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REVIEW ARTICLE

Varicella vaccination in Japan: necessity of implementing a routine vaccination program

Takao Ozaki

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Abstract Varicella-zoster virus (VZV) is the causative agent of varicella (chickenpox). It shows extremely high infectivity and is spread by airborne, droplet, and contact transmission. After a person is infected with VZV, the virus remains dormant in the dorsal root ganglia, but can be reactivated under circumstances where specific immunity declines, leading to the development of herpes zoster (shingles). Although varicella is a disease that usually resolves after about 1 week, it can cause various complications such as secondary bacterial skin infection, pneumonia, and encephalitis. In addition, varicella can become severe in immunocompromised persons, whereas VZV infection transmitted from an infected mother can cause the congenital varicella syndrome or serious neonatal varicella. In 1974, a live varicella vaccine (Oka strain) was developed in Japan for the prevention of varicella, and clinical trials performed during the development were mainly focused on high-risk children. In 1985, the Oka strain was recognized as the best varicella vaccine strain by the World Health Organization (WHO). Today, all the varicella vaccines used worldwide to immunize approximately 32 million people annually contain the Oka strain. In Japan, it has been commercially available since 1987 for the voluntary vaccination program, in which children over the age of 1 year with no history of previous varicella infection receive a single dose. In addition to healthy children, this vaccine can be used for immunocompromised children, and vaccination of elderly persons can also be done to enhance their immunity against VZV. Varicella vaccine is a highly safe vaccine with sufficient immunogenicity. The preventive effect of single-dose vaccination is believed to be approximately 80 % for all types of varicella, including mild cases; it is 95 % or greater for moderate to severe disease. Implementation of a two-dose vaccination schedule has proved to be effective against breakthrough varicella, which is observed in approximately 20–30 % of children vaccinated with a single dose. Because it is administered as part of the voluntary vaccination program, the varicella vaccination coverage rate in Japan has remained low until recently at around 20–30 %, with no sign of a decrease in the number of varicella patients. It is necessary to maintain a vaccination rate of 90 % or higher to prevent varicella epidemics. To achieve this goal, implementation of a routine vaccination program for varicella and introduction of a two-dose vaccination schedule, which is more effective than a single-dose schedule, would be highly desirable.

Keywords Varicella vaccine · Oka strain · Breakthrough varicella · Routine vaccination program · Two-dose vaccination schedule

T. Ozaki (✉)
Department of Pediatrics, Konan Kosei Hospital,
137 Ohmatsubara, Takaya-cho, Konan,
Aichi 483-8704, Japan
e-mail: takao-oz@konan.jaaikosei.or.jp

Introduction

The causative agent of varicella is varicella-zoster virus (VZV), which belongs to the α-subfamily of the Herpesviridae. VZV is a spherical enveloped virus (150–200 nm in diameter) that contains double-stranded DNA and has a genome consisting of approximately 125,000 base pairs. The entire nucleotide sequence of VZV has been determined, and it contains 71 genes.

Primary VZV infection leads to the development of varicella after an incubation period of 14–16 days from the

time of infection. The infectivity of VZV is extremely high. The virus invades the body through the airway mucosa or conjunctival mucosa after airborne, droplet, or contact transmission, and causes primary viremia [1]. Then, it multiplies in the reticuloendothelial system, including the liver and spleen, after which secondary viremia spreads VZV to the skin [2–4]. The virus grows in capillary endothelial cells and epithelial cells of the skin; the immune response to VZV increases capillary permeability and causes leakage of plasma components, leading to formation of the characteristic vesicles associated with this infection. There is no suitable animal model for varicella, so the pathogenesis of this disease has been speculated by the dual viremic model of mousepox [5]. According to a recent theory [6], VZV enters the upper respiratory tract and quickly reaches the skin via infected memory T cells. Then, it causes viremia and a rash after overcoming innate immunity in approximately 2 weeks. When a person becomes infected with VZV, the virus reaches the dorsal root (sensory) ganglia centripetally from the terminals of cutaneous sensory nerves at the sites of vesicles or via hematogenous spread, and it remains dormant in these ganglia. VZV can then be reactivated when specific immunity declines as a consequence of aging, with the trigger being an additional stress such as overwork, anxiety, chemotherapy, sunlight, surgery, or trauma. It then reaches the skin by traveling along nerve fibers to cause the typical rash of herpes zoster with its dermatome distribution.

The main symptoms of varicella include mild fever and a generalized vesicular rash. From 250 to 500 vesicles usually develop, and tend to be profuse on the trunk and sparse on the face or extremities. Papules change into vesicles, after which the vesicles eventually form crusts. It is characteristic for a mixture of eruptions at different stages of this process to exist on the skin. In general, the disease resolves after approximately 1 week, but it can become severe in patients who are in an immunocompromised state, such as those receiving anticancer agents for a malignant tumor or steroids for nephrotic syndrome. In addition, VZV infection of a pregnant woman during the period from 5 days before to 2 days after delivery can lead to serious neonatal varicella.

The most common complication of varicella is secondary bacterial skin infection, with the main causative bacteria being *Streptococcus pyogenes* (group A streptococcus) and *Staphylococcus aureus*. These bacterial infections produce impetigo, cellulitis, and staphylococcal scalded skin syndrome. In addition, varicella infection is a risk factor (incidence, 15–30 %) for fulminant Group A streptococcal infection in children [7]. Pneumonia is relatively less common among immunocompetent children but is the most common complication in adults. Neurological complications include varicella encephalitis (1/50,000) and acute cerebellar ataxia (1/4,000). An association of Reye's syndrome as well as influenza has also been pointed out. If women become infected with VZV up to the 20th week of pregnancy, approximately 2 % of their offspring develop congenital varicella syndrome, which features skin contractures, hypoplasia of the skin and muscles, cataract, ocular malformations, microcephaly, and mental retardation [8].

Live varicella vaccine (Oka strain)

In 1974, a live vaccine (Oka strain) for the prevention of varicella was developed in Japan by Takahashi et al. [9]. VZV was isolated from a young varicella patient whose last name was Oka and was subjected to attenuation by serial passage in human embryonic lung cells, guinea pig embryo cells, and human diploid cells. Then, extensive studies were conducted in Japan, as well as in Europe and the United States, providing comprehensive data on its safety and efficacy. In 1985, the Oka strain was selected by the WHO as the most desirable attenuated live varicella vaccine strain [10]. Today, all varicella vaccines used worldwide to immunize approximately 32 million people annually contain the Oka strain. In 1984, it was approved in several European countries (first approval worldwide) for use in high-risk children. In Japan, the vaccine was approved in September 1986 and has been commercially available since March 1987 (Varicella Vaccine Live Attenuated "BIKEN," The Research Foundation for Microbial Diseases of Osaka University).

The vaccine strain has mutations concentrated in gene 62, the product of which is a strong transactivator of VZV [11], and these mutations are believed to play an important role in attenuating the virus. It has been shown that some mutations involve mixtures of two kinds of base at each position, suggesting that the Oka strain is composed of a mixture of genotypically distinct viral strains [12]. Furthermore, based on the measurement of VZV DNA in vaccinated children, the in vivo multiplication of the vaccine strain is suggested to be weaker than that of the wild-type strain [13].

Use of varicella vaccine in Japan

In Japan, varicella vaccine is not included in the routine immunization program specified by the Preventive Vaccination Law. Instead, the vaccine is administered at the request of an individual or a child's legal guardian as part of the voluntary vaccination program. As one of the reasons the vaccine is in the voluntary vaccination program,

the Japanese Government does not seem to understand sufficiently the effectiveness and necessity of varicella vaccine. Vaccination under the routine program is given free of cost, but vaccination for varicella is not free, and each individual is responsible for the cost. Persons more than 1 year old without a history of varicella are eligible for vaccination, and they receive a single subcutaneous injection of 0.5 ml [at least 1,000 plaque-forming units (PFU) of the virus titer].

After exposure to VZV infection, varicella can be prevented by emergency vaccination, although the vaccine has to be administered within 72 h of contact with a varicella patient [14]. It is believed that immunity is induced rapidly because the vaccine strain is administered subcutaneously, after which it suppresses the growth of the infecting wild-type strain.

The vaccine can be administered to patients who are likely to develop complications of VZV infection, including those with acute leukemia or solid tumors and those on steroid therapy for nephrotic syndrome. The package insert lists test data that are used as the vaccination criteria. Clinical trials performed during the development of this vaccine were mainly focused on high-risk children [15–18], representing a difference from other vaccines for which clinical trials were mainly performed in healthy individuals.

Vaccination of the elderly has been shown to enhance their humoral and cellular immunity against VZV [19], so the package insert now contains a statement that elderly persons with decreased immunity to VZV can receive vaccination. Although vaccination of the elderly is possible, only a few elderly people actually request it.

Varicella vaccination coverage rate in Japan

In Japan, varicella vaccine sales have been on the rise since it became commercially available in 1987, gradually increasing from around 200,000 doses per annum to around 500,000 doses per annum in the past 2 years. The age distribution of vaccinees in Japan has not been determined. At the author's hospital, approximately 90 % of vaccinations are given to children up to 5 years old, with the peak at 1 year of age (35 %), based on data about vaccinees stratified by age group during the 10 years from 1987 to 1997 [20]. Although the surveillance data obtained by Mitsubishi Tanabe Pharma Co. have not been published, age-based data on persons who received vaccination at 466 clinics nationwide in 2011 also reveal that 1-year-old children formed the largest group (35 %), with children up to 4 years old accounting for approximately 90 %. Thus, there seems to have been no change in the targets of vaccination since the varicella vaccine became available, and the focus is on children at the age of 1 year.

The vaccination coverage rate among children in Japan has not been accurately determined. Instead, the figure obtained by dividing the annual vaccine sales by the number of births in the previous year is used as an estimated vaccination coverage rate. Postmarketing changes of the estimated varicella vaccination coverage rate among children are shown in Fig. 1. The rate remained at around 20 % for the first 15 years, after which there was a gradual increase, and the rate has been around 50 % for the past 2 years. It is likely that a subsidy for vaccination provided by local governments across the country has led to the rise in recent years. To further increase the vaccination coverage rate and decrease the number of patients, however, it may be necessary to make vaccination for varicella routine or to establish a national policy for the government to subsidize the cost nationwide. In the future, vaccine use is expected to increase because of adoption of schedules other than single-dose vaccination in children (e.g., two-dose vaccination, vaccination of healthcare professionals and adult overseas travelers, and vaccination of the elderly), which could lead to overestimation of the vaccination coverage rate by the current calculation method, so establishment of an alternative method that is more rational and accurate is desired. For example, the United States added varicella vaccination to its universal immunization program in 1995, and the vaccination coverage rate among children (more than one dose for children aged between 19 and 35 months) was 90.4 % in 2010 [21].

Safety and immunogenicity of varicella vaccine

Varicella vaccine is considered to be very safe. According to the results we have obtained so far [20, 22, 23], there has been no anaphylaxis, generalized rash, or other serious adverse reactions after vaccination, except for some cases of fever (≥37.5 °C) and mild rash. However, anaphylaxis

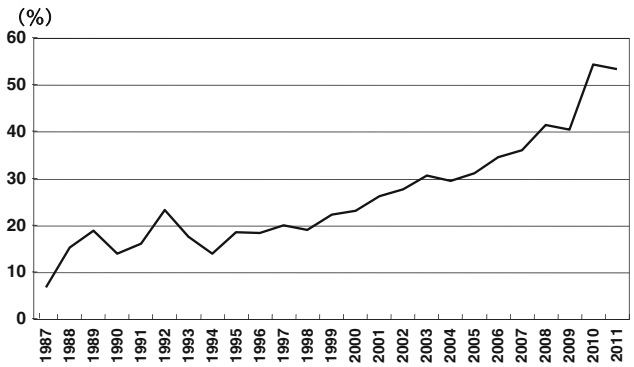

Fig. 1 Estimated varicella vaccination coverage rate among children in Japan. Vaccination coverage rate (%) was calculated as follows: vaccine dose sales/number of births in the previous year × 100

caused by allergic reactions to gelatin, which is used as a stabilizer [24], has occasionally been reported after varicella vaccination. Sensitization to gelatin in diphtheria-tetanus-acellular pertussis vaccine administered before the varicella vaccine was found to be the cause of such anaphylaxis [25]. The varicella vaccine used in Japan has not contained gelatin since January 2000, and there have been no reports of serious anaphylaxis following vaccination after that dose (Table 1) [23].

As the assay for varicella antibody, the immune adherence hemagglutination (IAHA) method is used in Japan, whereas a glycoprotein-based enzyme-linked immunosorbent assay (gpELISA) is commonly used in the United States. Our previous study [26] showed that the IAHA antibody titer is generally consistent with the neutralizing antibody titer, which is the gold standard for antibody measurement [27], suggesting that the IAHA method is effective for measuring varicella antibodies. The vaccine is considered to be sufficiently immunogenic, with a very high IAHA seroconversion rate of 93.6–98.6 % according to previous reports [20, 22, 23]. In a survey conducted by the author and colleagues between 2005 and 2008, however, the IAHA seroconversion rate was only 86.1 % (192/223), which was slightly lower than the rates obtained previously. Thus, careful monitoring of the vaccine's immunogenicity will be required in the future.

In recent years, the viral titer of the commercial varicella vaccine has been 42,000–67,000 PFU per dose [28], which is more than five times higher than that at the time of its development, and many times higher than the standard for the product listed in the package insert (1,000 PFU/dose or more). We compared a group of 20 subjects who received 0.1 ml (2,600–6,400 PFU) of the current vaccine (containing an amount of virus similar to that in the full dose at the time of development) with a group of 23 subjects who received the normal dose (13,000–32,000 PFU), and found that the former group had a lower seroconversion rate (Table 2) and that between the groups there was no significant difference in incidence of clinical reaction [29]. Thus, we think that the current viral titer, which greatly exceeds the product standard for this vaccine, is actually required to maintain sufficient immunogenicity. We also found that additional vaccination of non-seroconverted subjects with the normal dose resulted in a high seroconversion rate and high titer, possibly the result of a booster effect.

Effectiveness of varicella vaccine

Occurrence of breakthrough varicella in children who had been vaccinated was observed even in the early clinical trials [22], and it is widely known to occur at a slightly higher frequency than with other live vaccines. In a post-marketing survey conducted by the author and colleagues, 21 % of vaccinated individuals developed varicella, usually within 4 years after vaccination (Table 3) [20]. In Japan, the reported prevalence of breakthrough varicella after vaccination shows a wide range, from 6.2 % to 12.3 % [30] and up to 34.2 % [31]. Most cases of breakthrough varicella are mild.

The preventive effect of varicella vaccine was estimated to be 75 % according to a survey conducted by the author [20]. For comparison, the preventive effect of single-dose vaccination with the Oka/Merck strain in the United States was reported to be 79–88 % for all types of varicella, including mild cases, and 95–100 % for moderate to severe disease [32–36].

According to a survey of vaccine-preventable diseases in Aichi Prefecture from 1994 to 1998, hospitalization for varicella was relatively common and the number of inpatients was 654, following measles (1,936) and mumps (933), with high average hospitalization costs of approximately 270,000 yen per person [37]. The incremental cost:benefit ratio was calculated to be more than 4 if varicella vaccine was included in the routine vaccination program [38], which implies a strong effect of this vaccine on medical economy.

In 2005, Oxman et al. reported that administration of the Oka/Merck VZV vaccine ("zoster vaccine") to persons aged 60 years or older had a preventive effect on herpes zoster and postherpetic neuralgia, with an efficacy rate of

Table 1 Breakdown of anaphylactic/allergic reactions following immunization with gelatin-containing and gelatin-free varicella vaccine [23]

Varicella vaccine	Degree of seriousness	Anaphylactic reaction	Generalized urticaria	Dyspnea	Shock-like syndrome	Diarrhea	Swelling at injection site	Total
Gelatin containing	Serious	28	0	0	0	0	0	28
	Not serious	4	118	9	2	1	5	139
Gelatin free	Serious	0	0	0	0	0	0	0
	Not serious	1	2	0	1	0	1	5

Approximately 1,410,000 doses of gelatin-containing varicella vaccine, and approximately 1,300,000 doses of gelatin-free varicella vaccine, were distributed

Varicella vaccine was used alone in all cases

Table 2 Seroconversion and antibody titer after varicella vaccination [29]

Vaccination	0.1 ml ($n = 20$)		0.5 ml ($n = 23$)	
	After first	After second (0.5 ml)[a]	After first	After second[a]
Seroconversion (%)				
IAHA	25.0 (5/20)[b]	100 (15/15)	76.2 (16/21)	100 (4/4)
gpELISA	55.0 (11/20)[c]	100 (15/15)	87.0 (20/23)	100 (4/4)
Mean antibody titer[d]				
IAHA (log 2)	4.2	6.0[e]	4.5	5.5[f]
gpELISA (log 10)	2.3	3.7[g]	2.6	3.6[h]

[a] Additional vaccination was administered to subjects failing to seroconvert in immune adherence hemagglutination (IAHA) after initial vaccination*gpELISA*, glycoprotein-based enzyme-linked immunosorbent assay

[b] $p < 0.01$ vs. after initial 0.5-ml vaccination

[c] $p < 0.05$ vs. after initial 0.5-ml vaccination

[d] Postvaccination antibody titer of the seroconverters

[e] $p < 0.01$ vs. after initial vaccination in both vaccination groups

[f] $p < 0.05$ vs. after initial 0.1-ml vaccination

[g] $p < 0.01$ vs. after initial vaccination in both vaccination groups

[h] $p < 0.05$ vs. after initial vaccination in both vaccination groups

Table 3 Number of cases of breakthrough varicella according to the interval from vaccination [20]

Interval (years)	Number (%) of cases who developed breakthrough varicella
0.04[a]–1	19 (16.0)
~2	30 (25.2)
~3	25 (21.0)
~4	16 (13.4)
~5	8 (6.7)
~6	5 (4.2)
~9.9[b]	12 (10.1)
Unspecified	4 (3.4)
Total	119

A total of 119 (21.3 %) of 559 vaccinees who were initially seronegative contracted breakthrough varicella

[a] The shortest interval was 2 weeks from vaccination in one case. The other cases developed breakthrough disease at more than 1 month after vaccination

[b] The longest interval was 9 years 11 months from vaccination

51.3 % and 66.5 %, respectively [39]. In the United States, a varicella vaccine for the prevention of herpes zoster (Zostavax; MSD) was approved in 2006, with administration of this vaccine to elderly persons aged 60 years or older being recommended. In 2011, the target age for vaccination was lowered to 50 years or older. Given that the effectiveness of the vaccine has already been demonstrated in the United States [40], Japan should also consider another additional use of varicella vaccine for prophylaxis against herpes zoster in the elderly who are more than 50 or 60 years of age as soon as possible. However, because no clinical trial of varicella vaccine for prevention of herpes zoster has been performed in Japan, immediate conduct of the clinical trial is desirable.

Incidence of varicella in Japan

The current prevalence of varicella in Japan cannot be grasped accurately because we do not know the total number of cases. Instead, we have to rely on reports from pediatric sentinel clinics (there are approximately 3,000 clinics nationwide). Varicella is endemic/epidemic in Japan, with around 250,000 patients being reported annually by the pediatric sentinel clinics. The number of patients shows a marked decrease from August to October and then increases through the winter and spring until early summer, with this pattern being repeated every year. No significant decrease of cases has been observed since the varicella vaccine and two oral antiviral agents (acyclovir and valacyclovir) became available (Fig. 2). The exact number of varicella patients is unknown, but infection with VZV mainly occurs in childhood, so the annual number of patients can be estimated as approximately 700,000, which is calculated as the number of births minus the number of vaccinated children. Moreover, the Ministry of Health, Labour and Welfare has estimated that approximately 4,000 people are hospitalized and approximately 20 people die annually as a result of varicella [41].

The age distribution of varicella patients who presented to the author's hospital during the past 3 years (2009–2011) is shown in Fig. 3a. Their age distribution was not very different from that reported by the sentinel clinics

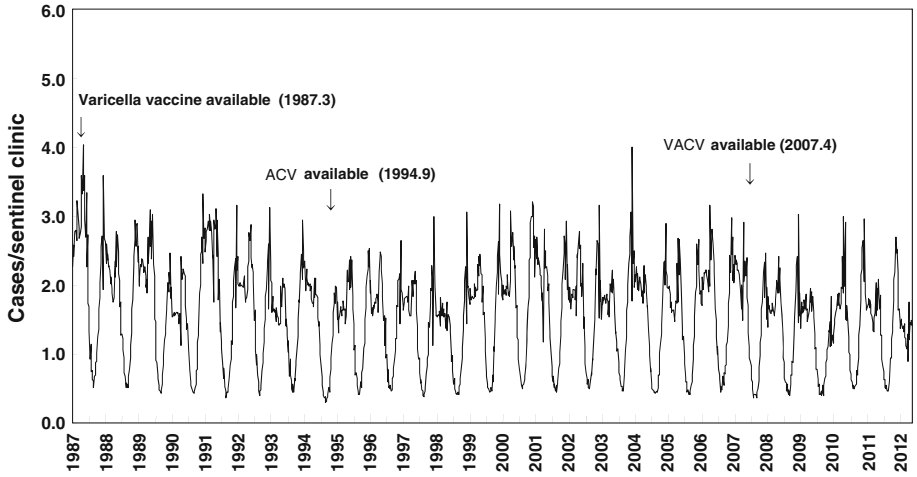

Fig. 2 Weekly cases of varicella per pediatric sentinel clinic from the 1st week of 1987 through 24th week of 2012, Japan. The figure was composed of data of the national epidemiological surveillance of infectious diseases. There are approximately 3,000 pediatric sentinel clinics throughout Japan. *ACV* acyclovir, *VACV* valacyclovir

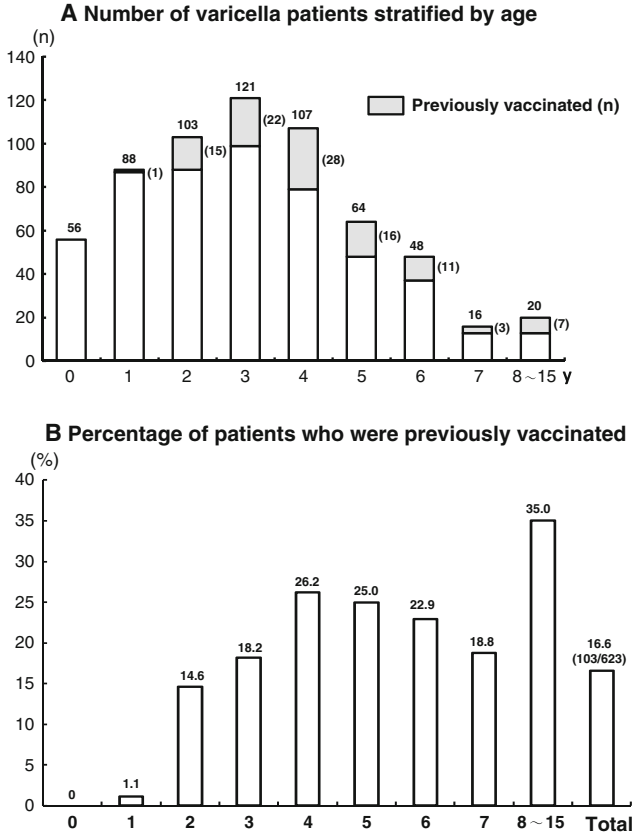

Fig. 3 Patients with varicella ($n = 623$) who visited the pediatric outpatient clinic of Konan Kosei Hospital during the 3-year period between 2009 and 2011. If the onset was within 4 weeks after vaccination, the case was regarded as "not previously vaccinated"

nationwide, with the peak of VZV infection occurring at the age of 3 years and most cases between 0 and 6 years of age. Among children older than 2 years, a certain level of vaccination was confirmed, and in total 17 % of the pediatric varicella patients had received vaccination. Among children between 4 and 6 years old, the vaccination rates of each age were more than 20 % (Fig. 3b). In the United States, varicella vaccine was introduced in 1995 and natural varicella decreased markedly. Instead, breakthrough cases gradually increased over the next 9 years until 2004, when the majority of patients had breakthrough varicella that only caused mild symptoms [42].

Improving the varicella vaccination coverage rate

The crude herd immunity threshold for varicella (percentage of people with immunity in the population at which infection of susceptible individuals is prevented) is thought to be approximately 90 % [$(1 - 1/R_0) \times 100$], which was calculated by setting the basic reproduction number (R_0, the average number of secondary cases generated by an index case when an epidemic begins in a completely susceptible population) at 8 to 10? [43]. The vaccination coverage rate among children in Japan has been only 20–30 % until recently, although it has reached about 50 % in the past few years. Furthermore, as shown in Fig. 2, a significant decrease in the number of varicella patients has never been observed. Control of this disease requires a vaccination rate of 90 %, and to achieve this, adding varicella vaccine to the routine immunization program will be necessary. Currently, varicella vaccine is part of the voluntary vaccination program, so costs are paid by the individuals who want the vaccine, which greatly hinders improvement of the vaccination coverage rate. Thanks to the efforts of various local governments, a subsidy for vaccination is now available in some areas. Although such a subsidy is certainly an effective measure, there seems to be a limit to how much it can increase the coverage rate. Instead, we should consider that implementation of routine varicella vaccination based on the Preventive Vaccination Law would be the most effective approach for improvement of the coverage rate and marked decrease of number of patients. That is, the government should understand the

effectiveness of varicella vaccine and recognize the need for varicella vaccination, and declare that improvement of the vaccination coverage rate is a national policy.

Along with the adoption of the routine vaccination program, it is also desirable to introduce a two-dose schedule, because, in addition to decreasing the prevalence of characteristic breakthrough varicella infection, the vaccination coverage rates are also expected to improve because of the increased opportunity of vaccination. In August 2012, a two-dose schedule (12–15 and 18–23 months) was recommended by the Japan Pediatric Society, but the package insert of the vaccine has not yet been revised. In some countries, including the United States, a two-dose schedule for varicella vaccination has already been implemented, and a decrease in the number of patients with varicella (including those with breakthrough disease), has been reported [44–46].

Overseas, two combined measles, mumps, rubella, and varicella live vaccines (MMRV, ProQuad from MSD; and PRIORIX-TETRA, from GSK) are available [47], whereas no combined live vaccines containing varicella vaccine have been approved in Japan. It seems likely that approval of combined vaccines will increase convenience, leading to further improvement of the vaccination coverage rate. Postlicensure studies of MMRV in the United States demonstrated the likelihood of slight increase of febrile seizures after receiving the first dose [48]. The American Academy of Pediatrics recommends either measles-mumps-rubella (MMR) and varicella vaccines separately, or the MMRV be used for the first dose. For dose 2, use of MMRV generally is preferred over separate injections of MMR and varicella vaccines [49].

Conclusions

There is a considerable need for varicella vaccination to prevent various complications, such as secondary bacterial infection of the skin, pneumonia, and encephalitis, as well as preventing infection (which often becomes severe) in high-risk children, serious neonatal varicella, and congenital varicella syndrome. Live varicella vaccine (Oka strain), which was developed in Japan in 1974, is a highly safe vaccine with a good seroconversion rate. The implementation of a two-dose schedule is an effective countermeasure for breakthrough varicella, which is observed in 20–30 % of individuals who receive a single dose. Because varicella vaccination is part of the voluntary vaccination program in Japan, the vaccination coverage rate remains low and a decrease in the number of varicella cases has not been observed. Adding varicella vaccination to the routine vaccination program and implementation of the two-dose schedule are thus desired.

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