

Importance of varicella vaccination in organ transplantation units in pediatric services .....	289	Dengue fever and chikungunya fever cases that occurred in the same tourist group returning from Cambodia .....	305
Severe form of varicella infection among immune deficient subjects -needing special attention to severe abdominal pain and low back pain.....	290	Change in clinical features of hand, foot and mouth disease (HFMD) within one epidemic season, which was observed in Matsumoto City in the central part of Nagano Prefecture -comparison of 2013 epidemic with the past epidemics.....	306
Adult varicella infection .....	292 & 293	Detection of enteroviruses from aseptic meningitis patients, 2013 -Oita Prefecture .....	308
Varicella infection during pregnancy-fetal death in the third trimester due to primary varicella infection .....	294	Detection of echovirus type 30 from aseptic meningitis patients, 2013-Shiga Prefecture .....	309
Journal Review "Near Elimination of Varicella Deaths in the US After Implementation of the Vaccination Program".....	295	An adult male rubella case, among those who had received measles-rubella vaccine, June 2013-Kawasaki City .....	310
Need of two doses of varicella vaccine .....	296	Hepatitis A virus outbreak due to intrafamilial transmission, March-July 2013-Kawasaki City .....	311
Epidemiological studies on varicella zoster in Miyazaki Prefecture..	298	Clinical characteristics of five severe fever with thrombocytopenia syndrome (SFTS) cases including two cases of intrafamilial infection, May-July 2013 .....	312
Epidemiological studies on varicella zoster in Shodo Island.....	300	A suspected Japanese spotted fever case, which was later diagnosed as endemic typhus by serological diagnosis, June 2013.....	313
Ramsay Hunt Syndrome-what is needed for reducing serious clinical consequences?.....	301		
Pathology of varicella zoster virus infections .....	302		
Geographical distribution of severe fever with thrombocytopenia syndrome (SFTS) cases in Japan (1 <sup>st</sup> report).....	303		
Two domestic infection cases of relapsing fever.....	305		

### <THE TOPIC OF THIS MONTH> Chickenpox/varicella zoster and vaccine in Japan

Chickenpox is caused by the primary infection of varicella-zoster virus (VZV). It is category V infectious disease under the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (Infectious Diseases Control Law) (<http://www.nih.go.jp/niid/images/iasr/34/404/de4041.pdf>) and category II school infectious disease under the School Health and Safety Act. VZV latently infects nerve ganglia, and is reactivated by immunosuppression causing herpes zoster.

**Incidence of chickenpox:** Number of cases increases from winter to spring, and then gradually decreases towards the autumn. Estimatedly about 1,000,000 chickenpox patients, mostly infants, occur every year, though the overall incidence is decreasing (though slightly) in the recent three years (Fig. 1). While 80% of the patients used to be under 4 years of age, since 2010 the percentage of this age group has been decreasing possibly owing to the increased vaccination coverage of this age group (Fig. 2). When chickenpox and rubella, both sentinel reportable infectious diseases, are compared, however, while rubella decreased dramatically after starting of rubella routine vaccination to infants of the both genders in 1995, the incidence of chickenpox, to which immunization has been conducted on voluntary basis, remained continuously high.

**Severe cases:** Transmissibility of VZV is strong. It spreads by the air-borne infection, and subclinical infection is very rare. On estimation, one in 400 natural chickenpox infections among unvaccinated children require hospitalization, and nearly 20 in 1,000,000 infections are fatal (Chickenpox fact sheet, National Institute of Infectious Diseases). The incidence of deaths due to chickenpox is the highest among all the deaths caused by vaccine preventable diseases including measles, rubella, mumps and chickenpox that have been reported since 2004.

Hospital infection of chickenpox is a serious problem in pediatric hospitals in Japan. It cannot be prevented even in hospitals using aggressive infection control, and it sometimes results in ward closure ([http://www.theidaten.jp/journal\\_cont/20130328J-41-2.htm](http://www.theidaten.jp/journal_cont/20130328J-41-2.htm)).

As chickenpox infection can be fatal to infants who are under immune-suppression, infection control including outpatient services should be further strengthened. Currently, utility of post-operative varicella vaccination to infant organ recipients is under study (see p.289 of this issue). Very often, among immune-compromised individuals with leukemia and other malignancies, etc., the first sign of chickenpox infection is abdominal or back or low back pain in place of rash, and may follow poor clinical consequence like multiple organ failure, disseminated intravascular coagulation, etc. (see p.290 of this issue). Adults as well as infants at high risk tend to follow severe clinical course, such as, pneumonia (see pp. 292 & 293 of this issue).

If a mother is infected during the first 20 weeks of gestation, infection causes in 1-2% of the cases serious damages to the fetus, which is known as congenital varicella syndrome. Stillbirth, though rare, may also occur (see p. 294 of this issue). When

Figure 1. Chickenpox (1982-week 37 of 2013) and rubella cases (1982-2007)\* reported on weekly basis from sentinel clinics

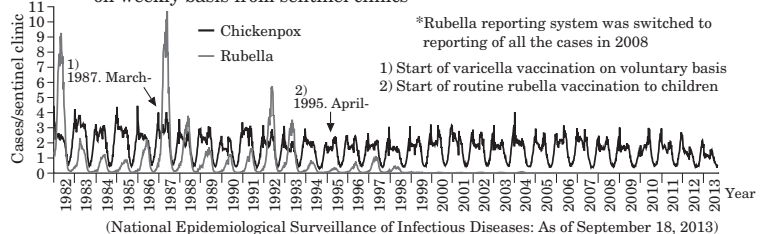
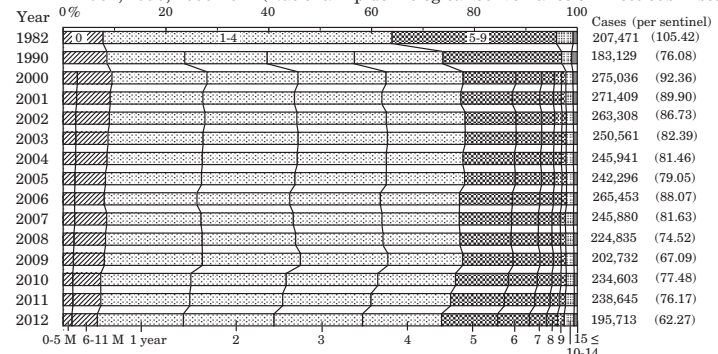


Figure 2. Age distribution of chickenpox cases reported from pediatric sentinel clinics, 1982, 1990, 2000-2012 (National Epidemiological Surveillance of Infectious Diseases)



(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Annual production of varicella vaccine from 2003 to 2012

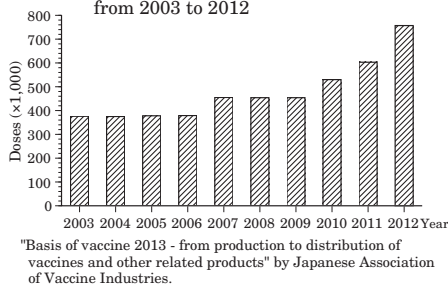
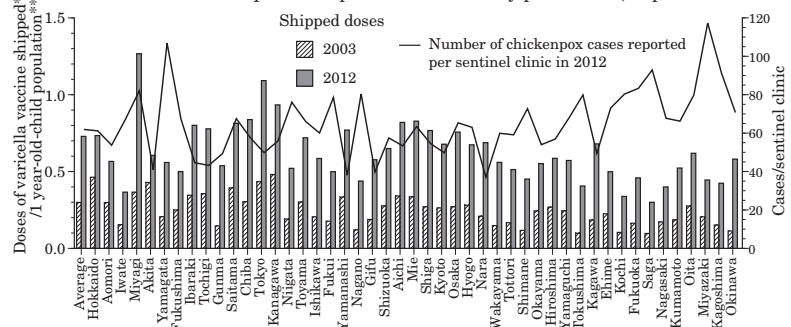


Figure 4. Amount of varicella vaccine shipped (doses per 1-year-old children) and number of chickenpox cases per sentinel clinic by prefectures, Japan



a mother catches chickenpox within 5 days before or 2 days after delivery, trans-placental infection occurs and the infected newborn often follows a serious consequence due to the lack of maternal antibody.

**Prevention and therapy:** Varicella vaccine is the best for prevention of chickenpox. When a person without immunization or infection history is exposed to varicella, immediate vaccination within 3 days after exposure can prevent disease onset or aggravation of symptoms. As a post-exposure treatment, anti-herpes drugs, such as, acyclovir (ACV) and valacyclovir (VCV), or anti-chickenpox/varicella zoster immunoglobulin (VZIG) is administered. ACV and VCV are not covered by the health insurance in Japan, and VZIG is primarily used abroad. As treatment of infants at high risk needs VZIG, clinicians request its approval and supply in Japan.

**Varicella vaccine:** The Oka strain varicella live vaccine is recognized by WHO as the most desirable varicella vaccine. In Japan, vaccination targets are people older than 12 months who have no history of chickenpox, people having risk of developing severe form of chickenpox, people having risk individuals in their family, or health care providers. As the vaccination has been conducted on the voluntary basis, exact coverage rate is unknown; so far, coverage rate has been calculated on the basis of number of shipped lots and number of births, which was 30-40%. From 2009 to 2012, the vaccine production doubled probably thanks to increased public recognition and local governments' expanded subsidy to vaccination (Fig. 3). The vaccination dose, which used to be one dose, is now becoming two doses under the influence of the world trend. Therefore, the increased shipment can't be translated directly into increased number of children receiving the vaccine. A system of more precise estimation of vaccine coverage is needed. The amount of the vaccine shipped dose 1-year-old children population is quite variable among prefectures in Japan (Fig. 4).

**Safety and efficacy of vaccine:** No serious side effects have been observed among the healthy vaccinees since gelatin, an allergen, was removed from vaccine in 2000. Secondary infection of vaccine strain is very rare; so far only 10 cases have been reported in the world. Its efficacy is evidenced by the drastic decrease of patients, hospitalizations and deaths in the United States, which adopted routine immunization of chickenpox in 1995 (see p. 295 of this issue). For those having received one dose, the probability of reinfection during an epidemic is 15-20%, and that of acquiring moderate to severe chickenpox is <5%. As the reinfection can be prevented by two doses (see p. 296 of this issue), implementation of two vaccine doses is desirable from the public health viewpoint. Comparison of costs of vaccination and patient care including burden on patient's family has indicated the cost-effectiveness of routine varicella vaccination. Currently, Vaccine Panel established by Health Science Council is working on incorporation of varicella vaccine into the routine immunization.

**Varicella zoster (VZ):** According to a survey in Miyazaki prefecture (see p. 298 of this issue), one in three persons acquires VZ if they live for 80 years. The risk of developing VZ can be assessed by an intradermal skin test (see p. 300 of this issue). VZ reduces quality of life on account of the skin rash and prodromal pain as well as postherpetic neuralgia. Ramsay Hunt syndrome occasionally observed is refractory to therapeutic intervention (see p.301 of this issue). Though early clinical intervention can alleviate associated complications, varicella control by vaccine is of prime importance.

As VZ development and decreased host cellular immunity are closely correlated, the United States considered use of varicella vaccine for control of VZ reactivation by taking advantage of its capacity to augment cellular immunity, and the FDA approved an Oka strain based VZ vaccine in 2006. Clinical trials in the United States revealed that incidence of VZ, postherpetic neuralgia and severe cases were decreased by more than 50% each.

As Japan's VZV vaccine for routine immunization has titer comparable to that of the United States' VZ vaccine, since 2004 the VZV vaccines sold in Japan have been attached with a package insert informing that, under "pharmacology", the vaccine can enhance cellular immunity to VZ when applied to persons with decreased immunity due to aging and other reasons.

**Diagnosis:** Clinical diagnosis of chickenpox and VZ is easy. Laboratory diagnosis using antibody test is available in the commercial laboratories, and is used as a confirmatory test. Virus genome can be detected from vesicles as they contain large amount of virus particles, but the test is not covered by the health insurance. Pathological characteristics of severe VZV infection cases are detailed in p. 302 of this issue.

For monitoring of efficacy and safety of varicella vaccine, a VZV pathogen surveillance system should be established. Differential diagnosis of wild type VZV and vaccine type VZV that is required for the surveillance is described in the "Pathogen Detection Manual: National Institute of Infectious Diseases".

*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.*