Causes of a nationwide rubella outbreak in Japan, 2012-2013

Hisanori Minakami,1)* Takahiko Kubo, 2) Nobuya Unno 3)

1) Department of Obstetrics, Hokkaido University Graduate School of Medicine
2) Department of Maternal-Fetal and Neonatal Medicine, National Center for Child Health
3) Department of Obstetric and Gynecology, School of Medicine, Kitasato University

*Corresponding author: Hisanori Minakami
Director Professor,
Department of Obstetrics, Hokkaido University Graduate School of Medicine,
N15W7 Kita-ku, Sapporo 060-8638 Japan
E-mail: minasho@med.hokudai.ac.jp
TEL: 81-1-11-706-6932

E-mail address of co-authors;
Dr. Takahiko Kubo: kubo-t@ncchd.go.jp
Director Professor Nobuya Unno: unno-tky@umin.ac.jp

Dear Editors,

Although rubella can lead to severe encephalitis [1], rubella infection is usually mild among children. However, rubella in pregnant women can cause congenital rubella syndrome (CRS) as a devastating consequence. Although congenital rubella syndrome (CRS) is a preventable disease **with universal immunization**, as many as 13 newborns contracted CRS in the nine months from October 2012 to July 2013 (1.5 per 100,000 live births) **in Japan** as a consequence of a rubella epidemic (Fig. 1). In **this outbreak**, the majority of cases of rubella occur among adult males [**2**]; among 11,489 patients (88 per 1.0 million) reported during the first six months of 2013, 8,845 (77%) were males and 8,059 (70%) were males 20 years of age or more [**2**]. As we experienced a rubella epidemic nine years ago in 2004, in which 10 infants were diagnosed with CRS, we knew what measures would be effective to prevent a rubella epidemic at that time. Therefore, the current disaster was predictable and may have been avoided if appropriate measures had been implemented.

In 1976, Japan introduced a single-antigen rubella vaccine to the national immunization program targeting girls in junior high school. Between 1989 and 1993, a measles-mumps-rubella (MMR) vaccine was targeted toward children 12–36 months of age. Since 1995, the single-antigen rubella and measles-rubella (MR) vaccines have been strongly recommended for children 12–90 months of age as a standard immunization; however the program is not mandatory. Although a supplemental vaccination campaign was conducted to increase population immunity, the vaccine coverage rate was too low, and adult males remain susceptible to rubella (Fig. 2). There are approximately 1.05 to 1.1 million annual births in Japan, and only one infant contracted CRS each year from 2000 to 2003. However, this period was followed by a rubella outbreak in 2004 in which 10 infants became infected with CRS. According to a population immunity survey that was strengthened after the rubella epidemic in 2004 and has been conducted yearly since 2006, the number of persons without immunity against rubella (less than 1:8 on an hemagglutination inhibition assay, HI test) is consistently higher among male than female adults 20–49 years of age, with a difference of approximately 7 to 22 points (%) in 2006 and 2012 [**3**] (Fig. 2).

In 2004, the Japanese Ministry of Health, Labour and Welfare (JMHLW) announced the following three emergency strategies to control the rubella epidemic [**4**]: the development of a vaccination campaign, including a strong recommendation for rubella vaccination among the family members of pregnant females, adult females and postpartum females, and an increase in the vaccine coverage rate for the standard immunization program; guidance for the creation of appropriate diagnostic procedures for managing rubella infection in pregnancy and prenatal screening of CRS; and the establishment of a new surveillance system to monitor rubella infection that requires all physicians to report any clinically and/or laboratory confirmed rubella cases [**4**]. However, male adults were not included as targeted subjects, and vaccination was not mandatory, even for the targeted population. The annual number of subjects who received supplementary vaccination under this program is estimated to be 270,000, 330,000 and 260,000 in fiscal years 2009, 2010 and 2011, respectively, according to the JMHLW [**5**], while the population of Japan is approximately 130 million people. As the proportion of pregnant females susceptible to rubella (less than 1:8 on an HI test) in Tokyo was 6.7% in 2003-2006 [**6**], the campaign decreased the fraction of the population that is susceptible to rubella among female adults by approximately 3% and male adults by approximately 5% (Fig. 2); however, a rubella outbreak occurred again in 2012-2013. Among the individuals affected in the current epidemic, the vaccination history was unknown in a majority of patients (7,393 [64%]). Among the 4,096 patients with a known vaccination status, 3,366 (82%) cases occurred in persons who had not received the rubella vaccine [**2**]. Based on the data shown in Figure 2, we estimate that approximately 5.1 million adult males 20–49 years of age were susceptible to rubella in 2006 (the population of males in the 20s, 30s and 40s totaled approximately 7.6, 9.4 and 7.8 million, respectively, in Japan in 2006). The rubella outbreak and CRS infections occurred in the presence of a high vaccination coverage rate among females, with a low coverage rate in some populations in the community [**7-9**]. Therefore, the current rubella epidemic was predictable. In order to achieve rubella elimination within several years after the time of the previous rubella outbreak, it was necessary to provide supplementary vaccination to more than 1.0 million male adults each year for the first several years.

As of October 2010, the WHO Region of the Americas and European Regions established rubella elimination goals for the years 2010 and 2015, respectively, while the Western Pacific Region has established targets for achieving accelerated rubella control and CRS prevention goals (an incidence of less than 1.0 per 100,000 live births) [**10**]. Programs to eliminate rubella have indeed been successful in the USA [**11**] and appear to be successful in some European countries [**12**, **13**]. In July 2013, three groups, including the Japan Society of Obstetrics and Gynecology, Japan Association of Obstetricians and Gynecologists and Japan Society of Perinatal and Neonatal Medicine, asked the JMHLW to establish a distinctive policy for eliminating rubella and providing an emergency strategy to overcome the shortage of vaccines in the current outbreak [**14**]. If effective measures regarding a vaccination program targeting male adults are not taken, it may not be possible to suppress the current rubella epidemic, and more patients will develop CRS. In addition, newborns with CRS continue to shed the infectious virus for several months [**15**], acting as a source of the rubella virus and a possible trigger of future rubella outbreaks. We fear exporting rubella to WHO Regions of the Americas and Europe, where health care providers are struggling to achieve and sustain a rubella vaccine coverage rate of ≥95% among the general population in order to eliminate rubella [**11-13**], and developing countries, in which national vaccination programs have not been implemented.

REFERENCES

1. Bahloul M, Chaari A, Ammar R, Medhioub F. Chabchoub I, Karray H, Berrajah L, Dammak H, Hamida CB, Chelly H, Bouaziz M. Management of severe rubella encephalitis requiring intensive care unit admission. J Infect 2013; 66: 109-11.

2. National Institute of Infectious Diseases (Japan). Cumulative number of rubella cases by week, 2009-2013. (cited in 8 July 2013 from URL: http://www0.nih.go.jp/niid/idsc/idwr/diseases/rubella/rubella2013/rube13-25.pdf)

3. National Institute of Infectious Diseases (Japan); Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labor, and Welfare (Japan). Rubella and congenital rubella syndrome in Japan, as of March 2013. IASR 2013; 34: 87–9.

4. Research group supported by the Japan Ministry of Health, Labour, and Welfare.

Emergency announcement against rubella epidemic and prevention of congenital rubella syndrome, August 2004 (cited 8 July 2013 from URL: http://idsc.nih.go.jp/disease/rubella/rec200408rev3.pdf)
5. Japanese Ministry of Health, Labour, and Welfare. Regarding rubella (cited in 8 July 2013 from URL: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansensho u/rubella/
6. Okuda M, Yamanaka M, Takahashi T, Ishikawa H, Endoh M, Hirahara F. Positive rates for rubella antibody in pregnant women and benefit of post-partum vaccination in a Japanese perinatal center. J Obstet Gynaecol Res 2008; 34: 168-73.
7. Macdonald A, PetaskiK. Outbreak of rubella originating among high-school students –Selkirk, Manitoba. Can Commun Dis Rep 1997; 23: 97–101.
8. Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunization in Greece: retrospective survey and systematic review. BMJ 1999; 319: 1462-7.
9. Centers for Disease Control and Prevention. Progress toward elimination of rubella and congenital rubella syndrome—the Americas, 2003–2008. MMWR 2008; 57 (43): 1176–9.
10. Centers for Disease Control and Prevention. Progress toward control of rubella and prevention of congenital rubella syndrome—worldwide, 2009. MMWR 2010; 59 (40): 1307-10.
11. Centers for Disease Control and Prevention. Elimination of rubella and congenital rubella syndrome---United States, 1969-2004. MMWR 2005; 54(11): 279-82.
12. Muscat M, Zimmerman L, Bacci S, Bang H, Glismann S, Mølbak K, Reef S, and the EUVAC.NET group. Toward rubella elimination in Europe: An epidemiological assessment. Vaccine 2012; 30: 1999– 2007.
13.WHO European Region 2012. Eliminating measles and rubella: framework for the verification process in the WHO European Region. (cited in 8 July 2013 from URL: http://www.euro.who.int/__data/assets/pdf_file/0005/156776/e96153-Eng-final-version.pdf)
14. Japan Society of Obstetrics and Gynecology. Regarding emergency strategy for the prevention of congenital rubella syndrome and the rubella elimination. (cited in 8 July 2013 from URL: http://www.jsog.or.jp/news/pdf/20130705_korosho_yobo.pdf)

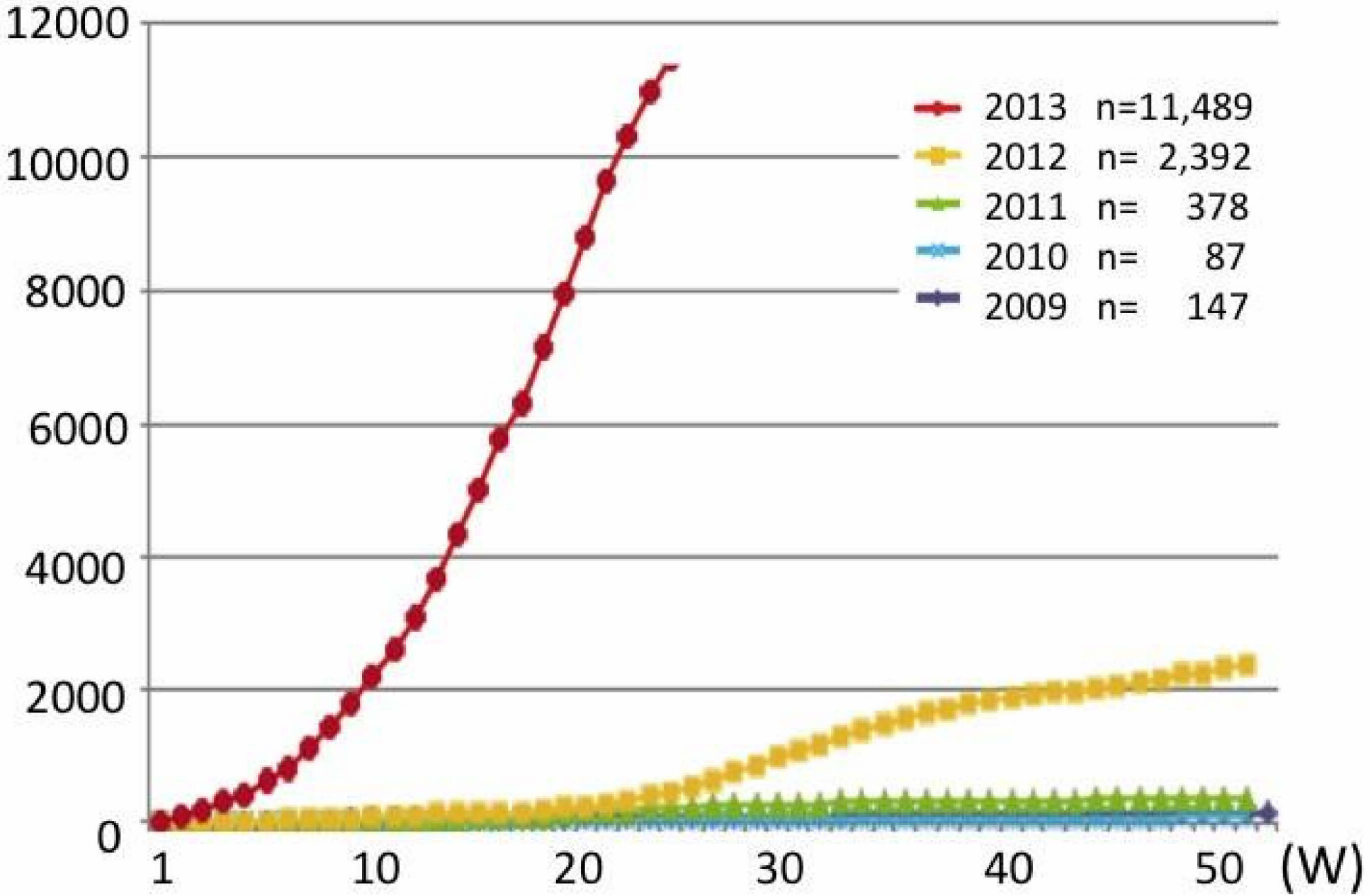
15. Greaves WL, Orenstein WA, Stetler HC, Preblud SR, Hinman AR, Bart KJ. Prevention of rubella transmission in medical facilities. JAMA 1982; 248: 861–4.

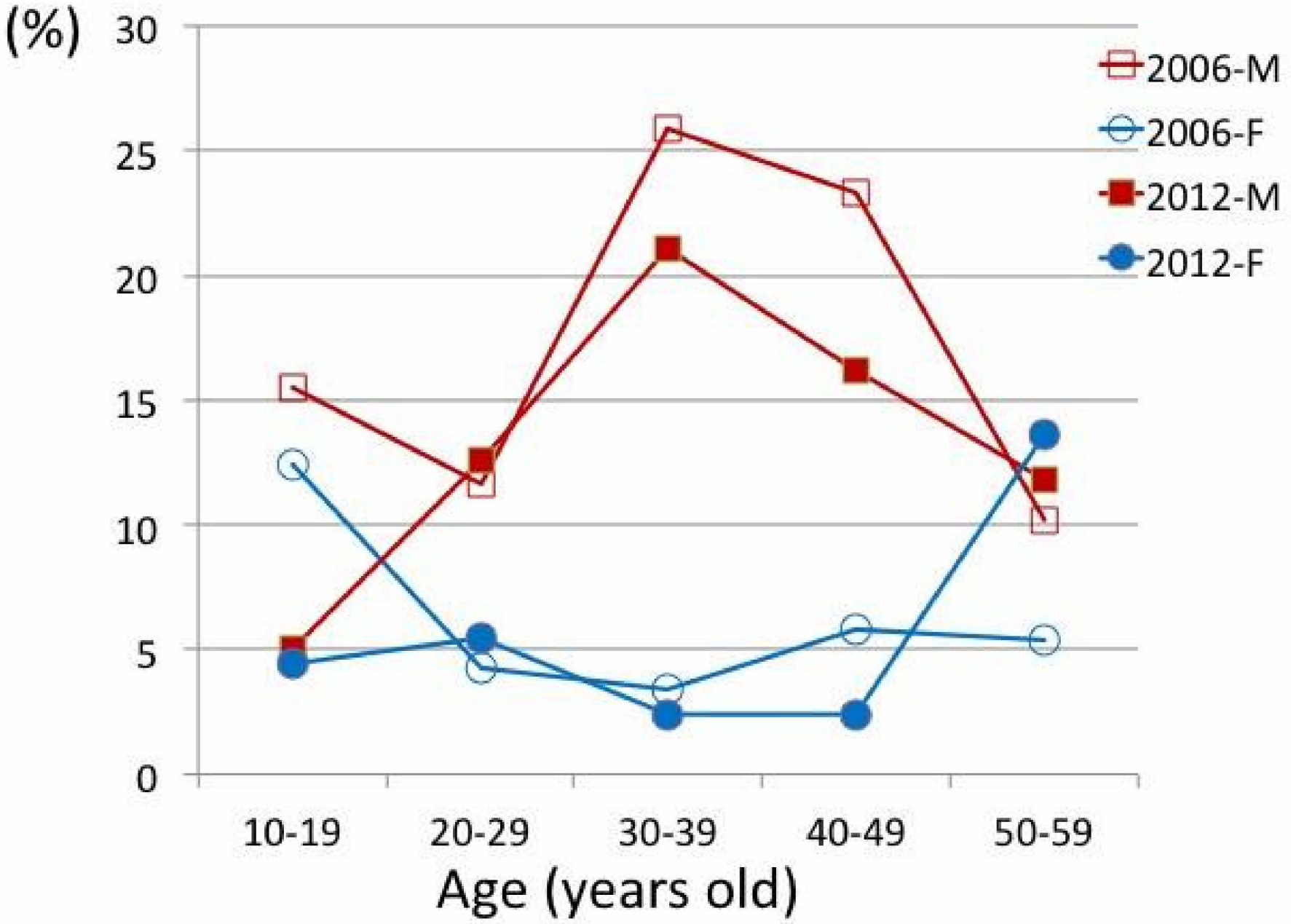
Figure legends

Fig. 1: Cumulative number of rubella patients by week, 2009–2013 (as of June 26, 2013) [1].

Fig. 2: Rates of male and female Japanese individuals who were susceptible to rubella in 2006 and 2012 according to age.

The rectangles and circles indicate males and females, respectively. Immunity against rubella was determined using the hemagglutination inhibition test. Persons with a test result of less than 1:8 were judged as being susceptible to rubella. The data were obtained from the website of the National Institute of Infectious Disease (Japan)(cited July 8, 2013 from the URL: http://www.nih.go.jp/niid/ja/y-graphs/3373-rubella-yosoku-serum2012.html and the URL: http://www.nih.go.jp/niid/ja/y-graphs/1917-rubella-yosoku-serum2006.html).


12000
10000
8000
6000
4000
2000
0
1
10
20
30
40
50
(W)
2013 n=11,489
2012 n= 2,392
2011 n= 378
2010 n= 87
2009 n= 147


(%)
30
25
20
15
10
5
0
2006-M
2006-F
2012-M
2012-F
10-19
20-29
30-39
40-49
50-59
Age (years old)