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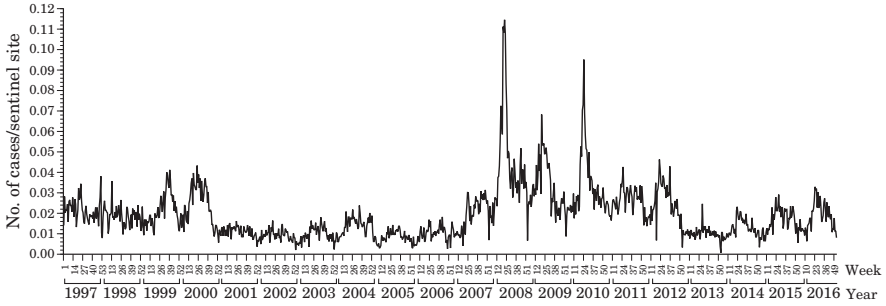
National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

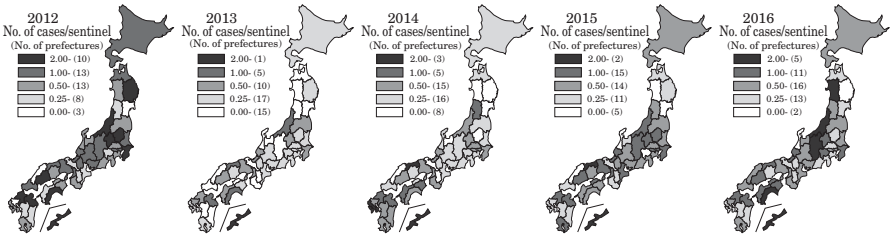
<THE TOPIC OF THIS MONTH>
Pertussis in Japan, as of January 2017

Figure 1. Weekly number of reported pertussis cases per sentinel site from week 1 of 1997 to week 52 of 2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of January 6, 2017)

Figure 2. Annual number of reported pertussis cases per sentinel site by prefecture, 2012-2016, Japan
(National Epidemiological Surveillance of Infectious Diseases: as of January 6, 2017)



Pertussis is defined as "acute respiratory tract infection caused by *Bordetella pertussis*" in the Infectious Diseases Control Law (see http://www.nih.go.jp/niid/images/iasr/38/444/de4441.pdf for the notification criteria). The main symptom is a prolonged cough. As severity may be greater among neonates and infants, vaccination is important.

Japan introduced the diphtheria-tetanus-acellular pertussis (DTaP)-inactivated polio virus (IPV) vaccine, DTaP-IPV, as a routine immunization in November 2012, replacing the "adsorbed diphtheria-tetanus-acellular pertussis (DTP) vaccine". Immunization schedule is completed with four doses of subcutaneous (s.c.) shots; three doses given with intervals at least 20 days apart (the recommended interval is 20-56 days) starting at 3 months of age, followed by one s.c. shot given at least 6 months after the third dose (recommended interval is 12-18 months after completion of the third dose) (http://www.nih.go.jp/niid/images/vaccine/schedule/2016/EN20161001.pdf for Routine/Voluntary Immunization Schedule in Japan, October 1, 2016).

Immunity acquired by vaccination, however, wanes within 4-12 years after vaccination, and vaccinated children and adults may become infected. In developed countries, there have been concerns regarding severe cases among unvaccinated infants, attributed to the increasing number of pertussis patients among adults and young adults, including asymptomatic cases, both of whom serve as sources of infection. In several countries such as the US and the UK, vaccination of the diphtheria-tetanus-pertussis (Tdap) vaccine is being recommended and/or implemented for adults, including adolescents and pregnant women (see p. 37 of this issue).

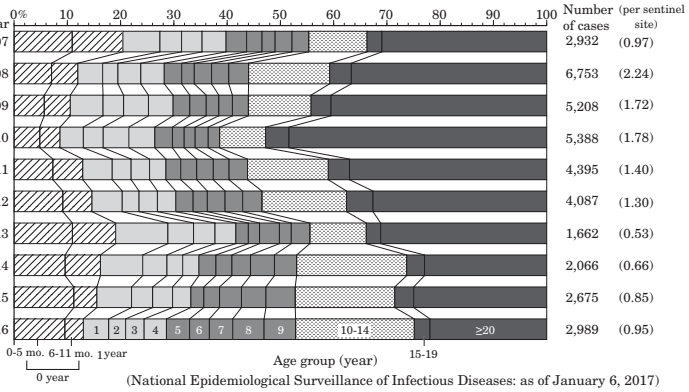
Pertussis reports under the National Epidemiological Surveillance of Infectious Diseases (NESID) system: Pertussis is a category V infectious disease under the Infectious Diseases Control Law. Clinically diagnosed cases are reported weekly from approximately 3,000 pediatric sentinel sites in Japan (Fig. 1). The annual number of reported cases per sentinel site was 0.44-0.73 during 2001-2006. It increased to 0.97 in 2007 and ranged from 1.30-2.24 during 2008-2012. In 2012, pertussis reports increased nationwide, and 10 prefectures reported ≥2.00 cases/site (Fig. 2). Reporting dropped to 0.53/site in 2013, but since 2014, it has been on the rise (0.66-0.95/site). Geographically, prefectures that reported ≥2.00/site was only Okinawa Prefecture in 2013, Okinawa, Tottori and Nagasaki prefectures in 2014, and Okinawa and Tottori prefectures in 2015 (Fig. 2). In 2016, Okinawa, Akita, Kochi, Niigata and Nagano prefectures reported ≥2.00/site (as of January 6, 2017).

In 2007, approximately 20% of the pertussis patients were <1 year old (Fig. 3 in p. 24). Patients aged 6-11 months occupied

(Continued on page 24′)

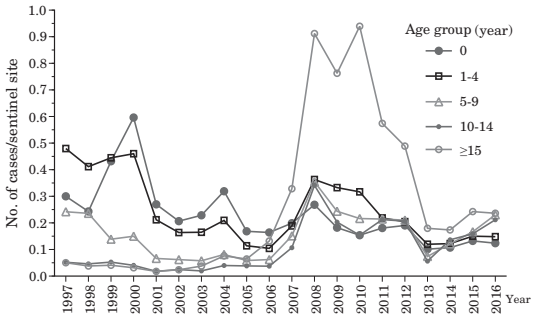
(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Age distribution of pertussis cases from pediatric sentinel sites, 2007-2016, Japan



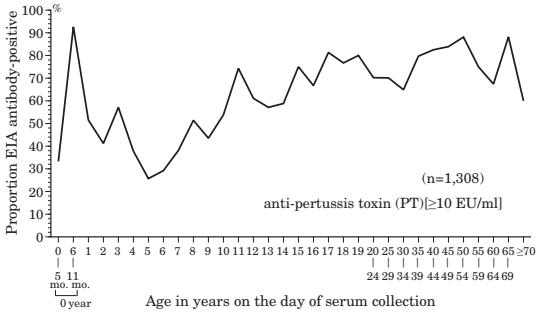
(National Epidemiological Surveillance of Infectious Diseases: as of January 6, 2017)

Figure 4. Annual number of reported pertussis cases per sentinel site by age group, 1997-2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of January 6, 2017)

Figure 5. Seroprevalence of pertussis in 2013, Japan



(National Epidemiological Surveillance of Vaccine-Preventable Diseases, 2013)

3.5% of the cases in 2016 in contrast to 9.5% in 2007. Those aged 0-5 months, most vulnerable to pertussis, occupied 10.9% in 2007 and 9.5% in 2016. Since 2001, reports of patients aged <1 year has remained continuously low (<0.04/site) and was ≤0.21/site except in 2004 and 2008 (Fig. 4).

Although reporting comes from pediatric sentinel sites, there are reported patients older than 15 years old; reports among this age group was 0.02/site in 2002, but became 0.86/site in 2010, reaching 53% of all reported cases. In 2016, reports of patients ≥15 years of age per sentinel was 0.24, occupying 25% of all pertussis patients (Fig. 3 & Fig. 4).

Outbreaks: In 2007, Japan experienced large-scale pertussis outbreaks in universities with more than 200 persons suspected to have been infected, which reconfirmed the high transmissibility of pertussis when a large number of people are in an enclosed space for a prolonged period of time (IASR 29: 65-66 & 68-69 & 70-71 & 71-73, 2008). Recently, several pertussis outbreaks have been reported, including in a junior high school (IASR 36: 142-143, 2015), a local community with cases originating from primary and junior high schools (see pp. 25 & 26 of this issue) and in urban cities (see pp. 28 & 30 of this issue).

Seroprevalence of the Japanese population: According to the latest results from the 2013 National Epidemiological Surveillance of Vaccine-Preventable Diseases (NESVPD) seroprevalence survey, the proportion positive for anti-pertussis toxin (PT) IgG antibody was 90% among age group 6-11 months, indicating high level of immunity among this age group (Fig. 5, see p. 31 of this issue). The antibody-positive rate decreased with age, dropping to 30% at age 5-6 years. However, with increase in age thereafter, the antibody-positive rate increased indicating natural infection.

Pathogens that cause pertussis-like clinical symptoms: Pertussis-like symptoms are also caused by other *Bordetella* species such as *Bordetella parapertussis* and *Bordetella holmesii*. However, only few such infections have been reported in Japan. Pathogens other than *Bordetella* that cause pertussis-like symptoms are *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, human bocavirus, and rhinovirus. As the current reporting criteria for pertussis consists of only clinical signs and symptoms, it is possible that some reported cases are caused by other bacterial species. A laboratory-based investigation of pertussis, using multitarget real-time PCR, conducted by a study group [supported by grants for Research on Emerging and Re-emerging Infectious Diseases from the Ministry of Health, Labour and Welfare (MHLW) of Japan] in 2013-2014, revealed that among 355 cases clinically diagnosed as "pertussis", 94 (26%) were positive for *B. pertussis*, 4 (1.1%) for *B. parapertussis* and 2 (0.6%) for *M. pneumoniae*. No *B. holmesii* was found.

Laboratory diagnosis of pertussis: For the laboratory diagnosis of pertussis, bacterial isolation, serological tests, and gene detection are available (see pp. 33 & 34 of this issue). Isolation of the bacteria has excellent specificity, but it requires special culture medium. The success rate of isolation is ≤60% even from infants with relatively high bacterial load; thus the sensitivity is very low, and isolation is difficult for patients with vaccination history or among adolescents or adults with a low level of the bacteria. Sero-diagnosis using anti-PT IgG is used widely in the world, but WHO does not recommend its use for infants whose immune system is immature or for those who were vaccinated less than a year ago. In Japan, a sero-diagnosis method detecting IgM and IgA antibodies against *B. pertussis* became covered by health insurance in 2016. In contrast, gene detection has high sensitivity and is widely used globally as a rapid detection method. The loop-mediated isothermal amplification (LAMP) developed in Japan is more rapid and simpler to perform than the real-time PCR, and became covered by health insurance in November 2016. National Institute of Infectious Diseases Japan (NIID) has developed a LAMP method and a multiplex PCR method, which can differentiate pertussis-related bacteria (*B. parapertussis* and *B. holmesii*). NIID provides the test reagent kit to prefectural and municipal public health institutes (PHIs) (Pertussis pathogen detection manual: http://www.nih.go.jp/niid/images/lab-manual/Pertussis20151222.pdf).

Conclusion: As pertussis has no specific clinical signs or symptoms, particularly among adolescents and adults, its diagnosis based solely on clinical manifestations is difficult. Furthermore, as cases are reported from pediatric sentinel sites, a full epidemiologic picture regarding pertussis in Japan is lacking. With increased use of genetic detection methods, the timeliness and accuracy of pertussis diagnosis will improve. Consequently, it is hoped that we will have a better understanding of pertussis epidemiology in Japan, which will contribute to effective prevention and interventions.

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.

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