Epidemiological Report

Epidemiological Characteristics of Rubella and Congenital Rubella Syndrome in the 2012–2013 Epidemics in Tokyo, Japan

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SUMMARY: A large rubella outbreak has been observed since June 2012 in Tokyo, Japan, and a rapid increase in the number of congenital rubella syndrome (CRS) cases have also been reported in Japan since October 2012. All the clinically diagnosed and laboratory-confirmed rubella cases reported in Tokyo from January 2012 to December 2013 and all the laboratory-confirmed CRS cases from January 2012 to March 2014 were analyzed. In total, 4,116 rubella cases were reported in Tokyo. Of these, 77.2% (n = 3,176) were male; the highest number of cases occurred in males aged 35–39 years and in females aged 20–24 years. Complications included arthralgia/arthritis (19.4%), thrombocytopenic purpura (0.5%), hepatic dysfunction (0.3%), and encephalitis (0.1%). The circulating rubella virus in Tokyo was genotype 2B. The most possible site of transmission was the workplace. Because of the rubella epidemic, 16 CRS cases were reported in Tokyo from March 2013 to February 2014. Domestic infection with rubella was proven for all mothers of 16 cases. This situation suggests that Japan is still working to achieve rubella elimination.

INTRODUCTION

Rubella is usually a mild, rash-producing, febrile illness in children; however, infection in pregnant women, particularly during the first trimester, can result in stillbirth, premature birth, or congenital defects known as congenital rubella syndrome (CRS). In the past, nationwide rubella epidemics have been reported to occur with a cycle of around 5–6 years in Japan (1). However, the infantile rubella immunization program led to major reductions in the number and scale of epidemics since 1994, and no rubella epidemic has been observed since 2005 (2). From 1978 to 2002, the CRS incidence in Japan was 0.2–8.1 cases/100,000 live births per year in epidemic years (3). Thereafter, only 0–2 cases were annually reported, with the exception of the 2004 rubella epidemic, when 10 cases of CRS were reported (2).

The rubella vaccination program was introduced into the national immunization schedule in 1977; however, until 1994, immunization was limited to girls in grades 7–9 (ages 12–15 years). In 1995, a vaccination program for all infants (12–90 months) was introduced. In 2006, a second dose of the measles-rubella (MR) vaccine was introduced upon entry to the first grade (5–6 years of age). In 2011, the MR vaccine coverage rate was 95.3% at the age of 1 year and 92.8% at the age of 5–6 years (4). After a large measles outbreak in 2007, a catch-up program using the MR vaccine was administered to children in grades 7 and 12 (ages 12–13 and 17–18 years) from April 2008 to March 2013.

A case-based reporting system for CRS was implemented in 1999 in Japan, with all physicians being required to report every case of CRS (2). From 1999 to 2011, 19 CRS cases were reported in Japan, including 3 in Tokyo.

For surveillance of rubella, till 2007 (from 1982 to 2007), aggregate case reporting was performed through pediatric sentinels (approximately 3,000 sentinels) (2). In 2008, rubella surveillance in Japan was improved to require notification from all health care providers. In Japan, the number of reported rubella cases had decreased to as low as 87 in 2010. With regard to Tokyo, from 2008 to 2011, the annual numbers of rubella cases were 46, 19, 15, and 39, respectively.

Since June 2012, the number of reported rubella cases has rapidly increased in Tokyo (5). Other large cities in Japan, besides Tokyo, also had unusually large numbers of reported rubella cases (4). In addition, since October 2012, the number of CRS cases has increased. Here we describe the epidemics of rubella in Tokyo from January 2012 to December 2013 and of CRS up to March 2014. Because epidemic data in Tokyo reflect those of the whole country, this communication will be meaningful to control rubella and prevent CRS in Japan.

MATERIALS AND METHODS

Rubella cases diagnosed between January 2, 2012 and December 29, 2013 in Tokyo and CRS cases diagnosed...
between January 1, 2012 and March 31, 2014 in Tokyo were included in this study. These cases were extracted from the National Epidemiological Surveillance of Infectious Diseases (NESID) system on April 16, 2014. NESID is the nationwide case-based surveillance system that was started in April 1999. CRS has been included in the system since April 1999, and rubella has been included since January 2008. All physicians are required to report all clinically diagnosed and laboratory-confirmed rubella cases as well as all laboratory-confirmed CRS cases to local health officials through a designated form.

Case information, which can be accessed at the national level, is then entered into the centralized notification system by local health officials. Case information for rubella includes the following: diagnosis method (clinical or laboratory), age, gender, diagnosis date, suspected route and location of transmission, vaccination history, complications, pregnancy status and location of medical facility. Case information for CRS includes the following: age, gender, birthweight, diagnosis date, duration of pregnancy, mother’s rubella infection history during pregnancy, mother’s suspected location of transmission, mother’s vaccination history, and location of the medical facility. In Tokyo, this surveillance system covers approximately 13 million people, 31 public health centers, and approximately 13,000 medical facilities.

A clinical rubella case was defined according to generalized maculopapular rash, fever, and lymphadenopathy. A laboratory-confirmed case was a clinical case with the detection of the rubella viral genome through reverse transcription-polymerase chain reaction (RT-PCR), detection of rubella-specific IgM antibody, or seroconversion tests.

CRS is clinically confirmed if an infant has more than 1 of the following complications: cataract, congenital glaucoma, congenital heart disease, hearing impairment, pigmented retinopathy, purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, or jaundice developed within 24 h after birth. A laboratory-confirmed CRS case was defined according to clinical confirmation with a positive blood test for rubella-specific IgM or the detection of the rubella viral genome by RT-PCR.

Patients’ history of vaccination was confirmed with maternity health records or by patient interview. Notification rates for rubella were calculated using the October 2012 census estimates for Tokyo. Notification rates for CRS were calculated using the number of live births in Tokyo in 2012.

**RESULTS**

**Rubella:** In total, 4,116 rubella cases were reported between January 2, 2012 and December 29, 2013 from 1,311 hospitals and clinics throughout Tokyo (Fig. 1). From week 6 (in February) to week 25 (in June) 2013, excluding week 18 (holiday season), more than 100 cases were reported per week. In week 15 of 2013, the number of reported cases reached a record high (n = 168) because the notification of rubella became mandatory. The number of cases has decreased since week 29 (in July). The total number of cases in 2013 was 3,423 (25.9 per 100,000 population), which was 4.9 times that in 2012 (n = 693; 5.2 per 100,000 population; Fig. 2).

The majority of reported cases (n = 2,927; 71.1%) were laboratory confirmed, and among them, 322 were confirmed by RT-PCR. There were 3,176 (77.2%) male cases. The overall male to female ratio was 3.4:1. In 2012, this ratio was 3.6:1, whereas in 2013, it was 3.3:1. The median patient age was 35 years for males and 27 years for females (Fig. 3). Males aged 20–49 years and females aged 20–29 years experienced the highest percentages of cases among all age groups throughout this epidemic (Fig. 4). Almost one-third of males (29.6%) and females (31.5%) had no recorded history of rubella vaccination, and information regarding the vaccination
status was missing for 65.3% and 55.3% of them, respectively (Fig. 3).
Complications included arthralgia/arthritis (19.36% overall; male 18.83%, female 21.17%), thrombocytopenic purpura (0.46%), hepatic dysfunction (0.34%), encephalitis (0.12%), and meningitis (0.05%; Fig. 5).
In 25 cases, the patients were pregnant women (median age, 28 years [19–39], 2.7% female cases). Approximately two-thirds of these patients (64.0%) had some symptoms of rubella without their recognition. Partners were the major source of rubella infection in pregnant women (Fig. 6). At least 7 of these patients gave birth to infants with CRS. We were not able to follow the outcome of pregnancy for the other 18 cases.
Viral genotypes were determined for 129 cases in 2012 and 2013, and 120 (93.0%) and 9 (7.0%) were genotypes 2B and 1E, respectively. Of the total 4,116 reported cases, domestic infection was suspected in 4,097 cases; 2,851 of these occurred in Tokyo. For the remaining 19 cases, 11 cases were suspected to be related to exposure outside Japan, and the exposure location (domestic or foreign) could not be determined for 8 cases. Detailed information regarding exposure was obtained for 786 (19.1%) cases (Fig. 7). The most commonly suspected location of transmission (45.0%) was parents’ workplaces.

**CRS:** In total, 16 CRS cases were reported between January 1, 2012 and March 31, 2014 by 12 hospitals in Tokyo. Previous numbers of reported CRS cases included 13 (12.1 per 100,000 live births) in 2013 and 3 (2.8) from January through March 2014 (Fig. 8).

Table 1 summarizes the clinical characteristics of CRS.
Characteristics of the Rubella Epidemics in Tokyo

Fig. 6. Summary of suspected route of transmission among pregnant women cases of rubella by weeks of gestation in Tokyo, Week 1, 2012 to Week 52, 2013.

Fig. 7. Detailed information regarding suspected route of transmission among reported cases of rubella in Tokyo, Week 1, 2012 to Week 52, 2013 (n = 786).

Fig. 8. Number of reported cases of congenital rubella syndrome (CRS) by month of diagnosis with trends in reported cases of rubella by gender (2012 to 2013) in Tokyo from January 2012 to March 2014.
patients. Five mothers who gave birth to infants with CRS had not received the rubella vaccine, and 8 had an unknown vaccination history. Two mothers with a vaccination history had no symptoms. In these 2 cases, the suspected route of transmission could not be specified. All mothers, except for the unknown and asymptomatic cases, were at less than 20 weeks of gestation when rubella symptoms appeared (Fig. 9). Domestic infection of rubella was proven for all mothers of the 16 cases of CRS, 11 of which were in Tokyo.

Table 1. Clinical characteristics at the time of diagnosis of congenital rubella syndrome (CRS) in Tokyo from January 2012 to March 2014

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Total</td>
<td>16</td>
<td>100.0</td>
</tr>
<tr>
<td>Gender (Males)</td>
<td>8</td>
<td>50.0</td>
</tr>
<tr>
<td>Age at diagnosis (&lt;1 mo)</td>
<td>13</td>
<td>81.3</td>
</tr>
<tr>
<td>Premature birth (&lt;37 w)</td>
<td>4</td>
<td>25.0</td>
</tr>
<tr>
<td>Low birthweight (&lt;2,500 g)</td>
<td>11</td>
<td>68.8</td>
</tr>
<tr>
<td>Major complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Congenital heart disorder</td>
<td>12</td>
<td>75.0</td>
</tr>
<tr>
<td>PDA (Patent ductus arteriosus)</td>
<td>9</td>
<td>56.3</td>
</tr>
<tr>
<td>PS (Pulmonary stenosis)</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>VSD (Ventricular septal defect)</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>AC (Aortic coarctation)</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>4</td>
<td>25.0</td>
</tr>
<tr>
<td>Minor complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpura</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>2</td>
<td>12.5</td>
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<tr>
<td>Mental retardation</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Radiolucent bone</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Jaundice developed within 24 h after birth</td>
<td>7</td>
<td>43.7</td>
</tr>
</tbody>
</table>

DISCUSSION

In Japan, there has been a large outbreak of rubella since 2012. As of March 26, 2014, a total of 2,392 rubella cases in 2012 and 14,357 in 2013 were reported through NESID, with 24.6% of those being reported in Tokyo. During the epidemic, rubella cases are reported all across Tokyo, and 16 cases of CRS were reported in Tokyo as a result of this rubella epidemic. Nationwide, as of March 26, 2014, the number of reported cases of CRS was 44, including 4 cases in 2012, 32 cases in 2013, and 8 cases so far in 2014 (6).

Most rubella cases were reported in males aged 20–49 years. This seems to be caused by the persistence of a susceptible population similar to the recent rubella outbreaks reported in Poland and Romania (7–9). On the other hand, cases reported among children were rare. The MR vaccine program with 2 doses seems to decrease the risk of childhood rubella infection.

In March 2013, as a response to the outbreak, the Tokyo Metropolitan Government provided financial support to the 62 local administrations in Tokyo for adult MR vaccination for 1 year. All the local administrations began offering free or reduced cost vaccinations; however, because of a limited budget, most administrations targeted only females of childbearing age and their partners. These special programs may have contributed to the decrease in rubella cases. Because of this epidemic, the Ministry of Health, Labour and Welfare (MHW) decided to set a goal of rubella elimination by 2020 and to provide financial support to females of childbearing age and their partners for antibody testing from 2014 (10). MHW will recommend vaccination to those who are susceptible.

Usually, thrombocytopenic purpura (1 in 3,000 cases) and encephalitis (1 in 6,000 cases) are infrequent complications of rubella (11,12). However, the frequencies of thrombocytopenic purpura and encephalitis in our
study were much higher (1 in 217 cases and 1 in 823 cases, respectively). There is a possibility of surveillance bias because of under-reporting of the reason for the higher frequency of thrombocytopenic purpura and encephalitis during this rubella outbreak. Physicians should be alert to the risk of such complications when treating adult rubella patients.

Although there is a high risk of transmission from a partner to a pregnant woman, the route of infection was not identified among more than half of the pregnant women who had rubella. This suggests that even if transmission from a partner could be prevented, there is always a possibility of rubella infection through other routes.

In this rubella epidemic, among adults, the most susceptible location of transmission was the workplace. Thus, an infection control measure such as mass vaccination is essential to eliminate rubella transmission at workplaces.

When mothers of infants with CRS developed rubella symptoms, the onset of symptoms was observed earlier than 20 weeks of gestation. This result agrees with the fact that no abnormalities were found when fetal infection occurred beyond the 20th week of gestation (11). Among mothers of the reported CRS cases, 2 showed no symptoms of rubella during gestation. Both these mothers had a vaccination history of 1 dose of the rubella vaccine, suggesting that the vaccination may prevent the onset of rubella but is insufficient to prevent fetal infection.

Hearing impairment most frequently appears among the major complications of CRS, being observed in up to 96% of cases (3,13). However, the incidence of hearing impairment observed at diagnosis in this study, was as low as 25%. Because some symptoms of CRS, including hearing impairment, could appear later, routine follow-up of infants with CRS is important (11).

Rubella is a mild disease; however, there may be substantial cases beyond those reported among the general population. In addition, because not all rubella cases were laboratory confirmed, some cases could have been clinically misdiagnosed as rubella. Furthermore, there may have been recall bias about an individual's vaccination history and rubella infection history.

The dominant genotypes in Japan were genotypes 1E and 2B (2). The circulating rubella virus in Tokyo was type 2B. This type 2B is reported throughout a wide area of East and Southeast Asia (14). Before 2010, there was no report of type 2B in Japan (15). Thus, these findings may indicate possible importation to Japan from other areas.

In Tokyo, the incidence of rubella in 2013 was 259 cases per million population, and the incidence of CRS in 2013 was 121 cases per million live births. The WHO Western Pacific Regional Office set a goal for a rubella incidence of less than 10 per 1,000,000 population and a CRS incidence of less than 10 per 1,000,000 live births by 2015 (16). Increased numbers of rubella cases in adults and 16 cases of CRS were reported in Tokyo during this epidemic, suggesting that Japan must make further progress to reach this goal.

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Conflict of interest None to declare.

REFERENCES