 using the current 486 rubella cases reported among women yields 7.5 CRS cases. Moreover, considering that Japan is a rapidly aging society with an ultra-low fertility rate, the decline in the absolute number of live births, from an average 1,023,526 in 2012–2014 to 946,066 in 2017, should result in fewer than 7.5 CRS cases. The reason for obtaining the predicted value of 9.7 CRS cases in the present study can be explained by the growing tendency among Japanese people in the past 5 years to delay marriage. The proportion of mothers aged in their 30 s and 40 s at delivery has increased from an average 62.3% in 2012–14 to 65.1% in 2017; the age of women who are infected with rubella virus has also increased in the past 5 years. The proposed model had the advantage that it can appropriately capture such demographic changes when estimating CRS, despite a gap as long as 5 years between the previous epidemic and that in 2018.

The use of the zero-inflated Poisson distribution is also useful for describing a scant number of CRS cases with many zero-count weeks in real time, while appropriately capturing the temporal pattern of non-zero weeks, as informed by rubella cases in women. Using this scheme, it is theoretically possible to classify CRS according to the type of complication. That is, depending on gestational age at infection, the pregnancy outcome would vary, as

would the range of congenital malformations; these patterns could also potentially be captured using the proposed modeling scheme.

The present study involved several limitations that must be briefly described here. First, we analyzed only 2012–14 epidemic data to parameterize the model and did not account for earlier epidemics; this is because CRS surveillance was not necessarily equally intensified during earlier epidemic periods. Second, as yet, CRS has been absent in the 2018 epidemic; incorporation of reported CRS cases in the future could improve prediction. Third, we used the distribution of mothers' age at live birth in 2017 as applicable to 2018–19; however, strictly speaking, the total number of births would be smaller during 2018–19 than in 2017 and the mother's age at delivery is likely to be older. Fourth, our simplified model relied on observed rubella cases in women and did not forecast CRS using the predicted rubella epidemic. Rather than the scenario analysis presented in Table 2, accounting for the transmission dynamics that involve men is required, for more precise temporal predictions. Fifth, CRS is likely underreported (Panagiotopoulos et al., 1999; Giambi et al., 2017), but our study had to rely on empirically observed data.

Despite these limitations, we believe that the present study successfully shows that about 13 CRS cases can already be expected during 2018–19. Scenario analysis of the impact of interventions on the cumulative number of CRS cases can be conducted using our proposed model.

During the preparatory phase of this study, there was a notification of first CRS in a baby boy in week 4, 2019, which is in line with our forecast. We did not incorporate this observation into our forecasting with some revision of the likelihood, because the incorporation of only 1 case in forecasting exercise does not necessarily reduce associated uncertainties. Post-epidemic evaluation with updated estimates will follow.

Funding

This work was supported as follows. HL received funding from the JSPS Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers. HN received funding from the Japan Agency for Medical Research and Development (AMED) [grant number JP18fk0108050 and JP18fk0108066]; the Japan Society for the Promotion of Science (JSPS) KAKENHI [grant numbers, HN: 16KT0130, 16K15356, 17H04701, 17H05808, and 18H04895], [grant number HL: 18H06385], the Inamori Foundation, and the Japan Science and Technology Agency (JST) CREST program [grant number JPMJCR1413]. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of interests

None.

Acknowledgment

We thank Analisa Avila, ELS, of Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

Amaku M, Coutinho FA, Azevedo RS, Burattini MN, Lopez LF, Massad E. Vaccination against rubella: analysis of the temporal evolution of the age-dependent force of infection and the effects of different contact patterns. Phys Rev E Stat Nonlin Soft Matter Phys 2003;67:051907.

Anderson RM, Grenfell BT. Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. J Hyg 1986;96:305–33.

Berger BE, Navar-Boggan AM, Omer SB. Congenital rubella syndrome and autism spectrum disorder prevented by rubella vaccination-United States, 2001-2010. BMC Public Health 2011;11:340.

Best JM, Castillo-Solorzano C, Spika JS, Icenogle J, Glasser JW, Gay NJ, et al. Reducing the global burden of congenital rubella syndrome: report of the World Health Organization Steering Committee on Research Related to Measles and Rubella Vaccines and Vaccination, June 2004. J Infect Dis 2005;192:1890–7.

Chua YX, Ang LW, Low C, James L, Cutter JL, Goh KT. An epidemiological assessment towards elimination of rubella and congenital rubella syndrome in Singapore. Vaccine 2015;33:3150–7.

Cutts FT, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. Int J Epidemiol 1999;28:1176–84.

Cutts FT, Lessler J, Metcalf CJ. Measles elimination: progress, challenges and implications for rubella control. Exp Rev Vaccines 2013;12:917–32.

Duszak RS. Congenital rubella syndrome—major review. Optometry 2009;80:36–43.

França GV, Schuler-Faccini L, Oliveira WK, Henriques CM, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet 2016;388:891–7.

Gao Z, Wood JG, Burgess MA, Menzies RI, McIntyre PB, MacIntyre CR. Models of strategies for control of rubella and congenital rubella syndrome-A 40 year experience from Australia. Vaccine 2013;31:691–7.

Giambi C, Bella A, Filia A, Del Manso M, Nacca G, Declich S, et al. Underreporting of congenital rubella in Italy, 2010–2014. Eur J Paed 2017;176:955–62.

Keegan LT, Lessler J, Johansson MA. Quantifying Zika advancing the epidemiology of Zika with quantitative models. J Infect Dis 2017;216:S884–90.

Kinoshita R, Nishiura H. Assessing herd immunity against rubella in Japan: a retrospective seroepidemiological analysis of age-dependent transmission dynamics. BMJ Open 2016;6:e009928.

Lambert N, Strebel P, Orenstein W, Icenogle J, Poland Rubella GA. Lancet 2015;385:2297–307.

Massad E, Azevedo-Neto RS, Burattini MN, Zanetta DM, Coutinho FA, Yang HM, et al. Assessing the efficacy of a mixed vaccination strategy against rubella in São Paulo, Brazil. Int J Epidemiol 1995;24:842–50.

Menser M, Forrest J, Bransby R. Rubella infection and diabetes mellitus. Lancet 1978;311:57–60.

Miyakawa M, Yoshino H, Yoshida LM, Vynnycky E, Motomura H, Tho le H, et al. Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam. Vaccine 2014;32:1192–8.

Mori Y, Miyoshi M, Kikuchi M, Sekine M, Umezawa M, Saikusa M, et al. Molecular epidemiology of rubella virus strains detected around the time of the 2012-2013 epidemic in Japan. Front Microbiol 2017;8:1513.

Mossong J, Hens N, Friederichs V, Davidkin I, Broman M, Litwinska B, et al. Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection. Epidemiol Infect 2008;136:1059–68.

National Institute of Infectious Diseases (NIID). Case report of CRS. Infectious Agents Surveillance Report. 2014. . [Accessed on 27 December 2018]. In Japanese http://www.nih.go.jp/niid/ja/rubella-m-111/rubella-top/700-idsc/5072-rubella-crs-20141008. html.

National Institute of Infectious Diseases (NIID). Emergency information about a rapid increase of rubella cases in 2018. 2018 https://www.niid.go.jp/niid/ja/rubella-m-111/rubella-top/2145-rubella-related/8278-rubella1808.html [Accessed 28 November 2018].

Nishiura H, Kinoshita R, Miyamatsu Y, Mizumoto K. Investigating the immunizing effect of the rubella epidemic in Japan, 2012-14. Int J Infect Dis 2015;38:16–8.

Nishiura H, Mizumoto K, Rock KS, Yasuda Y, Kinoshita R, Miyamatsu Y. A theoretical estimate of the risk of microcephaly during pregnancy with Zika virus infection. Epidemics 2016;15:66–70.

Ohkusa Y, Sugawara T, Arai S, Satoh H, Okuno H, Tanaka-Taya K, et al. Short-term Prediction of the Incidence of Congenital Rubella Syndrome. PLoS Curr 2014;6.

Panagiotopoulos T, Berger A, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review How does herd immunity work?. BMJ 1999;319:1462–7.

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;15:572.

Statistics Bureau, Ministry of Internal Affairs and Communications. Vital statistics/vital statistics of Japan final data natality. 2018 http://www.stat.go.jp/index.html (accessed on 28 November 2018). In Japanese.

Tanaka Y, Ueda Y, Yoshino K, Kimura T. History repeats itself in Japan: failure to learn from rubella epidemic leads to failure to provide the HPV vaccine. Hum Vac Immunother 2017;13:1859–60.

Tang JW, Aarons E, Hesketh LM, Strobel S, Schalasta G, Jauniaux E, et al. Prenatal diagnosis of congenital rubella infection in the second trimester of pregnancy. Prenatal Diag 2003;23:509–12.

Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar AM, Simons E, et al. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996-2010: a systematic review. PLoS One 2016;11:e0149160.

Wesolowski A, Mensah K, Brook CE, Andrianjafimasy M, Winter A, Buckee CO, et al. Introduction of rubella-containing-vaccine to Madagascar: implications for roll-out and local elimination. J R Soc Interface 2016;13:20151101.

Zanetta DM, Cabrera EM, Azevedo RS, Burattini MN, Massad E. Seroprevalence of rubella antibodies in the State of São Paulo, Brazil, 8 years after the introduction of vaccine. Vaccine 2003;21:3795–800.