Impact of vaccination policy on changes in rubella virus antibody in Japanese pregnant women

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Abstract

Aim As a result of the 2012–2013 rubella epidemics in Japan, many cases of congenital rubella syndrome have been reported. Given the frequent changes to rubella vaccination policy in Japan, we investigated antibody prevalence among pregnant women according to birth year.

Subjects and methods Participants comprised 55,400 pregnant Japanese women for whom rubella-specific hemagglutination inhibition antibody had been measured during early pregnancy in our institute from 1987 to 2016. Birth year was considered for the 47,978 cases for which age was known.

Results The ratio of rubella antibody-negative cases among pregnant women born after 1962 decreased significantly with mandatory vaccination. In the transition phase, during which the administration target was changed from schoolgirls to children of both sexes (born 1979–1987) as temporary vaccination, the ratio of rubella antibody-negative pregnant women started increasing in the latter period of this phase. For generations born in or after 1988, the ratio of rubella antibody-negative pregnant women clearly increased when the vaccination target changed to non-mandatory vaccination of children of both sexes.

Conclusions Prevalence of antibody titers depends on vaccine coverage rates. Suitable information needs to be provided prior to conception to all women, their husbands, and family members.

Keywords Rubella · Vaccination · Immunization · Pregnancy · Low antibody titer · Congenital rubella syndrome

Introduction

Rubella infection is well known to generally cause mild illness with febrile rash in children and adults, but rubella infection early in pregnancy (particularly during the first 16 weeks) may result in miscarriage, stillbirth, or birth of an infant with birth defects due to congenital rubella syndrome (CRS) (Castillo-Solórzano et al. 2011). The most important purpose of rubella vaccination is to prevent congenital rubella virus infections, including CRS.

Japan experienced multiple rubella epidemics in 2012–2013. As a result, the National Epidemiological Surveillance of Infectious Diseases received reports of about 15,000 cases of rubella and 43 cases of CRS between 2012 and 2014 (National Institute of Infectious Diseases, Japan 2014; Ujiie et al. 2014). Nationwide rubella epidemics had occurred around every 5 years in Japan until the early 2000s (1982, 1987–1988, and 1992–1993), with seasonal increases in spring and summer (National Institute of Infectious Diseases, Japan 2013a). Rubella vaccination for children of both sexes was included as routine immunization in April 1995. Since then, no nationwide epidemics have been reported (National Institute of Infectious Diseases, Japan 2003). Nationwide case-based surveillance for CRS was established in April 1999, and the sentinel surveillance system was introduced in January 2008. Very few rubella cases were reported until 2010, but some rubella cases were reported in 2011 among adult males in workplaces. A sharp increase in the number of reported rubella cases, to 2392, was seen in 2012, and the number of cases stayed high into 2013 (Centers for Disease Control and Prevention 2013). The World Health

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Organization US Region established the goal of eliminating rubella by 2010, and the European Region aimed to achieve the same goal by 2015 (Reef et al. 2011). Acceleration of rubella control and CRS prevention has been established as targets for the Western Pacific Region (World Health Organization 2012). Antibody titers against rubella virus are country-dependent and affected by the history of immunization in the country in addition to natural infections.

Elimination of rubella in Japan required a strategy to vaccinate susceptible individuals, and the history of immunizations against rubella in Japan is summarized Table 1 and Fig. 1 (Hanaoka et al. 2013). In 1977, the rubella vaccination program was started, targeting junior high school girls (girls, 12–15 years old). In 1989, rubella vaccine started to be administered as the measles, mumps, and rubella (MMR) vaccine. In 1993, the MMR vaccination program was terminated in response to adverse effects of aseptic meningitis resulting from the mumps vaccine. Rubella vaccination was continued as a monovalent rubella vaccine until 1994. In 1995, rubella vaccination became non-mandatory and was provided to children of both sexes. This represented a transition phase for the target group from schoolgirls to children of both sexes and the monovalent rubella vaccination program for junior high school girls was continued to include boys. The target age was then expanded for un-inoculated targets. With these changes in vaccination policy, the coverage rate of rubella vaccination fell below that of many other countries (Gomi and Takahashi 2004; Takahashi et al. 2011). In 2006, measles–rubella (MR) vaccine was introduced as a two-dose vaccination, with the first administration at 1 year old, and the second at 5 or 6 years old (National Institute of Infectious Diseases, Japan 2006).

Since 1999, no significant rubella epidemics have been observed. Coverage rates with MMR and monovalent rubella vaccines thus seem to have been sufficient to prevent rubella among children of both sexes. However, in recent years, local rubella epidemics have been observed among young adults. In

2004, ten cases of CRS were reported (Kadoya et al. 1998; Ueda 2009). During 2012–2013, nationwide rubella epidemics occurred in Japan.

Reference of the antibody titer to test year is unsuitable for identifying vaccine-susceptible ages, so this study investigated the prevalence of rubella antibody among pregnant women according to birth year under the frequently changing rubella vaccination policy in Japan.

Methods

Survey participants

We studied 55,400 cases of Japanese pregnant women for whom rubella-specific hemagglutination inhibition antibody had been measured during early pregnancy (first trimester) in our institute for the 30-year period from 1987 to 2016. Within the 55,400 cases, year of birth was considered for the 47,978 cases in which the ages of the pregnant women were known.

Hemagglutination inhibition (HI) test for measuring the rubella antibody titer

The rubella-specific HI test was performed on U-bottom microtiter plates (Corning, NY, USA), with goose erythrocytes and the Baylor strain as the antigen. Serum was pretreated with 12.5% of kaolin in phosphate-buffered saline at 15–25 °C for 20 min, and adsorbed into 25% of goose erythrocytes at 4 °C for 60 min with occasional shaking. Two-fold serial diluted sera was incubated in 4 U of hemagglutinin and 0.125% of goose erythrocytes at 15–25 °C for 60 min.

Guidelines for obstetrical practice in Japan define HI antibody $\leq \times 16$ as a low antibody titer (Minakami et al. 2014). Titers of specific antibodies were determined at the final dilutions that completely inhibited hemagglutination. Rubella HI

Table 1 History of immunization against rubella virus in Japan

Year	Target age (years)	Progress
Up to 1976	–	Vaccination unavailable
1977–1994	12–15	Monovalent rubella vaccination program for junior high school girls before pregnancy (girls only)
1989–1993	1–6	MMR vaccination program for children of both sexes overlapping with monovalent rubella vaccination program; started in 1989 and terminated in 1993 because of adverse effects (aseptic meningitis) from the mumps vaccine
1995–2003	12–23	Transition phase of target age from junior high school girls to children of both sexes. The monovalent rubella vaccination program for junior high school girls was continued while including boys, then age was expanded for un-inoculated targets
1995–2005	1–7.5	Monovalent rubella vaccination program for children of both sexes.
2006 onwards	1st: 1 2nd: 5–6	MR vaccination program started for children of both sexes.

Fig. 1 History of immunization for rubella virus in Japan (each vaccine policy is shown): *diagonal lines* represent the birth year.

antibody titers of 1:16 are approximately equivalent to 30 IU/ml (Terada et al. 2009).

Variations in rubella vaccination policies

In this study, we refer to the varied rubella vaccination policies as phases 0 through 4 (Table 2). In phase 0, vaccination was unavailable. The rubella vaccine was first introduced in Japan in 1977. During phase 1, rubella vaccination was mandatory, but was administered only to schoolgirls (12–15 years old). During phase 2, rubella vaccination was administered to school-age boys and girls, temporarily. During this time, the target of rubella vaccination was changed from schoolgirls to children of both sexes (1–6 years old). During phase 3, rubella vaccination was non-mandatory (but strongly recommended) and administered to children of both sexes as a single dose.

The present double-dose vaccination schedule (at 1 year old and 5–6 years old) represents phase 4.

In 1994, major changes were made to Japanese immunisation laws (started in 1995), such that all childhood immunisations were no longer mandatory. Individuals would be given “strong recommendations” to undergo vaccination, but ultimately it would be their choice. The reason was mainly because of strong public opposition to the reinforcement of mandatory vaccination. Since then, the Japanese government has played a very passive role in the formulation of vaccine policies.

Results

With respect to the history of rubella vaccination in our country, we retrospectively investigated transitions in the actual prevalence of antibody in pregnant women.

Table 2 Each phase with born age and past history of immunization

Phase	Era of birth	Policy	Vaccination target	Aim	Dose (coverage rate)	Vaccination method
0	Up to 1961	–	–	–	–	–
1	1962–1978	Mandatory	School-age girls	Prevention of CRS	1 (approximately 70%)	Targeted
2	1979–1987	Non-mandatory (strong recommendation)	School-age children of both sexes	Prevention of CRS, control of rubella	1	Targeted
3	1988–2004	Non-mandatory (strong recommendation)	Children of both sexes	Control of rubella	1 (50–60%)	Universal
4	2005 onwards	Non-mandatory (strong recommendation)	Children of both sexes	Control of rubella	2 (approximately 95%)	Universal

Baseline characteristics

In the 1980s, a total of 2341 cases were studied (mean age, 27.6 ± 4.1 years; range, 15–48 years). In the 1990s, a total of 8179 cases were studied (mean age, 27.8 ± 4.0 years; range, 16–47 years). In the 2000s, a total of 17,876 cases were studied (mean age, 30.2 ± 4.4 years; range, 15–46 years). In the 2010s, a total of 16,930 cases were studied (mean age, 31.3 ± 4.7 years; age range, 15–48 years). A significant increase in the ages of pregnant women was seen from the 1980s to the 1990s, from the 1990s to the 2000s, and from the 2000s to 2010.

Reference to test year

Regarding the transition of antibody prevalence among pregnant women, the ratio of rubella antibody-negative (test plate values < 8 by HI test) cases among pregnant women has decreased significantly since this study started in 1987 (Fig. 2a). Sufficient immunization, defined as under approximately 30% of patients showing a 16 HI antibody titer, was achieved from 1996 to 2011. The ratio started to increase in 2012.

Reference to birth year

In terms of antibody prevalence in pregnant women according to birth year, each phase showed characteristic changes (Fig. 2b). Phase 1 involved administration to schoolgirls before pregnancy (targets born 1962–1978). The ratio of rubella antibody-negative cases among pregnant women born after 1962 decreased significantly with vaccination of schoolgirls, which started in 1977 (Table 1). Phase 2 involved administration to school-aged boys and girls, temporarily. This phase represented a transition phase, during which time the administration target changed from schoolgirls to children of both sexes (targets born 1979–1987). Regarding the “trough generation” (transition phase) during which the target of vaccination changed from junior high school girls to children of both sexes, the ratio of rubella antibody-negative cases among pregnant women was clearly suggested to have increased in the latter period of this phase. Phase 3 involved administration to children of both sexes (targets born after 1988). As for generations born in or after 1988, as the time at which the target of vaccination was changed to children of both sexes, the ratio of rubella antibody-negative cases among pregnant women increased. Phase 4 represents the present double-dose vaccination schedule, as introduced in 2005 (not shown in figures).

The shift in rubella vaccination policy and targets from phase 1 (schoolgirls before pregnancy) to phase 3 (children of both sexes) was extremely complicated (Fig. 1).

Fig. 2 **a** Changes in antibody titers according to test year. The ratio of rubella antibody-negative cases among pregnant women has decreased significantly since this study started in 1987 under the policy of vaccination for schoolgirls started in 1977. The ratio started to increase again from 2012. **b** Changes in antibody titers according to birth year. After the latter part of the transition phase (phase 2) during which the administration target was changed from schoolgirls to all children of both sexes, the ratio of rubella antibody-negative cases among pregnant women has been increasing

Discussion

A large number of cases of CRS were reported during the nationwide rubella epidemic in Japan, which was considered to have been caused mainly by this unique transition in vaccination policies in Japan. After the latter part of the transition phase (phase 2) during which the administration target changed from schoolgirls to children of both sexes, the ratio of rubella antibody-negative cases has been increasing among pregnant women.

In April 2014, in response to the outbreak occurring at the time, Japan's Ministry of Health, Labour and Welfare provided a guidance notification to healthcare authorities (National Institute of Infectious Diseases, Japan 2013b). That guidance provided information on rubella disease and CRS for pregnant

women and their households, and encouraged vaccination for the family members of pregnant women (as rubella vaccination is contraindicated for pregnant women) and vaccination for women planning to get pregnant. CRS was classified as a Category V infectious disease requiring notification of all cases, and the Ministry set a goal of eliminating rubella by 2020.

Although immunization against rubella among susceptible individuals is most effective, Japan has faced various challenges in implementing mass vaccination. More than 80–90% of adults have already been immunized either by past vaccination or natural infection (National Institute of Infectious Diseases, Japan 2013a) and adults may thus be difficult to motivate, especially in the absence of an outbreak (Ujiie et al. 2014). In addition to routine immunization programs, adopting sero-surveillance is crucial to identify susceptible groups for targeted communication, to promote screening tests for antibody to identify individuals for selective vaccination, and, at the societal level, to encourage strong engagement of all stakeholders (including employers' associations) to support the national plan.

The most important purpose of rubella vaccination is to prevent congenital rubella virus infection, including CRS. We therefore retrospectively studied the transition of actual antibody prevalence among pregnant women. Our conclusion is that a large number of CRS cases were reported during the nationwide rubella epidemic in Japan, which is considered to have been attributable to this unique transition in vaccination policy in Japan. Once pregnant, women cannot receive the live rubella vaccine due to the infection risk to the fetus. The most important point is to provide necessary information including MR vaccination prior to conception to every woman planning to have a baby, as well as to her husband and family members.

Another problem, and a key limitation of this study, is that the most vulnerable group is young men, and many outbreaks therefore arise in workplaces. Most Japanese over 50 years old developed rubella in their youth and are immune. From January 1 to May 1 2013, a total of 5442 rubella cases were reported in Japan through the rubella surveillance system, with the majority (77%) of cases occurring among adult males. This resurgence of rubella has mainly affected adult men born between 1962 and 1978, who had not received routine rubella vaccine during childhood, as only schoolgirls were vaccinated at that time, and men and women born aged 1979–1987, for whom vaccine coverage rates were relatively low (National Institute of Infectious Diseases, Japan 2013a). Further improvement of rubella control may be realized by providing adults with a chance to receive rubella vaccine, which may require collaboration with various stakeholders, including industry physicians.

Author contribution MH and KY designed the study, and wrote the manuscript. SY contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have

contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Statement of ethics All patients provided informed consent for analysis of laboratory data and date of birth. All data were anonymized before analysis. This study method was approved by the ethics committee of Yamaguchi Hospital.

Disclosure statement The authors have no potential conflicts of interest to declare.

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