Short communications

Investigating the immunizing effect of the rubella epidemic in Japan, 2012-14

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A R T I C L E   I N F O

Article history:
Received 5 June 2015
Received in revised form 5 July 2015
Accepted 7 July 2015
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
rubella epidemic seroepidemiologic studies vaccination Japan

A B S T R A C T

Objectives: A rubella epidemic occurred in Japan from 2012-14, involving more than 15,000 cases. The present study aimed to estimate the immunizing effect of the epidemic, analyzing seroepidemiological data that were collected over time and age.

Methods: Annual nationwide cross-sectional surveys were conducted from July to September, collecting serum from at least 5,400 individuals. The proportions seropositive were estimated before (2012), during (2013) and after (2014) the epidemic.

Results: While the cases were mainly seen among men aged from 30-49 years, no significant increase was observed in the proportion seropositive in the corresponding age group. Even after the epidemic, age-standardized proportion seropositive of the total population remained 79.3% (95% confidence interval: 75.2, 83.4) and that among males was as small as 76.7% (95% CI: 73.8, 79.6).

Conclusions: Susceptible pockets remain in Japan, exposing the country to risk of additional rubella epidemics.

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1. Introduction

From 2012-14, Japan experienced a large-scale rubella epidemic, involving more than 15,000 cases along with 43 notified congenital rubella syndrome (CRS) cases. A peculiar feature of the epidemic has been seen in the age-distribution of cases: the highest incidence was observed among those aged from 30-39 years, followed by those aged from 40-49 years. As another remarkable observation, nearly 80% of cases were males. These features are associated with routine immunization schedules in the past. From 1977-94, only females at junior high school were targeted for rubella vaccination aiming to prevent CRS at an individual level, but subsequently, the country shifted the policy to target both males and females aged 12-90 months from 1995. A certain fraction of adult males aged from 20-49 years in the present day has remained susceptible.

As a consequence of the epidemic with immunizing effect, it is expected that some susceptible hosts have acquired immunity for two different reasons, i.e., natural infection and vaccination. Moreover, the immunity level among those who were immune before the epidemic is likely to have been elevated, due to a booster effect by exposure to infected individuals or by revaccination. The present study is aimed to estimate the immunizing effect of the epidemic, analyzing seroepidemiological data that were collected over time and age, thereby to assess if the susceptible fraction has been substantially lowered in Japan.

2. Materials and Methods

The seroepidemiological data were obtained from the National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD) after being approved by the Institutional Review Board. Every year from July to September, the cross-sectional serological survey is conducted and its area is non-randomly selected. More than 5,400 participants ranging from all age groups were manually recruited at regional levels, mostly among those who visited a prefectural medical facility or public health center for some other purpose. The timing of surveys from 2012-14 corresponds to...
before, during and after the rubella epidemic. The immunity against rubella has been assessed by hemagglutination inhibition (HI) assay. From 2012-14, serological testing covered a total of 2,225, 2,586 and 2,882 males and 2,869, 2,938 and 2,861 females, respectively.

From combinations of the three years of cross-sectional serological surveys, distributions of HI titer by sex were obtained in all ages. Gender-specific analysis was conducted because the epidemic from 2012-14 was clustered among adult males and past vaccination histories greatly differed by gender. Since the survey does not follow a cohort design, the ratio of the titer at an individual level cannot be measured, and thus, seropositive was defined as those with HI titer 32 times or greater (≥32), following the convention in Japan (corresponding to enzyme-linked immunosorbent assay at 7.3 IU/ml or greater). Seroprevalence data were compared against herd immunity level, as calculated from $1 - 1/R_0$, where $R_0$ is the basic reproduction number (i.e. the average number of secondary cases generated by a single primary case in a fully susceptible population) assumed at 6.1. Subsequently, the seroprevalence in two years $p_1$ and $p_2$ was determined, and

![Figure 1. Proportion seropositive against rubella before, during and after the epidemic in Japan, 2012-14](image-url)

Panels A, C and E. Age-dependent proportion seropositive against rubella before (2012), during (2013) and after (2014) the epidemic in Japan. The sample proportion positive is shown. Horizontal grey line indicates the herd immunity threshold of 83.6%, as calculated from $1 - 1/R_0$ (basic reproduction number), implies from above major epidemic is expected to be prevented. The basic reproduction number of rubella is assumed at 6.1. Panels B, D and F. Age-specific difference in proportions seropositive between 2012 and 2014 as well as 2013 and 2014. The horizontal solid line represents 0% difference. Whiskers extend to the upper and lower 95% confidence intervals as calculated from the binomial distribution.
the elevation of the proportion seropositive was assessed by the difference $p_2 - p_1$. The 95% confidence intervals (CI) were calculated as practiced elsewhere.  

3. Results

Figures 1A, 1C and 1E compare the proportion seropositive over time and age for the total population and also by gender. From visual assessment, three-year data were almost synchronized through age. Comparing seroprevalence data against herd immunity level, the sample proportions positive among males were frequently below the threshold, especially among 10s-40s. An evident fraction below the threshold was seen even after the epidemic (2014) among males aged from 35-49 years. Calculating the age-standardized proportion seropositive in 2014, the immune fraction of the total population remained 79.3% (95% confidence interval (CI): 75.2, 83.4). The estimate of seropositive males appeared to be 76.7% (95% CI: 73.8, 79.6), which was well below the herd immunity threshold. The estimate of females was 79.3% (95% CI: 75.2, 83.4).

Figures 1B, 1D and 1F show the change in the estimated proportions acquiring immunity towards rubella by sex, comparing 2014 data against before (2012) and during (2013) the epidemic. While an increase in the sample difference was seen among males aged from 30-39 years, the increase was not statistically significant. Moreover, no significant increase was observed across all age groups for both males and females. There were even significant decreases in seroprevalence when comparing 2012 and 2014 among 40-49 years old for both genders, presumably caused by decay in antibody titer or spatial sampling bias.

4. Discussion

The present study assessed the proportions seropositive against rubella in Japan, comparing estimates before, during, and after the epidemic and aiming to estimate the immunizing effect of the epidemic. Three notable findings were obtained. First, while the cases were mainly seen among men aged from 30-49 years old, no significant increase was observed in the proportion seropositive. Second, for several male birth cohorts, the seroprevalence was well below the herd immunity threshold level. Third, the age-standardized proportion seropositive was calculated, and that for males was as small as 76.7%. Not only men’s but also women’s seroprevalence was below our reference value of the threshold.

All three findings warn that there are susceptible pockets left, especially in unimmunized birth cohorts of adult men, which accounted for 80% of cases during the epidemic 2012-14. Susceptible cohorts could continue to fuel future rubella epidemics in Japan. An important limitation of our study is that our definition of seropositive (HI≥32 ×) rested on a convention in Japan based on small number of samples and the actual immune fraction could potentially be greater than we calculated. Nevertheless, our estimate is consistent with the occurrence of the major epidemic from 2012-14, and moreover, our finding of the absence of increase in seropositive fraction is seen with all other cut-off levels including HI:8× (results not shown). Limited herd immunity levels among adult men are likely attributable to (i) missed chance of vaccination and (ii) waning immunity. It must be noted that males aged from 10-19 years followed the new protocol of vaccination, but their seropositive fraction was below herd immunity threshold, and moreover, the seroprevalence decreased over three years, perhaps reflecting the loss of vaccine-induced immunity. To fill up the unvaccinated cohorts, the above mentioned findings call for strong supplementary vaccination, not only among women at child-bearing age, but also towards previously unvaccinated men aged from 10s-40s. Otherwise, the finding of the absence of increase in seroprevalence indicates that Japan will continue to be prone to further epidemics. Moreover, if it is certain that immunity in the substantial fraction of previously vaccinated adults has waned, it would be necessary to plan a catch-up vaccination program. Continuing monitoring of susceptible age groups by seroepidemiological survey would be essential, as they permit estimating the epidemic size and designing the most efficient vaccination strategy.

Acknowledgments

HN received funding support from Public Health Research Foundation, Daiwa Securities Health Foundation, the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 26670308, Japan Agency for Medical Research and Development, the Japan Science and Technology Agency (JST) CREST program and RISTEX program for Science of Science, Technology and Innovation Policy. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare no conflicts of interest.

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