

Prediction of the Number of Congenital Rubella Syndrome Cases in the 2018/2019 ongoing Rubella Outbreak in Japan as of October, 2018 and its ex-Post Evaluation

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Abstract

Background: A rubella outbreak has been ongoing since 2018 in Japan. As countermeasures first conducted against the 2012/2013 rubella outbreaks, Japan adopted the strategies of a rubella antibody titer check for adults and a Measles-Rubella vaccination for women who want to become pregnant and their partners. Mathematical models can be useful to understand the effects of such countermeasures. Using the model we proposed in our previous study on the 2012/2013 outbreak, here we predicted how many cases of congenital rubella syndrome (CRS) would occur in the current 2018/2019 outbreak based on the dataset available at October, 2018 and its ex-post evaluation. **Methods:** All parameters and procedures were borrowed from our previous study other than the number of rubella cases in women of childbearing age, which is from the current outbreak. The probability of developing CRS for different gestational ages of fetus when the pregnant woman acquires the rubella virus infection was derived from two studies conducted in the UK and the USA. **Results:** We estimated the number of CRS cases until 10 July 2019 to be 0.945 based on the UK study and 1.03 based on the USA study as of October, 2018. When we repeated the analysis using the data available at March 2019, only two CRS cases were predicted to occur during the overall current outbreak that was considered to last until November 28, 2019. Both of our model and the actual data thus far predicted that the ratio of CRS to rubella cases in 2018 was one-third that of the previous outbreak in 2012/2013. **Conclusion:** Both our model and the actual data predicted/showed a significantly lower ratio of CRS cases to rubella cases for the 2018/2019 outbreak compared to the 2012/2013 outbreak. This difference probably reflects the effectiveness of countermeasures taken against rubella and CRS between the two outbreaks. In conclusion, the countermeasures taken before the 2018 rubella outbreak appear to be effective in preventing cases of CRS.

Key words: CRS (Congenital Rubella Syndrome); Japan; MR vaccination; Policy evaluation; Women who want to become pregnant and their partners

Introduction

Rubella is one of the vaccine-preventable diseases with the severe complication of congenital rubella syndrome (CRS). A rubella outbreak has been ongoing since 2018 in Japan. Reflecting this situation, the US CDC (Center for Disease Control and Prevention) issued a level 2 alert for travellers on 22 October, 2018 recommending that pregnant women not travel to Japan [1]. As of 10 October, 2018, the number of rubella patients recorded was 1,103. This is the second largest outbreak in the last decade in Japan following the 2012/2013 outbreak, in which 14,344 cases of rubella and 45 CRS cases were recorded. Figure 1 shows the epidemiological curve of the current outbreak until 10 October 2018 [2], which indicates that the peak might have been reached in the last four weeks. After the 2012/2013 outbreak, the countermeasures taken by the central government comprised the recommendation for women who

want to become pregnant and their partner to get a rubella antibody check and a vaccination if their antibody titer was not adequate to protect them from infection. To promote these countermeasures, some local governments even subsidized the costs. These strategies may gradually spread among the targeted population who failed to be immunized in the six years between these two outbreaks.

As rubella is a self-limiting disease, the expected outcome of rubella vaccination should be focused on reducing or eliminating CRS. However, CRS is diagnosed and reported to the public health authorities only several months after rubella infection occurs. Some CRS cases might occur several months after the rubella outbreak is completely over. Therefore, if we wait for the report of the actual instances of CRS or its accumulation, we cannot conduct effective countermeasures during an ongoing rubella outbreak. In other words, to proceed with an evidence-based public health

approach, we need some procedure for predicting the number of CRS occurrence so that timely and effective countermeasures including emergency budget allocation for rubella control and real-time evaluation of the ongoing rubella outbreak can be conducted. Thus, we need a short-term but accurate procedure to predict the number of CRS to evaluate the effectiveness of the present policy to reduce and eliminate CRS.

During the former outbreak in 2012/2013, we proposed a short-term prediction procedure for CRS cases [3] that resulted in precise prediction in a prospective setting. On the basis of our previous study, we predicted how many CRS cases would occur due to the current ongoing outbreak. Moreover, we evaluated the effectiveness of the countermeasures taken against rubella and CRS through a comparison between the two outbreaks as of 10 October 2018. Then, we performed an ex-post evaluation of the prediction five months later. We also suppose ratio of CRS to rubella cases as a convenient measure to evaluate countermeasure for CRS.

Materials and Methods

First, we explain the method to predict the number of incident CRS, and later, the method to predict the ratio of CRS to rubella cases as a convenient measure to evaluate countermeasure for CRS.

Calculation procedure except for data and ex-post evaluation was the same as our previous study [3]. In the following, we explain the procedure mainly by simply citing our previous study, with the cited parts shown in *Italics*. Basically, the prediction was done using the three components: “Number of rubella cases in women of childbearing age”, “Proportion of pregnancies”, and “CRS risk” based on gestational age, where citation was written as *Italic*, as follows:

Number of rubella cases in women of childbearing age

This parameter was obtained from the epidemic curve of rubella cases. Childbearing age was defined as 15–49 years of age. As of 10 October 2018, there were 8 female cases of rubella in the 15–19 year olds, 37 cases in the 20–29 year olds, 21 cases in the 30–39 year olds, and 10 cases in the 40–49 year olds.

Proportion of pregnancies

The proportion of pregnancies was obtained by dividing the number of deliveries of the women in each age group by the population of the women in the same age group. In 2010, these proportions were 0.46% in the 15–19 year olds, 6.02% in the 20–29 year olds, 6.94% in the 30–39 year olds, and 0.41% in the 40–49 year olds [4].

CRS risk

Gestational age was assumed to be independent of rubella virus infection, i.e., the gestational age at which a

pregnant woman became infected with the rubella virus would be distributed uniformly. The probability of infection for each gestational week was assumed to be 1/39, as the duration of pregnancy can be defined as 2–40 gestational weeks. The probability of developing CRS depending on the gestational age of the fetus when the pregnant woman acquires the rubella virus infection was calculated from two studies conducted in the UK [5] and the USA [6]. Namely, when the gestational age in weeks was <10, 11–12, 13–14, 15–16, or >17, the incidence of CRS was 90, 33, 11, 24, and 0%, respectively, in the UK study. On the other hand, in the USA study, when the gestational age was <4, 5–8, 9–12, 13–16, or >17 weeks, the incidence of CRS was 70, 40, 25, 40, and 8%, respectively.

These three components suggest that the expected number of CRS cases during period t should be

$$\sum_{i=1}^n \text{Prob}(\text{CRS of } i \text{ at } t)$$

, where n is the total number of rubella-infected women, which represents the magnitude of the ongoing rubella outbreak, and

Prob(CRS of i at t) is defined as

$$q(a(i)) \frac{1}{39} p(t - r(i))$$

, where $a(i)$ is the age of patient i , which represents the age distribution of female rubella patients aged 15–49 years, $q(\cdot)$ is the probability of pregnancy by age i , $p(\cdot)$ is the probability of developing CRS by gestational age when pregnant and infected with rubella and $p(\cdot) = 0$ if $t - r(i) \geq 40$, and $r(i)$ is the date of implantation of i , where $t - r(i)$ is gestational age.

Hereafter

$$\sum_{i=1}^n \text{Prob}(\text{CRS of } i \text{ at } t)$$

is referred to as the CRS potential, which is defined as the theoretical predicted number of CRS cases. However, the CRS potential might not be equal to the number of reported CRS cases because of under-reporting of rubella and CRS cases or asymptomatic cases. To bridge these gaps, we regressed the number of reported CRS cases based on the CRS potential at birth using data from week 1, 2011 to week 40, 2013. As a result, we obtained the association as CRS cases = 0.0821 ($p=0.073$) + 0.993 ($p=0.000$) CRS potential for the UK study, and CRS cases = 0.0158 ($p=0.735$) + 1.463 ($p=0.000$) CRS potential for the USA study.

Analysis and ex-post evaluation period

It is of interest to examine to what extent a small dataset available at a relatively early time point within the outbreak suffices for the prediction. So, we carried out two sets of

analyses, varying the time point at which the data was truncated. In the analysis I, only the dataset available at 10 October, 2018 was used for the prediction. In the analysis II, the dataset available at 27 March 2019 was used. In both analyses, the outbreak was assumed to continue for the following 39 weeks after the time point of the data truncation.

We also performed an ex-post evaluation, that is, evaluation of accuracy of the prediction based on the information at the past time using actual observation after that time, for prediction of the number of CRS in the first and shorter analysis period in the duration from 10 October 2018 to 27 March 2019.

Ratio of CRS to rubella cases

To evaluate the effectiveness of the countermeasures for rubella and CRS control after the previous outbreak in 2012/2013, we also investigated the ratio of CRS to rubella cases among the two rubella outbreaks by using Fischer's exact test. We also compared the ratio of CRS to rubella cases

between the two rubella outbreaks, by applying Fischer's exact test to the datasets obtained from 2012 to 2013 and from Jan 2018 to Jun 2019. We adopted 5% as significance level.

Ethical consideration

Ethical approval for this study was not necessary because the data used in this study were all retrieved from published articles.

Results

We calculated 0.945 cases of CRS based on the UK study and 1.03 cases based on the USA study in the analysis I that used the dataset available at 10 October 2018, i.e, when the rubella outbreak was still active. This means that we predict that almost one CRS case will occur by the end of the next 39 weeks, which is 10 July 2019.

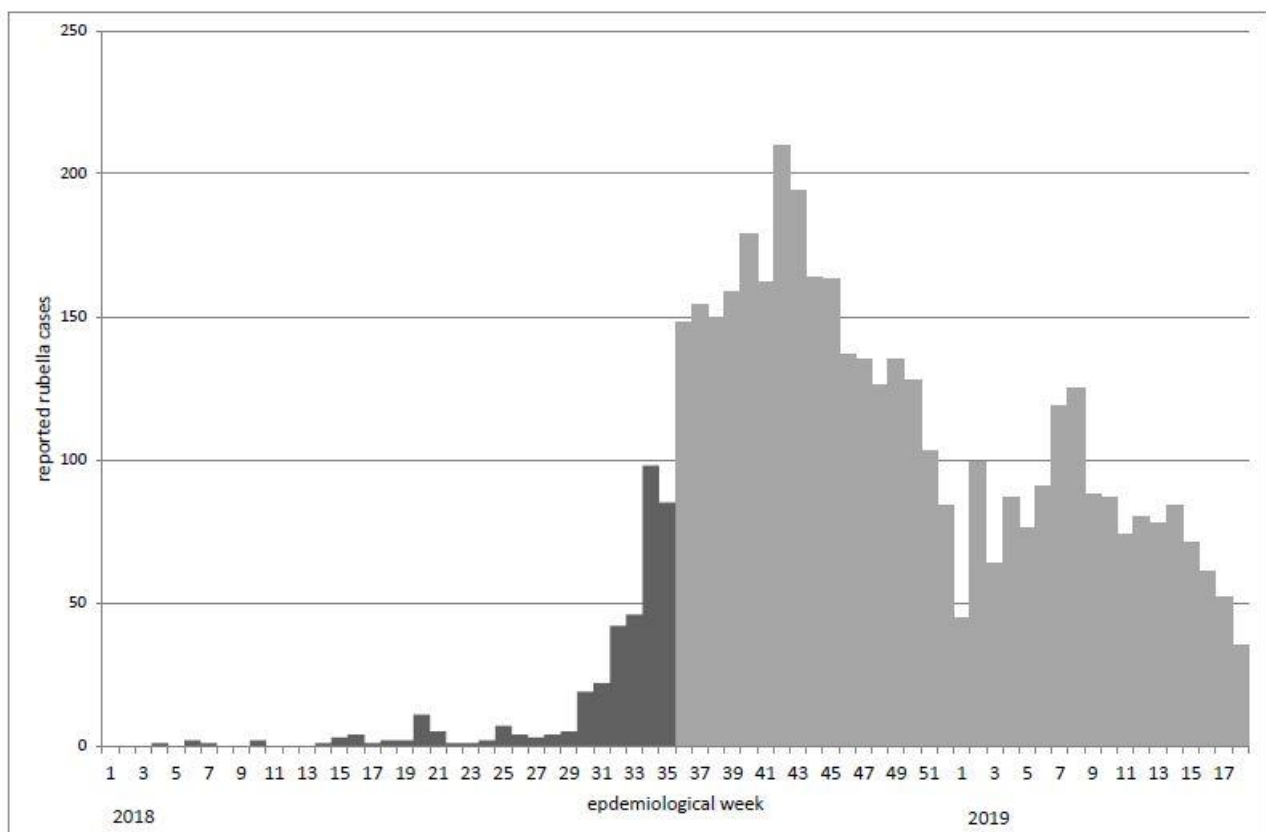


Figure 1: Reported number of rubella cases in 2018 in Japan until the 35th epidemiological week of 2018, the data as of October 2018 was shown as black bars and after that as of 9 May 2019 was shown as gray bars. This figure shows the number of rubella cases reported to the National Official Surveillance for Infectious Disease. For analysis I, we used the information of black bars only. Sex and age classes for each week were not published.

As Figure 1 shows that the outbreak might have reached its peak in the last four weeks, rubella cases will occur in almost the same number of patients for almost the same

duration. If we assume that the current outbreak began in the 19th week of 2018 and ceases within the following 20 weeks, which is 27 February, 2019, two CRS cases are expected to

occur by the end of the next 59 weeks, which is 28 November 2019.

In the analysis II period until 27 March, 2019, we predict that 1.93 or 1.54 CRS cases would occur by the end of the next 39 weeks, which is 22 December, 2019.

As of 27 March 2019, one CRS case was reported at the 4th epidemiological week. The ratio of CRS to rubella cases was 0.09% (1/1,103) in 2018, which is one third that of the ratio of 0.31% (45/14344) in the 2012/2013 outbreak. Moreover, based on the total number of rubella cases reported until 27 March, 2019, the ratio was 0.03% (1/3,860), which was no greater than one tenth of the previous outbreak of rubella. Although, compared to the 2012/2013 outbreak, the difference in ratio of CRS to rubella cases based on the information available at 10 October 2018 was not significant ($p=0.25$), the ratio based on the information available at 27 March 2019 showed a significant difference ($p=0.00$).

Discussion

Our model predicted one CRS case until 27 February, 2019 from data available at 10 October 2018, and the prediction accuracy was confirmed by the actual report of a single CRS case. Even though this was an ex-post evaluation, it proved our estimation model to be quite robust. Conversely, prediction for the rubella outbreak itself was not so good. As shown in Figure 1, the epidemic curve did not decline monotonically and rose a little in 2019, forming a second peak. Therefore, the period of the rubella outbreak might be longer than expected. Although our model predicted two CRS cases until the cessation of the current outbreak, which was estimated as 28 November, 2019 based on the data up to 10 October 2018, the actual number might exceed the previous prediction. When we recalculated the prediction of the number of CRS based on the information until 27 March, 2019, we predict that about two CRS cases would occur by 22 December, 2019. As the rubella outbreak did not cease on 28 March, 2019, if one more CRS case occurs, three CRS cases might be predicted in total during the whole of the current outbreak in 2018 and 2019.

We found significant difference in the ratio of CRS to rubella cases between two rubella outbreaks based on information until 27 March, 2019. This difference in rates may reflect the benefit of the countermeasures put in place against rubella and CRS after the former outbreak in 2012/2013. The recommendation from the Ministry of Health, Labour and Welfare (MHLW) to take rubella vaccination for women who wanted to pregnant and their partner and subsidization of costs by local governments after the 2012/2013 outbreak might have reduced the proportion of female patients capable of pregnancy and thus substantially decreased the number of CRS cases. Before 2012, rubella vaccination was recommended and subsidized from 2008 only in children of 1, 6, and 13 or 18 years of age. Couples who wanted to become pregnant were not covered before 2012.

It might reflect the fact that women in childbearing age might have more immunity in 2018/2019 because better vaccinated generation, 19-29 years old who were vaccinated in 13 or 18 years old in the period from 2008 to 2012, has

come into the childbearing age or some of them were infected in 2012/2013 outbreak. Therefore, the proportion of women in childbearing age might be smaller than the former outbreak and thus the ratio of CRS to rubella cases was much smaller than the former outbreak. In this sense, catch up rubella vaccination for 13 or 18 years old in the period from 2008 to 2012 might also contribute a countermeasure to CRS.

Unfortunately, we could not prevent CRS from occurring in the ongoing rubella outbreak. To eliminate CRS occurrence in the near future, we have to raise the rubella antibody titer level in the general population and especially in couples who want to become pregnant. In fact, beginning 1 April, 2019, the MHLW decided to subsidize the costs of the antibody test and vaccination if the antibody value is low in adult males aged 40-59 years. The target population selected was those who had never received a rubella vaccination in their life. Although this new policy would not reduce CRS in the current outbreak, it may contribute to the reduction or elimination of CRS in a future outbreak. However, additional vaccination for male adult might be somewhat indirect method to prevent pregnant to be infected rubella. As the next challenge, we would need to confirm the efficacy and cost effectiveness of this new MHLW policy by comparing it with additional testing and vaccination of adult females. To eliminate CRS, additional vaccination of females in their childbearing years might be a feasible option to consider.

The desired strategy of rubella control would be to achieve blanket coverage of rubella vaccination using a vaccine containing measles antigen in both females and males. For this purpose, three countermeasures would need to be thoroughly implemented. First, routine immunization should target all children aged 1 and 5 years old. Second, in addition to vaccination, ongoing titer checks should be undertaken in as many males as possible during routine health check-ups at the workplace or in the community. Third, companies should encourage to take rubella vaccination for all employees and their partners.

The present ratio of CRS to rubella cases might indicates how efficient policies can interrupt transmission of rubella to pregnant women during an outbreak. To our knowledge, this is the first reported study to use this index. As the prediction model reported here was the same as that used for the 2012-2013 outbreak, except for the different numbers of rubella patients among fertile women in the 2012-2013 outbreak versus the current outbreak, the situation of immunization of these women who want to pregnant and their families were incorporated into the number of patients. In other words, the model does not need vaccination rates or test results of population. Thus, we did not use or discuss this information, which has not been published nationwide since the 2012/2013 outbreak, except in some municipalities that uniquely subsidize them [7], because the MHLW only recommends that these activities be undertaken but does not subsidize them. Moreover, we estimated there to be some association between the reported number of patients among fertile women and the reported number of CRS cases, and thus the proportion of asymptomatic cases of rubella infection might not be important at any level if it remains constant. However,

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if we are trying to predict a rubella outbreak itself, this might be crucial information. It remains as a future challenge.

Our study has several limitations. First, the exact number of CRS cases is not available because of under-reporting of rubella and CRS cases including asymptomatic cases. This may affect the outcome of our prediction. Second, in the current outbreak, we could not use information on the timing of females diagnosed as having rubella, and thus we have to perform our evaluation at the end of outbreak. Although the number of rubella cases in women of childbearing age was different between the current and former outbreaks, other parameters were assumed to be the same between the two. However, these might be equivocal for policy evaluation if the proportion of asymptomatic cases was constant in the current and former outbreaks. Third, background information including herd immunity of rubella may be different among countries. In Japan, universal MR (Measles-Rubella) vaccination includes two doses for children 1 and 6 years old and a supplementary vaccination campaign for teenagers 12 or 18 years old that was started in 2008 but which was stopped in 2012. Therefore, we do not know whether our procedure is applicable to other countries. Fourth, as the current outbreak is continuing at the time this paper was submitted even though the peak appeared to be achieved, we cannot predict the number of CRS cases if a mother was infected during last half of the outbreak from 27 March, 2019 because the data was unavailable. Our prediction of two or three CRS cases in the whole of the outbreak might be wrong depending the situation in the last half of the outbreak. Fifth, we cannot use timing information of the week in which females were diagnosed as having rubella infection, and thus we cannot predict the number of CRS cases week by week as in our previous study and must perform our evaluation at the end of the outbreak.

Conclusion

We predicted that three CRS cases might occur during the whole of the current rubella outbreak in 2018 and 2019. As of March 2019, ex-post evaluation of our model shows it to be quite robust considering the actual reported number of CRS cases. So far, the countermeasures taken before the 2018 outbreak (titer check and vaccination for women who want to become pregnant and their partners) appear to be effective in preventing cases of CRS.

Disclosure

The authors declare no conflict of interest.

Author Contributions

Y.O. and T.S. designed the study; Y.O. and T.S. collected and analyzed the data; Y.O. and T.S. wrote the manuscript; and K.T. gave technical support and conceptual advice. All authors read and approved the final manuscript.

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