

17 Varicella (Chickenpox and Shingles)

17.1 Introduction

Varicella was at first confused with smallpox, and the first clinical differentiation was by Heberden in 1767. The varicella zoster virus (VZV) was first isolated in cell culture in 1952. Varicella (chickenpox) is a highly infectious disease caused by human herpes virus type 3 (varicella-zoster virus). It is usually, but not invariably, a mild, self limited disease in otherwise healthy children, but the severity of disease and risk of complications are usually greater in adolescents and adults. Varicella can also cause severe and even fatal disease in immune suppressed individuals (eg, children with acute leukaemia), in whom the mortality may be as high as 7–10 percent. Mortality in normal children is less than 2 per 100,000 cases, increasing up to 15-fold in adults. Reactivation of latent VZV results in herpes zoster (shingles), a disease with considerable morbidity.

17.2 The illness

A maculo-papular rash, which becomes vesicular, appears first on the face and scalp, later spreading to the trunk and abdomen and eventually to the limbs. The vesicles dry after three to four days, but may be followed by further lesions. A wide variation in the number of lesions is possible, ranging from a few to many hundred. The hallmark of the disease is the presence of lesions at all stages. Lesions may be found in the mouth and at times in the vagina, where they can be the cause of considerable distress. The rash is pruritic and is usually associated with mild fever, malaise, anorexia and listlessness.

The majority of hospitalisations from varicella are from severe chickenpox or bacterial superinfection of the skin lesions. Superinfection with Group A beta haemolytic streptococci is a potentially serious complication, which may be fatal. Other complications include varicella pneumonia (more common in adolescents and adults), acute cerebellar ataxia (more common in infants and children, and almost always self limited), and, rarely, encephalitis, with permanent neurological disability or fatal outcome. Transverse myelitis, thrombocytopenia and, rarely, involvement of the viscera and joints may also occur.

Salicylates (aspirin containing analgesics) should not be given to children with chickenpox, because of the association between Reye syndrome (an acute encephalopathy with hepatic failure) developing after an infectious illness such as influenza or natural varicella infection and the use of salicylates.

The incubation period of varicella is 10–21 days (usually 14–16 days). The virus is plentiful in the naso-pharynx initially and in the vesicles before they dry up. The infectious period is from one to two days before the rash emerges until the rash dries up about seven days later. The infectious period may be more prolonged in immune suppressed individuals.

The disease may be more serious in adults, particularly in pregnant women, and the risk of severe disease is greatly increased in neonates and immune suppressed individuals. Transplacental transmission is rare. Congenital varicella syndrome has been reported after varicella infections in the first half of pregnancy and may result in congenital malformations, skin scarring, other anomalies, abortion or fetal death. The observed incidence of congenital varicella syndrome, in retrospective and prospective studies, ranges from 0.7 percent to 2 percent.¹ There is a higher risk when maternal infection occurs between 13 and 20 weeks gestation compared with 0 and 12 weeks (2 percent compared with 0.4 percent).²

The onset of chickenpox in pregnant women, from five days before delivery to two days after delivery, is estimated to result in severe varicella in 17 to 30 percent of their newborn infants. Half the deaths from chickenpox before one year of age occur during the first month of life.

Herpes zoster (shingles) is due to reactivation of latent varicella virus infection. The majority of cases of zoster occur in adults over 40 years of age. The dermatomal distribution of the vesicular rash is the key diagnostic feature. Herpes zoster is uncommon in infants and children but may occur after chickenpox in infancy. When it occurs in those under two years of age it may reflect *in utero* chickenpox with the greatest risk following exposure between 25 and 36 weeks' gestation, with reactivation in early life. Herpes zoster occurs more commonly in immune suppressed individuals, and there is some evidence that up to 10 percent of children treated for a malignant neoplasm may develop herpes zoster.

17.3 Epidemiology

The epidemiology of this infection appears to be similar in all industrialised countries with temperate climates. Epidemics occur each winter/spring, with some variability from year to year. Approximately 3 percent of each birth cohort are infected during infancy. Thereafter, 8–9 percent of the birth cohort are infected each year throughout childhood, so that by 10 years of age less than 15 percent, and by 14 years of age less than 10 percent, remain susceptible. The average age for infection is seven years. The infection rate drops rapidly in adolescence and young adulthood to about 1 percent per year. By 40 years of age almost the entire birth cohort (over 97 percent) have been infected, so that only a few adults remain susceptible. Transmission of the virus is less efficient in tropical climates. Adolescent and adult immigrants to New Zealand from such countries are more likely to be susceptible, placing them at risk of contracting chickenpox in their new environment.

By contrast, herpes zoster is a sporadic disease occurring as a reactivation of the VZV in individuals who have previously had chickenpox. VZV is present in lesions of herpes zoster, and is transmissible from the vesicles to other susceptible individuals. About 4 percent of individuals will suffer a second episode of shingles. Third episodes are rare.

Varicella vaccine has been introduced into childhood immunisation programmes overseas, including the United States (US) from 1995 and Australia from 2005. Following introduction of varicella vaccine onto the childhood schedule, the incidence of infection with wild type virus decreases, and therefore adults are less likely to boost immunity to latent herpes zoster. It was hypothesised that lack of boosting may lead to an increase in herpes zoster in older adults. However, a study in the US³ from 1992 to 2002 has shown that although the incidence of varicella decreased in children, from 2.63 cases per 1000 person years in 1992 to 0.92 cases per 1000 person years in 2002, there was no increase in herpes zoster in adults of any age: the age adjusted rate of herpes zoster was 4.05 cases per 1000 person years in 1992 and 3.7 cases per 1000 person years in 2002.

A more potent form of the varicella vaccine has been tested as a zoster vaccine.⁴ By boosting cell mediated immunity in older adults, zoster might be prevented. In a large clinical trial of 38,586 adults aged 60 years and over, with either a history of chickenpox or of having lived in the US for more than 30 years, the participants received the high dose zoster vaccine or a placebo. The results showed that the zoster vaccine reduced the burden of illness of zoster by 61 percent in all age groups, and by 65.5 percent in the age group 60–69 years and 55.4 percent in those over 70 years. There was also a 66.5 percent reduction in post-herpetic neuralgia (PHN) in all age groups. Over five years of follow up, the incidences of zoster and PHN was reduced, and in the vaccine recipients who received the zoster vaccine but developed zoster the illness was less severe.

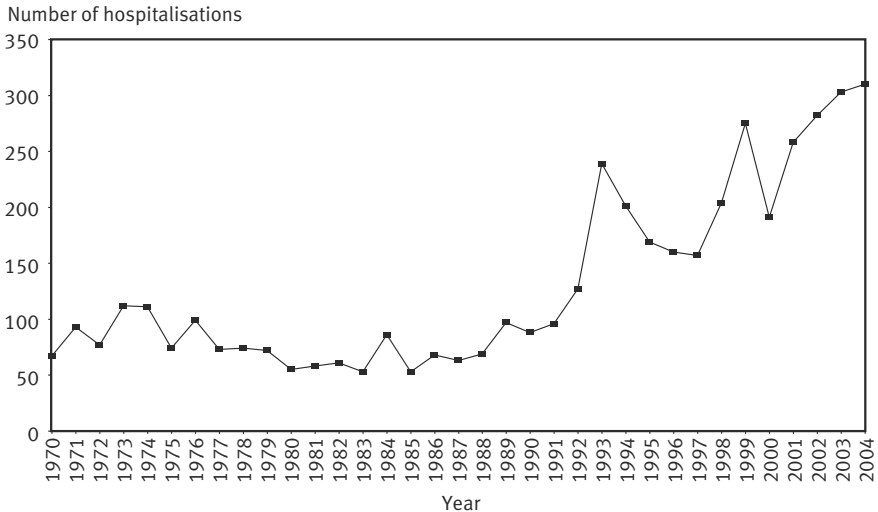
New Zealand epidemiology

In New Zealand it is expected that 90 percent of children would have had varicella infection before adolescence, with peak incidence in the five to nine years age group. With higher participation rates in preschool education, a greater proportion of infections may now be occurring in preschool aged children.

Hospitalisation⁵

New Zealand hospital discharge information for varicella between 1970 and 2004 is shown in Figure 17.1. Only 4 percent of hospitalisations involved people with an underlying disease associated with immune suppression. The rate of hospital discharges for the zero to four and five to nine years age groups was higher compared with older age groups because the disease is most common in childhood. However, adults, adolescents and infants are more likely to suffer severe illness or the complications of chickenpox.⁶

Figure 17.1: Hospitalisations for varicella, 1970–2004



Based on overseas rates, it is estimated that up to one case of congenital varicella syndrome may be expected in New Zealand each year, although few have been reported.

Mortality

Mortality data are available for the period 1980 to 2002. Nine deaths were attributed to chickenpox over the 14-year period 1980 to 1993, of which four occurred in children, two in infants and three in adolescents or adults. None of the cases who died had a contributory cause of death recorded. From 1994 to 2002 there were nine deaths associated with varicella, two were children aged five to nine years, four were adults aged 30 to 64 years and three were adults over the age of 65 years. Larger series from other developed temperate climate countries suggest that up to 10 percent of chickenpox deaths may involve individuals with immune suppression.

In summary, in a typical year New Zealand is estimated to experience approximately 50,000 chickenpox infections, of which 150–200 result in hospitalisation, one to two cases result in residual long term disability or death, and 0.5–1 cases result in severe congenital varicella syndrome. About two-thirds of this burden is borne by otherwise healthy children, and less than one-tenth by children with a disease associated with immune suppression.

17.4 Vaccines

VZV was first isolated in the 1950s. An attenuated (live) VZV (Oka strain) developed in Japan was found suitable for vaccine use. Currently, both VARILRIX and VARIVAX® (both based on the Oka strain) are licensed and are available in New Zealand.

VARILRIX

VARILRIX (GSK) is a live attenuated virus vaccine presented as a lyophilised powder for reconstitution with the supplied diluent. The vaccine should be stored in the refrigerator at +2°C to +8°C, although the diluent may be stored at room temperature. Reconstituted vaccine must be used immediately.

VARILRIX should be administered by subcutaneous injection. The upper arm (deltoid region) is the preferred site of injection. A single 0.5 mL dose provides protection for individuals nine months to 12 years of age, inclusive, with over 95 percent achieving seroconversion. The vaccine can be administered concurrently with other vaccines, but in a separate syringe and at a different site. If not administered concurrently, the vaccine must be separated from other live vaccines (eg, measles, mumps and rubella – MMR) by at least one month. (See section 2.3 for needle sites and sizes.)

People 13 years of age and over, and immune compromised individuals of all ages when indicated, require two doses of VARILRIX (a minimum of six weeks apart) to achieve a seroconversion rate similar to children.

VARIVAX®

VARIVAX® (MSD) is a live attenuated virus vaccine presented as a lyophilised powder for reconstitution with the supplied diluent. The vaccine should be stored in the refrigerator at +2°C to +8°C, but may also be stored in the freezer. When the vaccine is transferred from the freezer to the refrigerator it should not be refrozen. Reconstituted vaccine must be used immediately.

VARIVAX® should be administered subcutaneously, with the deltoid area the preferred site for injection. A single 0.5 mL dose is sufficient for children 12 months to 12 years of age inclusive; people 13 years of age and older require two doses, given four to eight weeks apart. (See section 2.3 for needle sites and sizes.)

Measles, mumps, rubella and varicella vaccine (MMRV)

In the US an MMRV vaccine (ProQuad®, Merck) that is freezer stable is now licensed and is likely to be available in New Zealand in the next one to three years (see section 9.4). Trials are ongoing to produce a refrigerator stable vaccine.

There is also a refrigerator stable two-dose MMRV vaccine (GSK) recommended for use in the second year of life. It is possible either or both of these vaccines will be licensed for distribution in the next one to three years.

Efficacy

Varicella vaccine is 95–98 percent effective in preventing moderate and severe disease during seven years of follow up post-vaccination. Mild cases of varicella rash and illness have been reported in children who have received vaccine, and the vaccine is estimated as being 70–100 percent effective against all disease.⁷ The duration of immunity has been 11 years in the vaccine trial participants in the US

and up to 20 years in studies from Japan.⁸ The estimated hospitalisation rates for varicella have decreased in the US⁹ after introducing the varicella vaccine, from 2.3 per 100,000 population in the pre-vaccination era in 1994/95 to 0.3 per 100,000 in 2002 following introduction of the vaccine programme. It is estimated that the varicella related annual national expenditure in the US for ambulatory visits and hospitalisations decreased by 74 percent, to \$22.1 million in 2002.

17.5 Recommended immunisation schedule

Varicella vaccine is not yet on the New Zealand National Immunisation Schedule

At present, the varicella vaccine has not been added to the New Zealand National Immunisation Schedule. There are two reasons for this decision: the costs, and the undesirability of adding another injection or immunisation visit to the Schedule. When a tetravalent MMRV vaccine becomes available, this recommendation could change.

Recommendations for use

Varicella immunisation is recommended, but not funded, for:

- adults and adolescents who were born and resident in tropical countries if they have no history of varicella infection
- children with chronic liver disease who may in future be candidates for transplantation – varicella vaccine has been found to be safe and immunogenic in children with chronic liver disease and is therefore recommended early in the disease and prior to liver transplantation¹⁰
- children with deteriorating renal function, as early as possible before transplantation – varicella immunisation of children with end stage and pre-end stage renal failure results in a high rate of seroconversion and persistence of protective antibody titres¹¹
- children likely to undergo solid organ transplant
- children with human immunodeficiency virus (HIV) infection at CDC stage N1 or A1 – a recent study has found varicella vaccine is safe and effective when given to children aged one to eight years who are mildly affected with HIV infection at CDC stage N1 or A1.¹² Two doses were given, four weeks apart.

Immune suppressed individuals

The vaccine should not be given to immune suppressed children except under the direction and care of a paediatric oncologist, following a suitable protocol.¹³ Immune suppressed individuals are at highest risk of severe varicella and zoster infections. The original vaccine formulations, in particular VARIVAX[®], have been studied in immune suppressed children. Approximately 20 percent of these vaccine recipients required acyclovir because of a rash developing up to one month after vaccination. Despite this, the study concluded that the vaccine VARIVAX[®] was safe, immunogenic and effective in these children.¹⁴

Where immune suppressed individuals cannot be vaccinated, it is important to vaccinate the household members and other close contacts (with either vaccine) to provide 'ring fence' protection. There is debate regarding the severity of disease that may result if a susceptible immune suppressed person is inadvertently exposed to a person who has a vaccine related rash. If this does occur, the administration of varicella zoster immunoglobulin (ZIG) should be considered, as should the use of acyclovir to treat any disease that develops. Any vaccine related rash or illness that occurs will be far less severe than illness with the wild virus in an immune suppressed child.

Immunisation of children with congenital T-cell immune deficiency syndromes is generally contraindicated, but those with impaired humoral immunity may be immunised (see below for further contraindications).

Health care workers

In 1999 all acute care hospitals were advised that the varicella vaccines were available for use in adults and that hospitals should incorporate the use of varicella vaccine for health care workers in their occupational health programme. All health care workers on obstetric, paediatric and neonatal units, and those caring for immune suppressed children and adults, should be immunised with varicella vaccine if they are susceptible to varicella. When a health care worker has a good history of prior varicella infection¹⁵, no blood test is required. If there is not a good history of varicella infection, a blood test to assess susceptibility will be necessary.

If a health care worker who has clinical contact with patients develops a rash as a result of the vaccine (around 5 percent), they must be excluded from contact with immune suppressed patients at risk and be allocated other duties, or excluded from their place of work for the duration of the rash.

Whenever exposure to wild chickenpox occurs, previously vaccinated health care workers should examine themselves daily for 21 days for a rash. If a rash appears they should seek advice from their occupational health service.

Healthy children

The varicella vaccine is available, but not publicly funded, for children whose parents/caregivers wish them to avoid having chickenpox. It can be given with the other two vaccines scheduled at 15 months of age. If not given concurrently it should be given at least four weeks after the MMR vaccine. One dose is required for children from nine months up to and including 12 years of age.

Healthy adolescents/adults

Immunisation could be offered to all susceptible adults and adolescents in view of their increased risk of serious varicella outcomes relative to children. Two doses of vaccine, one to two months (or more) apart, are required for adults and adolescents

from 13 years of age in order to achieve a seroconversion rate greater than 90 percent. To assess susceptibility, it has been found that maternal recall of varicella or characteristic rash is reliable evidence of immunity. In people with no history or recall of the rash, 70–90 percent are found to be immune.¹⁶

The US Advisory Committee on Immunization Practices (ACIP) recommends vaccinating susceptible individuals in the following high risk groups:

- people who live or work in environments where transmission of VZV is likely (eg, staff in early childhood services, residents and staff members in institutional settings)
- people who live and work in environments where transmission can occur (eg, college students, inmates and staff members of correctional institutions, and military personnel)
- non-pregnant women of childbearing age
- adolescents and adults living in households with children
- international travellers.¹⁷

17.6 Expected responses and adverse events following immunisation (AEFI)

Experience with the varicella vaccines used in Japan and other countries indicates that, in general, side effects including local reactions, fever and mild papulo-vesicular rash in normal healthy individuals are mild and self limiting. About 5–7 percent (VARIVAX®) or 2–6 percent (VARILRIX) of healthy child vaccinees develop a mild rash three to four weeks after vaccination. The mean number of vesicles is five, compared with several hundred in wild varicella in an unimmunised child. After VARIVAX®, PCR (polymerase chain reaction) analysis from rashes that occurred within 14 days of vaccination was more likely to identify the presence of wild type VZV, whereas PCR from a rash developing >14 days and ≤42 days post-vaccine was more likely to identify the vaccine virus.¹⁸

Only a small percentage of vaccinees who develop a rash appear able to transmit the Oka virus to susceptible contacts, and then only very inefficiently. Secondary transmission of the vaccine virus has been documented in immune competent people on only four occasions out of 47.5 million doses of the varicella vaccine, VARIVAX®, distributed.¹⁹ All four vaccinees developed a rash. Disease in the four contacts was mild. Of the four individuals, three were unvaccinated and one individual had a history of mild varicella in the past. One of the four was a pregnant woman who developed a rash with 100 vesicular lesions and subsequently had a therapeutic abortion (PCR negative for VZV). However, when an immune suppressed individual inadvertently comes in contact with a vaccinee who has a varicella like rash, the administration of ZIG should be considered (see below).²⁰ Acyclovir may also be considered for the immune suppressed individual if symptoms develop.

The Oka strain of varicella used in the available vaccines can establish latent ganglionic infection in vaccinees and later reactivate to produce clinical zoster (shingles). To date, there has been insufficient follow up time to determine whether the risk of zoster is lower in healthy vaccinees than in naturally infected individuals. However, a cohort study in children with acute lymphoblastic leukaemia (who have a high rate of zoster in childhood) has shown that vaccinees had less than one-fifth the zoster rate of their naturally infected counterparts.²¹

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

17.7 Contraindications

See section 1.9 for general contraindications for all vaccines.

Varicella vaccination is contraindicated for:

- individuals with primary or acquired T-cell immune deficiency states – consult the child's paediatrician for advice
- children on high dose steroids (ie, children on 2 mg/kg per day or more of prednisone or its equivalent, or 20 mg per day if their weight is over 10 kg)
- children on salicylates, because of the association between Reye syndrome, natural varicella infection and salicylates – the vaccine manufacturers advise against the use of salicylates for six weeks after varicella vaccine is given; there has been no reported association between the vaccine and Reye syndrome, but avoidance of salicylates is recommended as a precaution,²² and physicians need to weigh the theoretical risk from the vaccine against the known risk of varicella disease in children receiving long term salicylate therapy
- individuals with known systemic hypersensitivity to neomycin
- women during pregnancy – women should be advised to avoid pregnancy for three months after vaccination, because the vaccine's safety for the fetus has not yet been demonstrated.

17.8 Control measures

Post-exposure prophylaxis with zoster immunoglobulin (ZIG)

ZIG is a high titre immunoglobulin (IG), available from the New Zealand Blood Service for the passive prevention of varicella in high risk subjects. It is effective if given within 96 hours of exposure, and as soon as possible. Large doses of normal IG are indicated when ZIG is unavailable.

The decision on whether to offer ZIG will depend on:

- the likelihood that infection will result from a given contact
- the exposed individual's susceptibility to varicella
- the likelihood that an individual will develop serious complications if infected.

Contact can be defined as follows:

- household contact – individuals living in the same house are very likely to be infected if susceptible
- playmate contact – this can be defined as more than one hour of play indoors with an infected individual
- newborn infant contact – this occurs when the mother of a newborn infant develops chickenpox, but not shingles, from one week before to one week after delivery.

Susceptibility

In general, a positive past history of chickenpox can be taken as indicating immunity, provided there has not been an intervening bone marrow transplant. Please consult with the local laboratory about the availability and interpretation of tests.

Candidates for ZIG administration, provided exposure has occurred and susceptibility is likely, are:

- immune compromised individuals
- pregnant women (see below)
- newborn infants whose mother had onset of chicken pox but not zoster within seven days before delivery or after delivery (see below)
- hospitalised premature infants whose mothers have no history of chickenpox, or who are less than 28 weeks' gestation or 1000 g in weight, irrespective of maternal history.

Care of pregnant women after exposure

If an immune competent pregnant woman is exposed to varicella, it is recommended, where possible, that her varicella antibodies be assessed if she has no past history of varicella. If there is no evidence of immunity then ZIG should be administered. This is because pregnant women are at higher risk of severe complications, and acyclovir is not generally recommended in pregnancy, although some experts recommend oral acyclovir for pregnant women in the second and third trimesters. Seek specialist advice before administration.

Intravenous acyclovir is recommended for the pregnant patient with severe complications of varicella. ZIG given to a pregnant woman within five days of delivery may not protect the fetus/neonate. The neonate should receive ZIG on delivery and

may need treatment with acyclovir. For further information on the management of exposure to varicella during pregnancy and care of the newborn, see Appendix 10.

Dosage of ZIG

The ZIG prepared by CSL in Melbourne, from New Zealand donors, contains 100 IU/mL (ie, 200 IU/2 mL vial). The recommended dose is 6 mL for adults, 4 mL for children aged 6–12 years, and 2 mL for children aged 0–5 years. ZIG should be given intramuscularly, not intravenously.

Hospital outbreaks

It is advised that:

- susceptible staff be excluded from contact with high risk patients from day 8 to day 21 after exposure to varicella or zoster
- hospital staff who have no past history of chickenpox and who will be in contact with pregnant women or high risk patients be screened for varicella zoster antibodies; those who are not immune should be offered immunisation.

Exclusion from school or childcare

Parents/caregivers should be advised that:

- cases should be excluded from early childhood services or school until fully recovered or all lesions have crusted
- high risk children should be excluded from early childhood services or school for the duration of the outbreak.

Post-exposure vaccination and outbreak control

Varicella vaccine may be used for post-exposure prophylaxis.

Data from the US and Japan from household, hospital and community settings indicates that the varicella vaccine is effective in preventing illness or modifying varicella severity if used within three days, and possibly up to five days, of exposure. The US ACIP now recommends the vaccine for use in susceptible individuals following exposure to varicella.²³ If exposure to varicella does not cause infection, post-exposure vaccination should induce protection against subsequent exposure. If the exposure results in infection, no evidence indicates that administration of the varicella vaccine during the pre-symptomatic or prodromal stage of illness increases the risk for adverse events following immunisation. Note that although this method of immunisation may be successful, it is not necessarily reliable.²⁴ Immunisation before exposure is recommended as the preferred method of preventing outbreaks.

For more details on control measures, refer to the *Control of Communicable Diseases Manual*.²⁵

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