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National Institute of Infectious Diseases and
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Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Rubella and Congenital Rubella Syndrome in Japan, as of March 2013

The principal symptoms of rubella are fever, rash and lymphadenopathy. As some cases show only a part of these symptoms and as not a few other diseases show similar symptoms, definitive diagnosis requires laboratory data. The virus when infecting a pregnant woman within 20 weeks of gestation occasionally causes congenital rubella syndrome (CRS) in newborns such as cataract, congenital heart disease (very frequently patent ductus arteriosus), hearing loss, low birth weight, thrombocytopenic purpura etc. (Note, however, that more than 40% of infected fetuses develop CRS.) To avoid such consequences, preventive measures including vaccination are necessary (pp. 92, 93, 95 & 97 of this issue).

The National Epidemiological Surveillance of Infectious Diseases (NESID): Rubella had been a sentinel surveillance infectious disease before 2008, when it was classified as a Category V infectious disease requiring notification of all the cases (IASR 32: 250-251, 2011) (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-14-02.html).

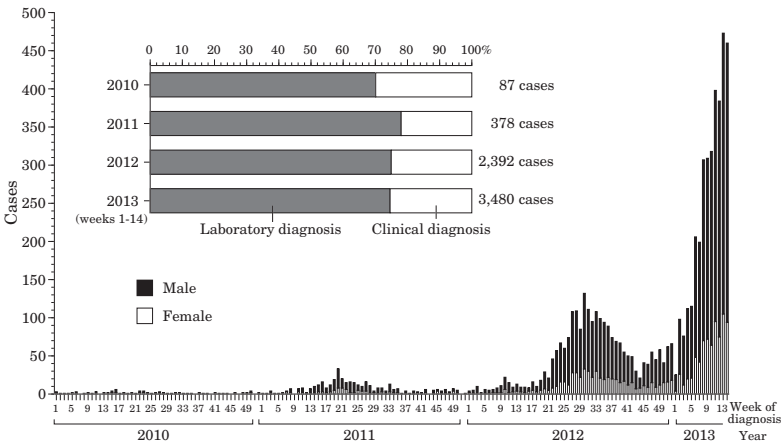
Until recently nationwide epidemics used to occur every five years, e.g., 1982, 1987-1988, and 1992-1993. Since April 1995 when rubella vaccine to children of both sexes was included in the routine immunization in, no nationwide epidemic has been reported (IASR 21: 1-2, 2000 & 24: 53-54, 2003, http://idsc.nih.go.jp/iasr/24/277/graph/f2771.gif). The 2004 epidemic was regionally limited but accompanied with estimatedly 39,000 cases. However, in 2011 after 7 years of silence, rubella cases started to increase (Fig. 1), and reported number during the weeks 1-12 of 2013 exceeded the total number in 2012. Considering the possibility that some patients failed to consult doctors or to be properly diagnosed, the reported number can be a low estimate (p. 100 of this issue).

Large cities reported more cases (Fig. 2 on p. 89) (pp. 101 & 102 of this issue), and the weekly report in 2013 indicated spread of rubella from the Metropolitan areas to its surrounding prefectures (http://www.nih.go.jp/niid/images/idsc/disease/rubella/2013pdf/rube13-13.pdf).

As for age distribution in 2013, most frequent were those in 30's (33%) followed by those in 20's (28%), 40's (21%), ≥50 years (8.0%), 15-19 years (5.5%) and <15 years (4.8%). Thus, adults occupied about 90% of the patients. Among males, the most frequent were those in 20-40's, while among females the most frequent were those in 20's (Fig. 3). Ratio of male patients to female patients was 3.0 in 2012 and was 3.7 in the first 14 weeks of 2013. The gender ratio appears increasing. Vaccination history was zero for 29% and unknown for 65% of the total cases.

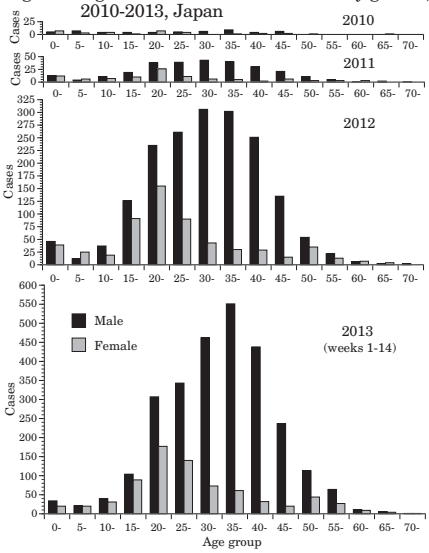
CRS was classified as a Category V infectious disease requiring notification of

Figure 1. Weekly cases of rubella, week 1 of 2010-week 14 of 2013, Japan



(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 10, 2013)

Figure 3. Age distribution of rubella cases by gender, 2010-2013, Japan



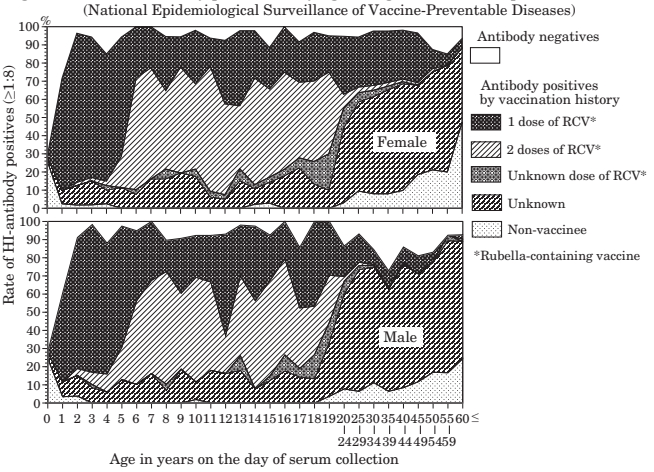
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 10, 2013)

(Continued on page 88′)

(THE TOPIC OF THIS MONTH-Continued)

all the cases (http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-10.html). Since enforcement of the Infectious Diseases Control Law in April 1999, 27 CRS cases have been reported in Japan (pp. 95 & 97 of this issue), 10 cases from the 2003-2004 epidemic and 8 cases from the 2012 epidemic (Table 1 on p. 89). Among these incidents, 19 mothers were diagnosed as rubella during pregnancy. Only one case had a clear vaccination record of the mother. Eight cases reported from the week 42 of 2012 to the week 12 of 2013 were all infected in Japan and many of them were from prefectures that reported rubella cases at frequencies higher than 10 per million population in 2012.

Figure 4. Rubella antibody prevalence by age and gender, 2012, Japan
(National Epidemiological Surveillance of Vaccine-Preventable Diseases)



Transition of vaccination schedule: The 2012-2013 rubella epidemic that principally affected age groups 20's-40's can be explained firstly by vaccination schedule from August 1977 focusing on female students (Group 2 in Table 2 on p. 89) and males born in FY1962-FY1979 were not included in the junior high school immunization.

In 1994, Preventive Vaccination Law was amended to the effect that the mass vaccination was replaced by strongly recommended vaccination on individual basis. The target population was set to 12-90 months old boys and girls (Group 5 in Table 2). Male and female junior high school students were given the first chance of vaccination during the period of FY1995-FY2001 (Group 3 in Table 2), but the coverage of this age cohort was low on account of requirement of accompaniment of a guardian for immunization (http://www.mhlw.go.jp/topics/bcg/other/5.html).

In FY2006, the one dose rubella vaccination was replaced by the two dose measles-rubella (MR) combined vaccine immunization, the first at one year of age and the second within 1 year before primary school entrance. In addition, as a 5 year program from FY2008 to FY2012, the second chance of immunization was given to the children in the first year class of junior high schools and those in the third year class of the high schools. However, the coverage of the latter cohort was found low in prefectures, which reported higher number of rubella cases (p. 103 of this issue).

Antibody prevalence rate among the population (National Epidemiological Surveillance of Vaccine Preventable Diseases): Fourteen prefectural public health institutes in Japan jointly surveyed rubella hemagglutination inhibition (HI) antibody level of 5,094 healthy individuals (Fig. 4). The percentage of antibody positives (HI titer ≥ 8 HI) was 30% among zero year babies, increased in one year children and attained ≥90% in ≥2 year children.

Among adults in their 30's and 40's, antibody positive rate was 73-86% in males in contrast to 97-98% in females (11-25 point lower in males than in females). However, there was little gender gap among people in 20's and ≥50 years of age (p. 105 of this issue).

Woman whose antibody level is found lower than HI titer ≤16 in the prenatal checkups are advised to receive MR vaccine on in an earliest occasion after the delivery in preparation to the next possible pregnancy (p. 93 of this issue).

Rubella virus and laboratory diagnosis: There are 13 genotypes specified by the E1 protein coding gene. In Japan, the dominant genotype including that of the 2004 epidemic was genotype 1j, which was replaced in 2011 by genotypes 1E and 2B of the South-, East- and Southeast-Asia origins (pp. 91, 95, 96, 97 & 99) (http://www.nih.go.jp/niid/en/iasr-rubella-e.html).

Laboratory diagnosis of rubella consists of virus isolation/identification or PCR detection of viral genome from throat swab, blood or urine specimens from the acute phase patients, detection of IgM antibody in the serum of acute phase, or increase of antibody titer in the serum of recovery phase compared with the acute phase. Currently, 70-80% of the reported rubella cases are laboratory diagnosed (Fig. 1). The IgM test, while widely used, often gives false negative data if the specimen is obtained earlier than three days after appearance of rash. Therefore, PCR test is recommended for earlier diagnosis (pp. 96 & 97 of this issue). The most sensitive is the PCR test using throat swabs obtained on the next day of the rash appearance. When the PCR test is done with the blood samples, however, it may become negative several days after appearance of rash.

HI antibody test uses goose red blood cells. In case of short supply of goose red blood cells, EIA can be used by converting EIA titer to HI titer by using the conversion table proposed by the Ministry of Health Labour and Welfare (MHLW) working group (pp. 93 & 107 of this issue).

Challenges in future: MHLW issued a notice "Strengthening Measures for Prevention and Control of Rubella and Congenital Rubella Syndrome" on January 29, 2013 and partially revised on February 26, 2013 (http://www.nih.go.jp/niid/en/iasr-sp/2250-related-articles/related-articles-398/3427-de3981.html). National Institute of Infectious Diseases and MHLW, supported by academic societies, made campaign posters for rubella control and sent them to local governments and medical institutions in Japan (http://www.nih.go.jp/niid/ja/rubella-poster2013.html).

Currently, in order to provide correct information on CRS, consulting services are provided to obstetricians and gynecologists by the Research Group of MHLW (p.93 of this issue).

Technical Advisory Group to Western Pacific Regional Office of WHO has recommended inclusion of rubella vaccine in the routine immunization particularly to countries which have not yet done so. It also recommended to maintain the vaccine coverage ≥80% (p. 91 of this issue).

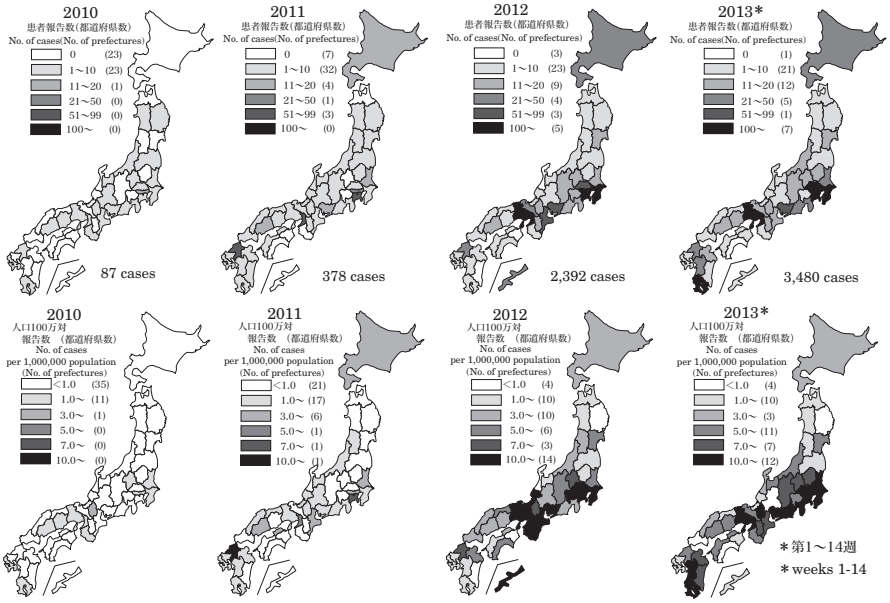
As of the week 14 of 2013, rubella incidence in Japan was 28 cases per million population, and 8 CRS cases have been reported since October 2012. As the peak season of rubella is often early summer, the rubella patients are expected to increase from now. Once pregnant, women cannot receive the live rubella vaccine on account of potential infection to the fetus. Therefore necessary information including MR vaccination prior to conception should be provided to every woman who is planning to bear a baby and to her husband and family members. For further improvement of rubella control, it is important to provide adults with chance of receiving rubella vaccine, which may require collaboration with various stakeholders including industry physicians.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

Infectious Disease Surveillance Center, National Institute of Infectious Diseases
Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, JAPAN Tel (+81-3)5285-1111

（特集つづき）（THE TOPIC OF THIS MONTH-Continued）

図2. 都道府県別風疹患者発生状況，2010～2013年
Figure 2. Incidence of rubella by prefecture, 2010-2013, Japan



（感染症発生動向調査：2013年4月10日現在報告数）
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 10, 2013)

表1. 先天性風疹症候群報告症例，2011年9月～2013年3月（感染症発生動向調査：2013年4月10日現在）
Table 1. Reported cases of congenital rubella syndrome in Japan, September 2011-March 2013

診断年/週 Year/Week of diagnosis	都道府県 Prefecture	母親の感染地域 Place of mother's infection	母親のワクチン接種歴 Mother's rubella vaccination history	母親の妊娠中の風疹罹患歴 Mother's rubella infection history during pregnancy
2012/42	兵庫 Hyogo	兵庫 Hyogo	不明 Unknown	あり Yes
2012/46	香川 Kagawa	香川 Kagawa	なし No	あり Yes
2012/47	兵庫 Hyogo	兵庫 Hyogo	不明 Unknown	不明 Unknown
2012/49	大阪 Osaka	大阪 Osaka	不明 Unknown	なし No
2012/50	埼玉 Saitama	埼玉 Saitama	なし No	あり Yes
2013/02	大阪 Osaka	大阪 Osaka	なし No	あり Yes
2013/10	愛知 Aichi	愛知 Aichi	なし No	あり Yes
2013/12	東京 Tokyo	東京 Tokyo	なし No	あり Yes

1999年4月～2011年8月までは前回特集（IASR 32: 252, 2011）参照。 See IASR 32: 252, 2011 for the cases during April 1999-August 2011
(National Epidemiological Surveillance of Infectious Diseases: Data based on the reports received before April 10, 2013)

表2. 風疹の定期予防接種制度の変遷 Table 2. Schedules of rubella routine immunization in the history of Japan

接種時期・接種方法・接種ワクチン Group: Schedule of immunization and type of vaccine	2013年4月時点の年齢 Age as of April 2013	生年月日 Birthday of the target population
無し Group 1: Vaccination unavailable	51歳以上 ≥51 yrs	1962(S37)年4月1日以前 1962 April 1 and before
女子中学生に風疹ワクチンを、学校で集団接種。接種率高い。 Group 2: School rubella vaccination to female junior high school students with high coverage. No vaccination to male students	34～51歳 34-51 yrs	1962(S37)年4月2日～1979(S54)年4月1日 1962 April 2—1979 April 1
中学生の時に風疹ワクチンを、医療機関で個別接種。接種率激減。但し、未接種者は2001(H13)年11月7日～2003(H15)年9月30日までならいつでも接種可能 Group 3: Rubella vaccination to junior high school students on individual basis at clinics and hospitals with the consequent low coverage (Note: any unimmunized persons of this age group were given an additional chance of immunization during the period of November 7, 2001-September 30, 2003)	25～34歳 25-34 yrs	1979(S54)年4月2日～1987(S62)年10月1日 1979 April 2—1987 October 1
1～6歳時[1989(H1)年4月～1993(H5)年4月26日]に麻疹ワクチンのかわりにMMRワクチンを選択接種 Group 4: MMR vaccination in place of measles vaccination at 1-6 years after birth (from April 1989 to April 26 1993)	21～30歳の一部の者 21-30 yrs	1983(S58)年4月2日～1992(H4)年4月27日の一部の者 1983 April 2—1992 April 27
生後12～90か月未満の男女幼児に1回目の風疹ワクチン接種 Group 5: 1st dose of rubella vaccine to all children 12-90 months after birth	8～25歳 8-25 yrs	1987(S62)年10月2日～2005(H17)年4月1日 1987 October 2—2005 April 1
2回目の接種機会無し Group 5-1: No chance of the second dose	うち、23～25歳 23-25 yrs	うち、1987(S62)年10月2日～1990(H2)年4月1日 1987 October 2—1990 April 1
高校3年生相当年齢の時に2回目の接種（原則、MRワクチン）。接種率低い。 Group 5-2: 2nd dose (usually as MR vaccine) at the 3rd year class of high school; coverage low	うち、18～23歳 18-23 yrs	うち、1990(H2)年4月2日～1995(H7)年4月1日 1990 April 2—1995 April 1
中学1年生相当年齢の時に2回目の接種（原則、MRワクチン）。接種率低い。 Group 5-3: 2nd dose (usually as MR vaccine) at the 1st year class of junior high school; coverage low	うち、13～18歳 13-18 yrs	うち、1995(H7)年4月2日～2000(H12)年4月1日 1995 April 2—2000 April 1
小学校入学前1年間に2回目の接種（原則、MRワクチン）。接種率高い。 Group 5-4: 2nd dose (usually as MR vaccine) during one year preceding primary school entrance; coverage high	うち、8～13歳 8-13 yrs	うち、2000(H12)年4月2日～2005(H17)年4月1日 2000 April 2—2005 April 1
生後12～24か月未満に1回目の接種（原則、MRワクチン）。接種率高い。 Group 6: 1st dose (usually as MR vaccine) 12-24 months after birth; coverage high	8歳以下 ≤8 yrs	2005(H17)年4月2日以降 2005 April 2 and later
小学校入学前1年間に2回目の接種（原則、MRワクチン）。接種率高い。 Group 6-1: 2nd dose (usually as MR vaccine) during one year preceding primary school entrance; coverage high	うち、5～8歳 5-8 yrs	うち、2005(H17)年4月2日～2008(H20)年4月1日 2005 April 2—2008 April 1
2014(H26)年度以降に、小学校入学前1年間に2回目の接種機会あり（原則、MRワクチン） Group 6-2: 2nd dose (usually as MR vaccine) during one year preceding primary school entrance from FY2014	うち、5歳以下 ≤5 yrs	うち、2008(H20)年4月2日以降 2008 April 2 and later