World Health Organization
Global Vaccine Safety,
Immunization, Vaccines and Biologicals
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
VARICELLA ZOSTER VIRUS VACCINE

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The Vaccines

Monovalent varicella vaccine

The varicella-zoster virus (VZV) vaccine to protect against varicella (varicella vaccine) is composed of the Oka strain of live attenuated virus. The Oka strain was isolated in Japan from a healthy child with natural varicella, and was attenuated through sequential passages in cultures of human embryonic lung cells, embryonic guinea-pig cells and human diploid cell line WI-38. The virus underwent further passages through human diploid cell line MCR-5 for one of the available vaccines. The vaccine is presented as lyophilized virus. Its medium is also supplied for reconstitution immediately before injection.

Each 0.5 ml vaccine dose also contains 12.5 mg of hydrolyzed gelatine or human albumin, 25 mg of sucrose or lactose, trace amounts of neomycin and fetal bovine serum, and traces of residual components of substrate cell cultures (including DNA and protein), all within allowed range (see table below). The vaccine does not contain any preservative (CDC, 1996).

Combination varicella vaccine

Introduction of varicella vaccination for public health use in young children would be facilitated if varicella vaccine could be combined with a measles–mumps–rubella (MMR) vaccine. The titre of VZV is ~14 times higher in MMRV vaccine than in the monovalent varicella vaccine. The vaccine has been proven safe, with the exception of an increase in febrile seizures in infants receiving their first dose of MMRV.

Types of vaccines

	Vaccine antigens	Excipients
Monovalent	Live attenuated Oka strain, propagated in MRC_5 human diploid cells (Varilix) Live attenuated Oka strain propagated in MRC_5 human diploid cells (Varivax)	Amino acids, Human albumin, lactose, neomycin, sorbitol, mannitol Sucrose, hydrolyzed gelatine, urea, monosodium glutamate, sodium chloride, sodium phosphate, potassium phosphate, potassium chloride, neomycin, fetal bovine serum
Combination	Live attenuated OKA strain propagated inMRC_5 human diploid cells, plus Measles (Edmonston strain), Mumps (Jeryl Lynn) and Rubella (Wistar RA 27/3)	Sucrose, hydrolyzed gelatine, urea, monosodium glutamate, sodium chloride, sodium phosphate, potassium phosphate, potassium chloride, neomycin, fetal bovine serum

Adverse events

Mild adverse events

Local adverse events

In a double-blind placebo-controlled study of 914 healthy susceptible children and adolescents, pain and redness at injection site occurred statistically significantly more often ($p<0.05$) in vaccine recipients than in placebo recipients (Kuter et al., 1991). In children aged 12 months to 12 years (in uncontrolled clinical trials, 8,900 healthy children) receiving one dose of vaccine, 19.3% of vaccine recipients reported pain/soreness, swelling, erythema, rash pruritus, haematoma, induration at injection site, or stiffness of injected limb. In 3.4% of the children, a mild, varicella-like rash developed at the injection site, consisting of a median number of two lesions and occurring during 5–26 days post-vaccination. In uncontrolled studies including approximately 1,600 vaccinees ≥13 years of age, 24.4% of single dose recipients and 32.5% of two dose recipients reported injection site soreness, swelling, erythema, rash, pruritus, haematoma, induration or numbness and/or fever. A varicella-like rash at the injection site consisting of a median number of two lesions occurred during 6–20 days and 0–6 days post-vaccination in 3% of single dose recipients and 1% of two dose recipients.

Systemic adverse events

In uncontrolled clinical trials including children aged one to 12 years, 14.7% of the vaccinees developed fever (oral temperature ≥ 39°C) usually associated with an intercurrent illness. Febrile seizures following vaccination occurred in <0.1% of children, with no causal relationship having been established. In uncontrolled studies including persons ≥13 years of age approximately 1,600 single dose recipients and 955 two dose recipients of varicella vaccine were monitored for 42 days for adverse events. After the first and the second dose, 10.2% of the single dose recipients and 9.5% of the two dose recipients developed fever (oral temperature ≥37.7°C) usually associated with an intercurrent illness. A mostly vesicular rash, distributing away from injection site and consisting of a median number of five lesions, was developed during 7–21 days in 5.5% of single dose recipients and during 0–23 days in 0.9% of two dose recipients (CDC, 1996).

Combination varicella vaccines – MMRV (Local and Systemic adverse events)

Following studies on the safety of two dose levels (5300 and 200 PFU) of varicella vaccine combined and not combined with standard MMR vaccine, varicella vaccine at both titre levels was found safe. 10% of the children had minor skin reactions, possibly attributable to the vaccine. Reactions typically associated with MMR vaccination did not significantly increase after MMRV vaccination (Vesikari et al., 1991). A similar safety profile was observed when MMRV and Hib vaccines were injected during the same visit (Reuman et al., 1997), and when DPT-Hib vaccine MMR and varicella vaccines were given during the same visit (Shinefield et al., 1998). At least two more recent open randomized, controlled studies evaluating tetravalent MMRV vaccine have shown a higher incidence of low grade fever (axillary temperature ≥ 37.5 °C) in the MMRV group compared with those given MMR and varicella vaccines given separately after first dose. However, no differences were observed following second dose of the MMRV vaccine (Knuf et al., 2006, Goh et al., 2007).

Severe adverse events

Post-licensure surveillance data

During March 1995–July 1998, a total of 9.7 million doses of varicella vaccine were distributed in the United States. During this time (CDC, 1999), the Vaccine Adverse Event Reporting System (VAERS). received 6,580 reports of adverse events following immunization (not necessarily vaccine-related). 4% of these were severe. Approximately two thirds of reports were for children aged <10 years. The most frequently reported adverse event was rash (rate: 37/100 000 vaccine doses distributed). However, polymerase chain reaction (PCR) analysis confirmed that most rash events occurring within 2 weeks of vaccination were caused by wild-type virus. Accordingly, these were due to natural varicella infection and occurred coincidentally following vaccination. Severe adverse events that have been reported and may not necessarily be vaccine-related, included encephalitis, ataxia, erythema multiforme, Stevens Johnson syndrome, pneumonia, thrombocytopenia (on blood examination), seizures, neuropathy, and herpes zoster. For severe adverse events for which background incidence data are known, VAERS reporting rates are markedly lower than the rates expected after natural varicella or the background rates for such diseases in the community (Wise R et al., 2000, Sharrar RG et al., 2000). Thus, most of the reported adverse events were temporal coincidences rather than being caused by the vaccine.

Post-marketing evaluation of the short-term safety of live, attenuated varicella virus in 89,753 vaccinated adults and children was conducted using the automated clinical databases of hospitals, emergency room visits, and clinic visits, during April 1995 – December 1996 (Black et al., 1999). No severe adverse events were associated with vaccination, including ataxia or encephalitis that are recognized complications of natural varicella.

Combination varicella vaccines – MMRV (Local and Systemic adverse events)

Febrile seizures - In MMRV vaccine pre-licensure studies, an increased rate of fever was observed after the first vaccine dose, compared with administration of MMR vaccine and varicella vaccine at the same visit (Shinefield H et al., 2005). The risk of febrile seizures has been evaluated by the Vaccine Safety Datalink (VSD) project which evaluates post-licensure surveillance data from health maintenance organizations in the United States of America. This initial evaluation has demonstrated that a rate of febrile seizure of nine per 10,000 vaccinations among MMRV vaccine recipients compared with four per 10,000 vaccinations among MMR vaccine and varicella vaccine recipients (adjusted odds ratio = 2.3; 95% confidence interval [CI] = 1.6--3.2; p<0.0001). These rates are in children 12-23 months of age and in the 7 - 10 day post-vaccination period. The absolute risk would be one additional febrile seizure for every 2,000 children vaccinated with MMRV vaccine, compared with children vaccinated with MMR vaccine and varicella vaccine separately administered at the same visit (CDC 2008, Klein NP et al., 2010, and Fireman B et al., 2010)., Administration of MMRV as a first dose to children beyond 23 months of age and as a second dose of varicella vaccine has not been associated with an increase in febrile seizures.

Other safety issues

Vaccination of individuals who have had varicella

Inadvertent vaccination of persons immune to varicella has not resulted in an increase in adverse events.

Immunocompromised individuals

a) Without HIV

Persons with impaired humoral immunity may be vaccinated but individuals with impaired cellular immunity maybe at risk of general adverse events and more common skin rashes.

There are no studies that have examined the safety of varicella vaccine in individuals receiving systemic steroids. General guidelines recommend vaccination if an individual is receiving <2 mg/kg of body weight or a total of <20 mg/day of prednisone or its equivalent. Safety is not likely to be an issue with individuals receiving inhaled, nasal, or topical doses of steroids (CDC, 2006).

Patients with haematological malignancy such as leukaemia are at increased risk of skin rash (about 50%) after the first dose and in some this may be severe varicella-like disease. Vaccination of individuals with leukaemia who are in remission and those who have had treatment for malignancy should be undertaken only with expert guidance and with antiviral therapy available in case complications ensue (CDC, 2006).

b) With HIV -
HIV-infected children with CD4+ T-lymphocyte percentage >15% should be considered for vaccination with the single-antigen varicella vaccine (Marin et al., 2007). Children eligible for 2 doses of single-antigen varicella vaccine should receive these 3 months apart. Vaccine recipients should be monitored for generalized skin rash (Marin et al., 2007). The safety of MMRV in HIV-infected children has not been evaluated. Recommendations, which are similar to those for healthy children, have been proposed and include immunization of individuals who have comparable levels of immune function (CD4+T-lymphocyte count >200 cells/µl) using 2 doses of monovalent varicella vaccine administered 3 months apart (Marin et al., 2007). In HIV-infected children who appear healthy and have a CD4 cell count of more than 15%, varicella vaccine (preferably 2 doses) provides protection against both varicella and herpes zoster (Son M et al., 2010).

Transmission of vaccine virus
Transmission of vaccine virus has been reported but is a rare event. All cases have been mild and associated with a rash in vaccinees. Immunosuppressed individuals may have a higher chance of spreading vaccine virus presumably because they more often develop a rash which is likely to be more extensive (Tsolia M et al., 1990). Globally only 9 instances of transmission of the Oka strain by healthy vaccinees have been reported. Three of these transmissions originated from vaccinees that developed herpes zoster (Gershon et al., 2011).

Vaccination in pregnancy
Varicella vaccine is not to be given in pregnancy as its safety has not been quantified. Therefore vaccinees should not become pregnant within 28 days of vaccination. However, post-licensure registry monitoring of varicella vaccination in pregnancy has not documented any signals of risk of adverse events including birth defects resembling congenital varicella syndrome. Therefore, inadvertent vaccination during or shortly before pregnancy requires no antiviral therapy, but clinical monitoring

Vaccination of breast feeding mothers
Breast feeding mothers who are not immune are not to be excluded from vaccination in case of epidemiological need. Breast feeding can be continued, as no adverse events have been reported (Marin et al., 2007)

Summary of mild and severe adverse events

Nature of Adverse event	Description	Rate/doses
Mild	Monovalent varicella vaccine	
	Fever	15 per 100
	Injection site reactions	7-30 per 100
	Skin rash at injection site	3-5 per 100
	Skin rash generalized	3-5 per 100
	Combination MMRV	
	Fever	27 per 100
	Skin rash	10 per 100
Severe	Monovalent varicella vaccine	
	Febrile seizures (with MMR via separate injection)	4 per 10,000
	Combination MMRV (age 12-23 months)	
	Febrile seizures	9 per 10,000

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al., 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomized controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: **http://www.who.int/vaccine_safety/vaccrates/en/index.html**

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