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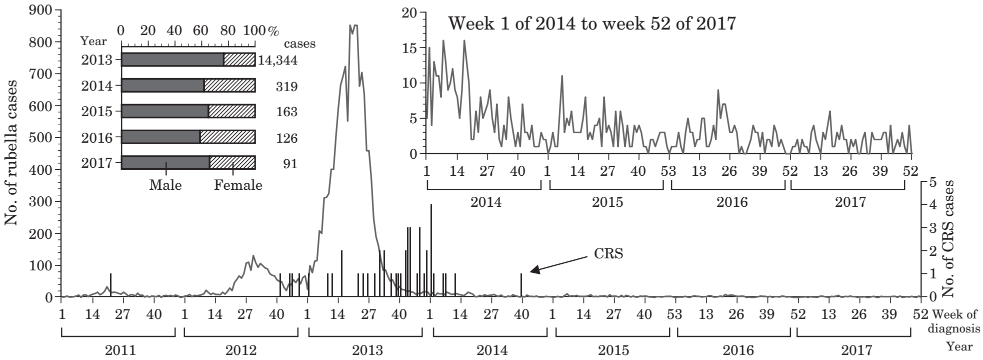
National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Rubella and congenital rubella syndrome in Japan as of January 2018

Figure 1. Weekly number of reported rubella cases and congenital rubella syndrome (CRS) cases, week 1 of 2011 to week 52 of 2017, Japan

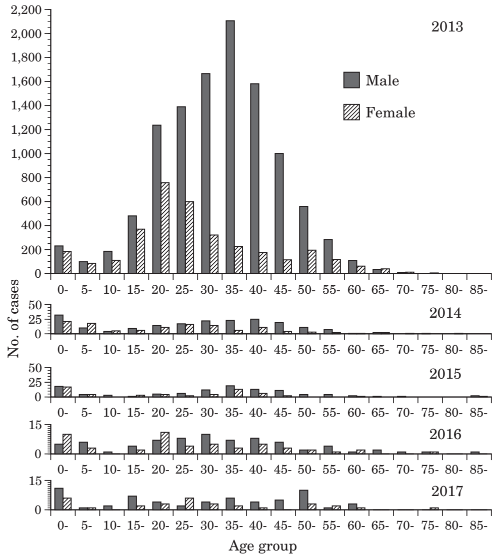


(National Epidemiological Surveillance of Infectious Diseases: as of February 1, 2018)

Rubella is an acute infectious disease caused by rubella virus. The three major clinical signs of rubella are rash, fever, and lymphadenopathy. Although the symptoms of rubella are generally mild, serious complications, including encephalitis and thrombocytopenic purpura, can occur in rare cases. Rubella virus infection in susceptible pregnant women can result in prenatal transmission to the fetus. In particular, maternal infections that occur before a gestational age of 20 weeks can cause infants to be born with congenital rubella syndrome (CRS), which manifests as various signs/symptoms, including heart defects, cataracts, hearing loss, low birth weight, thrombocytopenic purpura, and psychomotor retardation (see p.33 of this issue). Effective and safe vaccines are available for preventing rubella and CRS.

Together with the elimination of measles, the World Health Organization (WHO) and others are promoting various activities aimed at accelerating the elimination of rubella. The "Global Vaccine Action Plan 2011-2020", which was endorsed by the 65th World Health Assembly in 2012, aims to eliminate measles and rubella in at least five WHO regions by 2020. The Japanese Ministry of Health, Labour and Welfare has issued "Guidelines for the Prevention of Specific Infections: Rubella" (Ministry of Health, Labour and Welfare notice No. 122, March 28, 2014), which describes measures that would help attain the goal of eliminating CRS occurrence in newborns as soon as possible, along with elimination of rubella by FY2020 in Japan. Furthermore, in December 2017 the guidelines were revised as follows: from January 1, 2018, 1) patients diagnosed with rubella should be immediately notified, 2) active epidemiological investigation should be conducted after occurrence of even a single case of rubella, and 3) as a rule, viral genome testing should be conducted for all suspected cases (see p.31 of this issue).

Figure 2. Age distribution of rubella cases by gender, 2013-2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of February 1, 2018)

Notifications of rubella and CRS according to the National Epidemiological Surveillance of Infectious Diseases (NESID) system

Rubella is classified as a Category V infectious disease, requiring notification of all cases (http://www.niid.go.jp/niid/images/iasr/36/425/de4251.pdf). A nationwide rubella epidemic occurred in Japan between 2012 and 2013, and 2,386 and 14,344 cases were reported in 2012 and 2013, respectively (Fig. 1). After this epidemic, the number of cases decreased, with 319, 163, 126, and 91 cases in 2014, 2015, 2016, and 2017, respectively (Fig. 1).

As for the sex distribution of rubella, while males accounted for 77% of all cases in 2013, they accounted for 58-66% between 2014 and 2017 (Fig. 1). Adults comprised 90% of male cases and 78% of female cases in 2013 (Fig. 2). Many of the male cases were in their 20s-40s, while many female cases were in their 20s (Fig. 2). Approximately half of all female cases (16 cases) in 2017 were in their 20s-30s.

Between 2013 and 2017, 19-30% of all rubella cases had no history of vaccination with rubella-containing vaccine (1-7% of all cases were those aged <1 year and did not have the opportunity to receive the routine vaccine), 5-19% had received 1 dose, 1-9% had

(Continued on page 30′)

(THE TOPIC OF THIS MONTH-Continued)

Figure 3. No. and proportion of rubella cases by vaccination status, 2013-2017, Japan
(National Epidemiological Surveillance of Infectious Diseases: as of February 1, 2018)

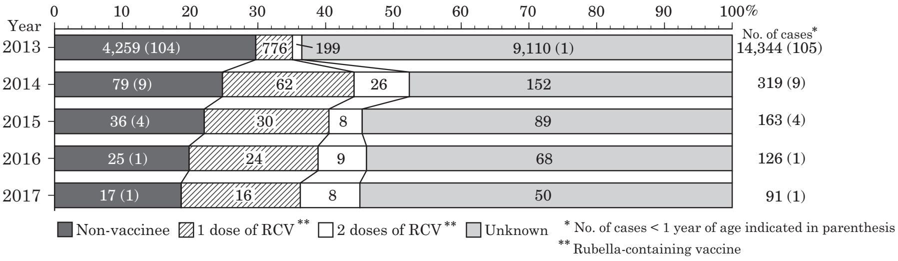
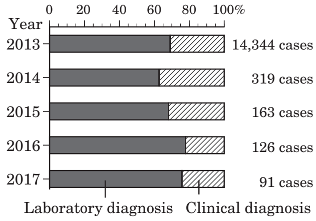


Figure 4. No. and proportion of rubella cases by diagnosis, 2013-2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of February 1, 2018)

received 2 doses, and 48-65% had unknown vaccination history (Fig. 3).

CRS is also classified as a Category V infectious disease requiring notification of all cases, based on the Infectious Diseases Control Law (http://www.niid.go.jp/niid/images/iasr/36/425/de4252.pdf). Associated with the 2012-2013 epidemic, 45 CRS cases were notified between 2012 and 2014. A follow-up study found that, at the time of investigation, the case fatality of CRS cases was 24% (see p.33 of this issue). Since 2015, no further CRS cases have been reported as of February 1, 2018.

Current practice regarding laboratory diagnosis of rubella and CRS

Laboratory-confirmed cases of rubella accounted for 63-78% of all rubella cases that were reported under the NESID system between 2013 and 2017 (Fig. 4). Among laboratory-confirmed cases reported between April 1, 2014 and December 31, 2016, the most frequent method was detection of rubella-specific IgM (72%), followed by PCR-based detection of the rubella virus (23%) (some detected by both methods) (see p.34 of this issue). Throat swab, blood, and urine specimens are recommended for detection of the rubella virus genome. The detection rate of the rubella virus genome is high in the early stages after rash onset, and can be detected until about 7 days after rash onset (see p.35 of this issue). In contrast, as serum samples collected between 0 and 3 days after rash onset often do not have detectable rubella-specific IgM titers, it is recommended that tests be performed using serum samples collected ≥4 days after rash onset (ideally ≥5 days) to confirm the diagnosis (see p.37 of this issue). According to the revised guidelines, physicians are required to immediately notify a clinically diagnosed case of rubella; conduct tests for detecting serum antibodies, such as rubella-specific IgM; and send specimens to the public health institute (PHI) for conducting tests such as viral genome testing.

Laboratory testing is required for CRS notification. Between 2012 and 2014, 93% and 82% of CRS cases were identified via the detection of rubella-specific IgM and PCR-based detection of the rubella virus, respectively (some detected by both methods) (see p.33 of this issue). For diagnosing CRS based on the detection of specific IgM or the rubella virus genome, the sensitivity of detection is highest within the first 6 months after birth, and diagnosis becomes more difficult over time. Detecting the virus genome from a preserved umbilical cord is being considered as a possible laboratory method for diagnosing CRS for situations where a period of time has passed since birth (see p.38 of this issue).

Routine vaccination coverage of rubella-containing vaccines

Since FY2006, the routine immunization program in Japan has included the measles-rubella (MR) combination vaccine; children receive the first dose at 1 year of age (1st vaccination) and the second dose within 1 year prior to primary school entry (2nd vaccination). In FY2016, the vaccination coverage for the first and second doses of the vaccine were 97.2% and 93.1%, respectively. Thus, the target of 95% vaccination coverage was achieved for the first dose. To achieve the target for the second dose, further efforts are being made (http://www.niid.go.jp/niid/ja/diseases/ma/655-measles/idsc/7536-01-2016.html).

National epidemiological surveillance of vaccine-preventable diseases

In FY2017, the rubella hemagglutination-inhibiting antibody (HI) titers of serum samples collected from 5,656 healthy people (2,886 males and 2,770 females) from 18 prefectures were determined (Fig. 5 in p.31). The antibody positivity rate (HI titer: ≥1:8) of males in their late 30s to early 50s was about 80%, which was considerably lower than that of their female counterparts. The seroprevalence of the HI antibody among males born between 1962 and 1978 (39-55 years of age at the time of the survey) remained unchanged at around 80% for 10 years between FY2008 and FY2017, and a large number of susceptible individuals still remain (see p.39 of this issue).

Efforts in the WHO Western Pacific Region (WPR)

In the WPR, the region which includes Japan, elimination of rubella has been set as a target goal. Rubella-containing vaccines have been introduced into routine immunization programs in most WPR countries or areas, and pediatric cases of rubella have declined markedly; however, outbreaks involving adults have been reported in some countries. In addition, a CRS surveillance system has yet to be established in some countries (see p.44 of this issue).

Future measures to be taken

To eliminate the occurrence of CRS as soon as possible and rubella by FY2020, measures such as the following should be taken. First, vaccination coverage rates of ≥95% should be achieved and maintained for each of the two routine rubella vaccination doses. Second, women of childbearing age, adult males (especially males who live with or have close contact with pregnant women), travelers to rubella-endemic countries, and medical personnel should be recommended to get vaccinated with a rubella-containing vaccine, and an environment that facilitates vaccination should be fostered. Third, there should be early detection of rubella patients along with interruption of disease transmission. Lastly, the nucleotide sequence of the rubella virus genome should be actively analyzed to clarify the transmission routes of the virus.

In the 2012-2013 epidemic, the majority of rubella patients were adult males, and transmission mainly occurred in the workplace. To prevent the resurgence of a similar epidemic, it is important to reduce the number of susceptible individuals among adult males. Furthermore, the implementation of control measures at workplaces and those pertaining to travel to endemic countries is necessary. In Tokyo, a project to support companies that take measures to prevent infectious diseases, including rubella, was launched in October 2015 (see p.41 of this issue). The project, "Rubella Zero", defined February 4 as "Rubella Zero" Day and raises awareness and disseminates information about rubella prevention (see p.43 of this issue). For these rubella response activities, cooperation among companies, medical personnel, local public health centers, and PHIs is imperative.

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 Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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＜特集関連情報＞

風しん対策に係る省令等の改正

風しんは，麻しんとともに，現在，世界的な排除を目指して対策が進められている感染症の一つであり[1, 2]，世界的に風しんの報告数が減少する中で，日本でも，風しんの報告数は概ね減少を続けている[3]。即ち，風しんの報告数は，小児科定点把握疾患であった1999（平成11）年から2007（平成19）年にかけて定点医療機関あたり1.03件から0.15件と減少し，全数把握疾患となった2008（平成20）年以降も概ね年間100～400件の間を推移しており，特に2015（平成27）年以降は年間200件以下となっている。このように，現在，風しんは麻しんと同程度の発生状況となっているが，風しんに関しては，2012（平成24）年には2,386件，2013（平成25）年には14,344件と，時に大規模な発生が見られることからも，依然として重点的な対策が必要な感染症である。

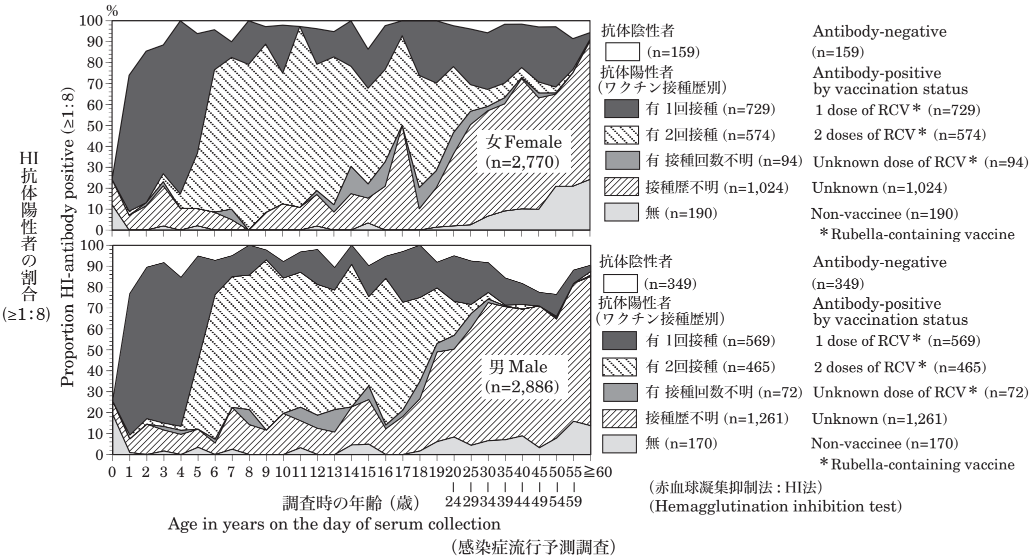
このような中，2018（平成30）年1月1日付で，風しん対策のさらなる推進に向けて，省令等の改正が施行された[4, 5]（次ページ表）。第21回〔2017（平成29）年6月19日〕，第22回（平成29年9月15日）および第23回（平成29年12月15日）の感染症部会，第19回（平成29年9月14日）および第20回（平成29年12月8日）の予防接種基本方針部会，第1回麻しん・風しんに関する小委員会（平成29年10月19日）での審議の結果を踏まえて，省令である感染症の予防及び感染症の患者に対する医療に関する法律施行規則（平成十年厚生省令第九十九号）（以下，「省令」という。）の改正（平成29年12月15日）および感染症の予防及び感染症の患者に対する医療に関する法律（平成十年法律第百十四号）および予防接種法（昭和二十三年法律第六十八号）に基づき作成される「風しんに関する特定感染症予防指針」（以下，「予防指針」という。）の改正（平成29年12月21日）が施行されたことで，麻しんと同様に，さらに踏み込んだ対策が，風しんにおいても行われることとなった。

麻しんに関しては，平成27年3月27日に世界保健機関西太平洋事務局より日本において排除状態にあることが認定されている[6]が，風しんについても，日本での排除状態を達成することを目指した対策が進められてきた。予防指針では風しんの排除の定義を「適切なサーベイランス制度の下，土着株による感染が一年以上確認されないこと」[5]としており，同一ウイルス株による持続的な感染伝播（土着性の伝播）がないことを確認する必要がある。その確認のためには，検出した風しんウイルスの遺伝子配列の解析を行うとともに，1例ごとに感染経路の把握等を行い，その動向を丹念に調査することで，土着性の感染伝播が途絶されていることを確認する必要がある。改正前の予防指針では，遺伝子配列の解析に関して，都道府県等は「可能な限りウイルス遺伝子検査等を実施する」としていた[5]が，遺伝子配列が決定された症例は10％台に過ぎない状況にあった[3]。このことを踏まえて，改正された予防指針では「原則として全例にウイルス遺伝子検査等を実施する」こととした。なお，改正後の予防指針においても「原則として」とすることで，風しんの大規模な集団発生が生じた場合に，家族内での発生など感染経路が明確な症例での遺伝子検査の省略を可能にするなど，自治体が優先順位をつけた対応を行えるようにしている。

また，改正前の予防指針では，「地域で風しんの流行

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

図5．年齢別風疹抗体保有状況，2017年度
Figure 5. Proportion seropositive against rubella virus by age, gender and vaccination status, fiscal year 2017, Japan



（感染症流行予測調査）
(National Epidemiological Surveillance of Vaccine-Preventable Diseases)