4.22 VARICELLA

4.22.1 Virology

Varicella-zoster virus (VZV) is a DNA virus within the herpes virus family. Primary infection with VZV causes varicella (chickenpox). Following primary infection, VZV establishes latency in the dorsal root ganglia. Reactivation of the latent virus manifests as herpes zoster (shingles) (refer to 4.24 Zoster).

4.22.2 Clinical features

Varicella is a highly contagious infection spread by respiratory secretions, including aerosol transmission, or from the vesicle fluid of the skin lesions of varicella or zoster infection. Varicella is usually a mild disease of childhood. However, complications occur in approximately 1% of cases. It is more severe in adults and in persons of any age who are immunocompromised, in whom complications, disseminated disease and fatal illness can occur.

The average incubation period is 14 to 16 days (range 10 to 21 days), but may be longer in persons who are immunocompromised, especially after receipt of zoster immunoglobulin (ZIG). The period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred. A short prodromal period of 1 to 2 days may precede the onset of the rash, especially in adults. In otherwise healthy children, skin lesions usually number between 200 and 500. Acute varicella may be complicated by secondary bacterial skin infection, pneumonia, acute cerebellar ataxia (in 4000 cases), aseptic meningitis, transverse myelitis, encephalitis (1 in 100 000 cases) and thrombocytopenia. In rare cases, it involves the viscera and joints.

Congenital varicella syndrome has been reported after varicella infection in pregnancy and may result in skin scarring, limb defects, ocular anomalies and neurologic malformations. There is a higher risk to the fetus if maternal infection occurs in the second trimester compared with infection in the first trimester (1.4% versus 0.55%). Infants with intrauterine exposure also risk developing herpetic zoster in infancy (0.8–1.7%), with the greatest risk following exposure in the third trimester. Severe neonatal varicella infection can result from perinatal maternal varicella. The onset of varicella in pregnant women from 5 days before delivery to 2 days after delivery is estimated to result in severe varicella in 17 to 30% of their newborn infants.

Reactivation of latent VZV as a result of waning cellular immunity results in herpes zoster (HZ), a localised vesicular rash. HZ can occur at any age, but is more common in older adults and persons who are immunocompromised. Complications may include post-herpetic neuralgia and disseminated zoster with visceral, central nervous system and pulmonary involvement (refer to 4.24 Zoster).

There is no specific therapy for uncomplicated varicella infection. Antiviral therapy is used in the treatment of complicated or severe varicella, herpes zoster disease, and disease in persons who are immunocompromised.

4.22.3 Epidemiology

In an unimmunised population in temperate climates, the annual number of cases of varicella approximates the birth cohort. Tropical regions have a higher proportion of cases in adults. Approximately 5% of cases are subclinical. A serosurvey conducted in 1997–1999 found that 83% of the Australian population were seropositive by 10–14 years of age. Prior to the introduction of a varicella vaccination program in Australia, there were about 240 000 cases, 1500 hospitalisations and an average of 7 to 8 deaths each year from varicella in Australia. The highest rates of hospitalisation occur in children 5 years of age.

In Australia, there was a 69% decline in varicella hospitalisations in children aged 1.5–4 years in the first 2.5 years following the inclusion of varicella vaccine on the NIP in late 2005. Declines have also been observed in hospitalisation rates in other age groups and in general practice consultations. In the United States, where universal varicella vaccination has been in place since 1995, there has been an even greater decline in varicella disease (85%) and hospitalisations (70–88%). The greatest decline in hospitalisation rates has been in 0–4-year olds. However, reductions in hospitalisation rates have also occurred in infants, older children and adults, due to herd immunity.

There has been no evidence of a change in the rates of herpes zoster incidence, healthcare utilisation or hospitalisations in the United States attributable to the introduction of the varicella vaccine, although herpes zoster rates in children have declined in the United States.

4.22.4 Vaccines

Live attenuated varicella vaccine (VV) is currently available as a monovalent vaccine. Two combination vaccines containing live attenuated measles, mumps, rubella and varicella viruses (MMRV) are also registered in Australia. All available varicella-containing vaccines are derived from the Oka VZV strain, but have some genetic differences.

Monovalent VVs have been available in Australia since 2000, and, since November 2005, a single dose of VV has been funded under the NIP for all children at 18 months of age, with a catch-up dose funded for children 10 to <14 years of age who have not received varicella vaccine and who have not had the disease. At the time of implementation of a
universal varicella vaccination program in Australia, a single dose was considered adequate for protection of infants and children <14 years of age. However, recent data from the United States suggest that a 2nd dose of varicella-containing vaccine in children is optimal to provide an immune response more like that acquired after natural infection, reducing the risk of vaccine failure and increasing population immunity.27 Vaccine failure, also known as breakthrough varicella, is defined as a case of wild-type varicella occurring more than 42 days after vaccination. The majority of cases of breakthrough varicella are mild with fewer lesions than natural infection. However, breakthrough varicella infections can be contagious, particularly if many lesions are present.28

Post-marketing studies in the United States have estimated the effectiveness of 1 dose of VV in children to be 80 to 85% against any disease and 95 to 98% against severe varicella.29-32 Although earlier data suggested persistence of immunity in most healthy vaccine recipients,1 some, but not all, long-term follow-up studies have shown that rates of vaccine failure increased over time in 1-dose vaccine recipients. For example, in one study, vaccine failure was increased 2.6 times in children who received 1 dose of vaccine more than 5 years previously, compared with those who had received 1 dose of vaccine within 5 years.33 Follow-up from a randomised controlled trial in children 12 months to 12 years of age, comparing 1 dose with 2 doses of VV over a 10-year period, showed significantly higher protection with 2 doses (98.3% versus 94.4%).34 Based on current evidence, 2 doses of a varicella-containing vaccine in children from 12 months of age will minimise the risk of breakthrough varicella (refer to 4.22.7 Recommendations below).

Healthy adolescents (≥14 years of age ) and adults require 2 doses of varicella vaccine, at least 4 weeks apart, as the response to a single dose of VV decreases progressively as age increases and is insufficient to provide adequate protection.35

Combination MMRV vaccines have been shown in clinical trials, conducted predominantly in children 12 months to 6 years of age, to produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered concomitantly at separate injection sites.36-39 In one comparative study assessing seroresponses to a single MMRV vaccine dose in 12–14-month-old children, the seroresponse rates to measles, mumps and rubella were similar, but varicella seroresponses were lower in Priorix-tetra varicella vaccine recipients than in ProQuad recipients.40 However, the clinical significance of this is not clear, particularly for MMRV given after MMR vaccine.

### Monovalent varicella vaccines (VV)

- **Varilrix** – GlaxoSmithKline Australia Pty Ltd (live attenuated Oka strain of varicella-zoster virus). Lyophilised powder in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains ≥10³ plaque-forming units (PFU) of varicella-zoster virus; human albumin; lactose; mannitol; sorbitol; neomycin.

- **Varivax Refrigerated** – bioCSL Pty Ltd (live attenuated Oka/Merck strain of varicella-zoster virus). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥1350 PFU of attenuated varicella-zoster virus; 18 mg sucrose; 8.9 mg hydrolysed porcine gelatin; 3.6 mg urea; 0.36 mg monosodium glutamate; residual components of MRC-5 cells; traces of neomycin and bovine serum.

### Combination measles-mumps-rubella-varicella (MMRV) vaccines

- **Priorix-tetra** – GlaxoSmithKline Australia Pty Ltd (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥10⁵⁰ cell culture infectious dose 50% (CCID₅₀) of measles virus, ≥10⁵⁰ CCID₅₀ of mumps virus, ≥10¹⁰ CCID₅₀ of rubella virus, and ≥10¹² PFU of varicella-zoster virus; lactose; neomycin; sorbitol; mannnitol.

- **ProQuad** – bioCSL Pty Ltd (live attenuated measles virus [Enders’ attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥10⁴⁰ tissue culture infectious dose 50% (TCID₅₀) of measles virus, ≥10⁴⁰ TCID₅₀ of mumps virus, ≥10¹⁰⁰ TCID₅₀ of rubella virus, and ≥10³⁹⁰ PFU of varicella-zoster virus; 20 mg sucrose; 11 mg hydrolysed porcine gelatin; 2.5 mg urea; 16 mg sorbitol; 0.38 mg monosodium L-glutamate; 0.25 mg recombinant human albumin; 5 µg neomycin; residual components of MRC-5 cells; 0.5 µg bovine serum albumin.

### 4.22.5 Transport, storage and handling

Transport according to National vaccine storage guidelines: Strive for 5.41 Store at +2°C to +8°C. Do not freeze. Protect from light.

Varicella-containing vaccines are less stable than other commonly used live viral vaccines, and adherence to storage and reconstitution requirements is very important. All vaccines must be reconstituted by adding the entire contents of
the diluent to the vial containing the pellet, and shaking until the pellet is completely dissolved. Available monovalent VVs and MMRV vaccines have different requirements following reconstitution.

Reconstituted Varilrix vaccine should be used as soon as practicable. If storage is necessary, hold at 25°C for not more than 90 minutes, or at +2°C to +8°C for not more than 8 hours.

Reconstituted Priorix-tetra (MMRV) vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Reconstituted ProQuad (MMRV) vaccine should be used immediately. If storage is necessary, hold at +20°C to +25°C for not more than 1 hour or at +2°C to +8°C for not more than 2.5 hours.

4.22.6 Dosage and administration

The dose of VV and MMRV vaccines is 0.5 mL, to be given by SC injection. Priorix-tetra may also be given by IM injection.42

MMRV vaccines are not recommended for use in persons aged ≥14 years.

The minimum interval between doses of varicella-containing vaccine is 4 weeks.

Co-administration with other vaccines

VV and MMRV vaccines can be given at the same time as other live attenuated parenteral vaccines (e.g. BCG, yellow fever) or other inactivated vaccines (including DTPa, hepatitis B, Hib, IPV, MenCCV, hepatitis A and pneumococcal conjugate vaccine),30 using separate syringes and injection sites. If VV or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines, they should be given at least 4 weeks apart.

If VV is given at the same time as MMR vaccine, they should be given using separate syringes and injection sites. MMR vaccine and monovalent VV should not be mixed together prior to injection.

Interchangeability of varicella-containing vaccines

In general, the two brands of varicella vaccine can be considered interchangeable; that is, the 2nd varicella dose does not have to be of the same brand as the 1st. The same principle applies to the two available MMRV vaccines,40 although they are not routinely recommended in a 2-dose schedule.

4.22.7 Recommendations

Children (aged <14 years)

It is recommended that at least 1 dose of a varicella-containing vaccine be given to all children <14 years of age. One dose of varicella-containing vaccine is recommended to be given routinely at 18 months of age as either VV or as MMRV vaccine; refer to Table 4.22.1. (Refer also to 4.9 Measles.) Prior varicella infection is not a contraindication and such children can still receive either VV or MMRV, as appropriate. (Refer also to ‘Serological testing for varicella immunity from infection and/or vaccination’ below.) There is no known increase in adverse events from vaccinating those with pre-existing immunity to one or more of the vaccine components (refer to 4.22.11 Adverse events below).

Administration of varicella vaccine from as early as 12 months of age will provide earlier protection from varicella and can be considered on a case-by-case basis when appropriate, for example, in the context of travel or a varicella outbreak. However, note that MMRV vaccine is not recommended for use as the 1st dose of MMR-containing vaccine in children aged <4 years, due to a small but increased risk of fever and febrile seizures when given as the 1st MMR-containing vaccine dose in this age group (refer to 4.9 Measles and 4.22.11 Adverse events below).

If MMRV is inadvertently administered as dose 1 of MMR-containing vaccine, the dose does not need to be repeated (providing it was given at ≥12 months of age); however, parents/carers should be advised regarding the small but increased risk of fever and febrile seizures (compared with that expected following MMR vaccine).

Receipt of 2 doses of varicella-containing vaccine provides increased protection and minimises the chance of breakthrough varicella in children <14 years of age.34 However, routine administration of a 2nd dose of varicella-containing vaccine for children is not included on the NIP schedule. If parents/carers wish to minimise the risk of breakthrough varicella, administration of 2 doses of varicella-containing vaccine is recommended (refer to 4.22.4 Vaccines above). MMRV vaccine is also suitable for use as the 2nd dose of varicella-containing vaccine in children <14 years of age. (For further information, refer also to 4.9 Measles.) The minimum interval between doses of varicella-containing vaccine in children (and adults) is 4 weeks.

Table 4.22.1: Recommendations for varicella vaccination with (a) monovalent varicella vaccine (VV) (currently available), and (b) once measles-mumps-rubella-varicella (MMRV) vaccines are available from July 2013


3
### Vaccines and Schedule Point (age)

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>12 months</th>
<th>18 months</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Only monovalent varicella vaccine available</td>
<td>MMR</td>
<td>VV</td>
<td>MMR*</td>
</tr>
<tr>
<td>b) When MMRV vaccine available (from July 2013)</td>
<td>MMR</td>
<td>MMRV</td>
<td>–</td>
</tr>
</tbody>
</table>

* The 2nd dose of MMR-containing vaccine is recommended to be provided at 18 months of age to improve 2-dose coverage and protection against measles in young children. However, until June 2013 the 2nd dose of MMR vaccine is included under the NIP schedule for administration at 4 years of age. From July 2013, the 2nd dose of MMR vaccine will move to the 18-month NIP schedule point and be provided as MMRV vaccine.

### Adolescents (aged ≥14 years) and adults

Vaccination is recommended for all non-immune adolescents (≥14 years of age) and adults. Every effort should be made to identify and immunise non-pregnant seronegative women of child-bearing age (refer to 4.22.2 Clinical features above). Adolescents (≥14 years of age) and adults must receive 2 doses of VV to achieve adequate protection from varicella. The 2 doses should be administered at least 4 weeks apart. However, a longer interval between vaccine doses is acceptable. Lack of immunity to varicella should be based on a negative history of previous varicella infection and can be supplemented by serological testing for evidence of past infection (refer to ‘Serological testing for varicella immunity from infection and/or vaccination’ below).

MMRV vaccines are not recommended for use in persons ≥14 years of age, due to a lack of data on safety and immunogenicity/efficacy in this age group. If a dose of MMRV vaccine is inadvertently given to an older person, this dose does not need to be repeated.

### Serological testing for varicella immunity from infection and/or vaccination

Children who have an uncertain clinical history or no documentation of age-appropriate varicella vaccination should be considered susceptible and offered vaccination. Although a reliable history of varicella infection correlates highly with serological evidence of immunity in young children, due to the decreasing incidence of varicella in Australia and reduced familiarity with the disease, vaccination should be offered, unless confident clinical diagnosis of prior natural infection is made. Testing of children to assess serologic status prior to vaccination is generally not recommended. Provided there are no contraindications, children can safely receive either VV or MMRV vaccine, even if prior infection with VZV has occurred (refer to ‘Children (aged <14 years)’ above).

In older adolescents and adults with a negative history of varicella infection and no documented history of age-appropriate vaccination, serological testing before vaccination is more likely to be helpful, as a majority of those with a negative history are immune, and thus may not require vaccination. Screening for varicella immunity (from natural infection) or a past history of vaccination should be undertaken as part of pre-pregnancy planning and varicella vaccine given to non-immune women prior to conception.

Testing to check for seroconversion after varicella vaccination is not recommended. Commercially available laboratory tests are not usually sufficiently sensitive to detect antibody levels following vaccination, which may be up to 10-fold lower than levels induced by natural infection. Protection (commensurate with the number of vaccine doses received, refer to 4.22.4 Vaccines above) should be assumed if a child or adult has documented evidence of receipt of age-appropriate dose(s) of a varicella-containing vaccine. If serological tests to investigate existing immunity to varicella are performed, interpretation of the results may be enhanced by discussion with the laboratory that performed the test, ensuring the relevant clinical information described above is provided.

### Post-exposure vaccination

If varicella-containing vaccines are not contraindicated, vaccination can be offered to non-immune age-eligible children and adults who have a significant exposure to varicella or HZ, and wish to be protected against primary infection with VZV. Post-exposure vaccination is generally successful when given within 3 days, and up to 5 days, after exposure, with earlier administration being preferable. MMRV vaccine can be given to children in this setting, particularly if MMR vaccination is also indicated (refer to 4.22.7 Recommendations above).

### Household contacts of persons who are immunocompromised

Vaccination of household contacts of persons who are immunocompromised is strongly recommended. This is based on evidence that transmission of varicella vaccine virus strain is extremely rare and it is likely to cause only mild disease (refer to 4.22.11 Adverse events below). This compares with the relatively high risk of severe varicella disease from exposure to wild-type varicella-zoster virus in persons who are immunocompromised. If vaccinated persons develop a rash, they should cover the rash and avoid contact with persons who are immunocompromised for the duration of the rash. Zoster immunoglobulin (ZIG) need not be given to an immunocompromised contact of a vaccinated person with a rash.
rash, because the disease associated with this type of transmission (should it occur) is expected to be mild (refer to 4.22.12 Public health management of varicella below).

**Healthcare workers, staff working in early childhood education and care, and in long-term care facilities**

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.7 Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases for more information.

Vaccination against varicella is recommended for all non-immune adults, but especially for all healthcare workers (HCW), staff working in early childhood education and care, and staff working in long-term care facilities. Persons in such occupations who have a negative or uncertain history of varicella infection, and who do not have documentation of 2 doses of varicella vaccine, should be vaccinated with 2 doses of varicella vaccine or have serological evidence of immunity to varicella**7** (refer to ‘Adolescents (aged ≥14 years) and adults’ above). Testing to check for seroconversion after VV is not recommended (refer to ‘Serological testing for varicella immunity from infection and/or vaccination’ above). However, since varicella vaccination is not 100% effective, HCWs and other carers should still be advised of the signs and symptoms of infection and how to manage them appropriately according to local protocols if they develop varicella.

### 4.22.8 Pregnancy and breastfeeding

Varicella-containing vaccines are contraindicated in pregnant women (refer to 4.22.9 Contraindications below). Pregnancy should be avoided for 28 days after vaccination.

Varicella-containing vaccines can be given to breastfeeding women. Most live vaccines have not been demonstrated to be secreted in breast milk. Women who received varicella vaccine while breastfeeding showed no evidence of VZV DNA in breast milk samples, and no effects on breastfed infants have been reported.**58** Post-partum vaccination of women without evidence of varicella immunity need not be delayed because of breastfeeding.

MMRV vaccines are not recommended for use in persons aged ≥14 years.

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

### 4.22.9 Contraindications

**Anaphylaxis to vaccine components**

Varicella-containing vaccines are contraindicated in persons who have had:

- anaphylaxis following a previous dose of any varicella-containing vaccine
- anaphylaxis following any vaccine component.

**Persons who are immunocompromised**

Measles-, mumps-, rubella- and varicella-containing vaccines contain live attenuated vaccine viruses and are contraindicated in persons who are immunocompromised. Thus, both VV and MMRV vaccines are contraindicated in the following groups:

- Persons immunocompromised due to HIV/AIDS. Vaccination with live attenuated vaccines can result in a more extensive vaccine-associated rash or disseminated infection in persons with AIDS.**59-62** However, varicella vaccination (with a 2-dose schedule of VV) of asymptomatic HIV-infected persons >12 months of age with an age-specific CD4+ count of ≥15% may be considered**63,64** (refer to ‘HIV-infected persons’ in 3.3.3 Vaccination of immunocompromised persons). Since studies have not been performed using combination MMRV vaccines in asymptomatic HIV-infected persons or persons with an age-specific CD4+ count of ≥15%, it is recommended that only MMR vaccine and monovalent VV be considered for use in this setting.**60,64,65**

- Persons with other medical conditions associated with significant immunocompromise (refer to 3.3.3 Vaccination of immunocompromised persons).

- Persons receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids. Varicella-containing vaccines are contraindicated in persons taking high-dose oral corticosteroids for more than 1 week (in children equivalent to >2 mg/kg per day prednisolone, and in adults >60 mg per day) (refer to 3.3.3 Vaccination of immunocompromised persons). Those who have been receiving high-dose systemic steroids for more than 1 week may be vaccinated with live attenuated vaccines after corticosteroid therapy has been discontinued for at least 1 month**66** (refer to 3.3.3 Vaccination of immunocompromised persons).

Refer also to 3.3 Groups with special vaccination requirements and 4.9 Measles for more information.
Pregnant women

Refer also to 4.22.8 Pregnancy and breastfeeding above.

Varicella-containing vaccines are contraindicated in pregnant women.

This is due to the theoretical risk of transmission of the varicella component of the vaccine to a susceptible fetus. However, no evidence of vaccine-induced congenital varicella syndrome has been reported. A registry in place from 1995 to 2013 in the United States recorded the maternal–fetal outcomes of pregnant women who were inadvertently administered VZV-containing vaccine within 3 months before or at any time during pregnancy. Data from the registry showed that, among the 860 prospectively enrolled women (including 95 live births to women known to be VZV-seronegative who were exposed during the first or second trimester when the risk for congenital varicella syndrome is greatest), there was no evidence of congenital varicella syndrome. The overall occurrence of major congenital anomalies among liveborn infants was 2.2%, similar to reported rates in the general United States population.

A non-immune pregnant household contact is not a contraindication to vaccination with varicella-containing vaccines of a healthy child or adult in the same household. The benefit of reducing the exposure to varicella by vaccinating healthy contacts of non-immune pregnant women outweighs any theoretical risks of transmission of vaccine virus to these women.

4.22.10 Precautions

For additional precautions related to MMRV vaccines, refer to 4.9 Measles.

Vaccination with other live attenuated parenteral vaccines

If a varicella-containing vaccine is not given simultaneously with other live attenuated parenteral vaccines (e.g. MMR, BCG, yellow fever), the vaccines should be given at least 4 weeks apart.

Vaccination after immunoglobulin or blood product administration

Administration of MMR or MMRV vaccine should be delayed after administration of immunoglobulin-containing products. After receipt of immunoglobulin-containing blood products, the expected immune response to measles, mumps, rubella and varicella vaccination may be impaired. VV or MMRV vaccine should not be given for between 3 and 11 months following the administration of immunoglobulin-containing products. The interval between receipt of the blood product and vaccination depends on the amount of immunoglobulin in each product, and is indicated in 3.3 Groups with special vaccination requirements, Table 3.3.6 Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination. For further information, refer to 3.3.4 Vaccination of recent recipients of normal human immunoglobulin and other blood products and 4.22.13 Variations from product information below.

Recent blood transfusion with washed red blood cells is not a contraindication to VV or MMRV vaccines. Varicella vaccine may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. Anti-D immunoglobulin does not interfere with the antibody response to vaccine.

Immunglobulin or blood product administration after vaccination

Immunoglobulin-containing products should not be administered for 3 weeks following vaccination with varicella-containing vaccines, unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinated person should be revaccinated later at the appropriate time following the product (as indicated in Table 3.3.6 Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination).

Rh (D) immunoglobulin (anti-D) may be given at the same time, in different sites with separate syringes, or at any time in relation to varicella vaccine, as it does not interfere with the antibody response to the vaccine.

Persons receiving long-term aspirin or salicylate therapy

Persons receiving long-term salicylate therapy (aspirin) should be vaccinated if indicated, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination. Natural varicella infection and salicylate use has been associated with an increased risk of developing Reye syndrome. However, there have been no reports of an association between Reye syndrome and varicella vaccination (refer to 4.22.13 Variations from product information below).

4.22.11 Adverse events

If using MMRV vaccine, additional adverse events relating to the measles, mumps and rubella vaccine components are discussed in 4.9 Measles, 4.11 Mumps and 4.18 Rubella.

Adverse events following administration of varicella-containing vaccines are generally mild and well tolerated.
Injection site reactions (pain, redness or swelling) are the most common adverse events reported after varicella vaccination, occurring in 7 to 30% of vaccine recipients, but are generally well tolerated.\textsuperscript{2,7,11}

A maculopapular or papulovesicular rash may develop after varicella vaccination (usually within 5 to 26 days). A VV-associated rash is likely to occur in less than 5% of vaccine recipients, and to last for less than 1 week.\textsuperscript{7,23} Rashes typically consist of 2 to 5 lesions and may be generalised (3–5%), or also commonly occur at the injection site (3–5%).\textsuperscript{66} VV-associated rash may be atypical and may not be vesicular. Most varicelliform rashes that occur within the first 2 weeks after vaccination are due to wild-type VZV, with median onset 8 days after vaccination (range 1 to 24 days), while vaccine-strain VZV rashes occur at a median of 21 days after vaccination (range 5 to 42 days).\textsuperscript{7,23}

Transmission of vaccine virus to contacts of vaccinated persons is rare. In the United States, where more than 56 million doses of VV were distributed between 1995 and 2005, there have been only six well-documented cases of transmission of the vaccine-type virus from five healthy vaccine recipients who had a vaccine-associated rash.\textsuperscript{66,76} Contact cases have been mild.\textsuperscript{66,76,78}

Fever >39°C has been observed in 15% of healthy children after varicella vaccination, but this was comparable to that seen in children receiving placebo.\textsuperscript{66} In adults and adolescents, fever has been reported in 10% of VV recipients. It is recommended that parents/carers/vaccine recipients be advised about possible symptoms in the period 5 to 12 days after vaccination and given advice on their management, including the use of paracetamol for fever (refer to 2.3.2 Adverse events following immunisation). Higher rates of fever were observed in clinical trials of both MMRV vaccines, particularly following dose 1, when compared with giving MMR vaccine and monovalent VV at the same time but at separate sites.\textsuperscript{6–35} Two post-marketing studies in the United States identified an approximately 2-fold increased risk of fever and febrile convulsions in 1st dose recipients of MMRV vaccine, who were predominantly 12–23 months of age, in the period 7 to 10 days\textsuperscript{80} (or 5 to 12 days)\textsuperscript{80} after vaccination, compared with recipients of separate MMR and VV vaccines. MMRV vaccination resulted in 1 additional febrile seizure for every 2300 doses compared to separate MMR and VV vaccination.\textsuperscript{79} An increase in fever or febrile convulsions has not been identified after the 2nd dose of MMRV vaccine in the United States, although most 2nd dose recipients were aged 4–6 years, an age at which the incidence of febrile convulsions is low.\textsuperscript{81} These post-marketing studies were in children who received ProQuad; however, it is anticipated that this side effect profile would be similar in Priorix-tetra recipients.

A post-marketing study in the United States reported serious adverse events temporally, but not necessarily causally, linked to varicella vaccination, such as encephalitis, ataxia, thrombocytopenia and anaphylaxis, were very rare and occurred in <0.01% of doses distributed.\textsuperscript{49,75} There were no neurological adverse events following VV in which the Oka vaccine virus strain was detected in cerebrospinal fluid (CSF).

Herpes zoster (HZ) has been reported rarely in vaccine recipients and has been attributed to both the vaccine strain and to wild-type varicella virus reactivation.\textsuperscript{74} Reactivation of the vaccine virus resulting in HZ is rare and most cases of HZ in vaccine recipients can be attributed to reactivation of wild-type virus following unrecognised prior infection. The risk of developing HZ is currently thought to be lower after vaccination than after natural varicella virus infection, and reported cases have been mild.\textsuperscript{2} Rates of herpes zoster in children 0–9 years of age after natural VZV infection were estimated to be between 30 and 74 per 100 000 per year,\textsuperscript{2,83} while a rate of 22 per 100 000 person-years was reported in a 9-year follow-up of 7000 varicella vaccinated children.\textsuperscript{77} (Refer also to 4.24 Zoster.)

Persons with egg allergy can be safely given MMRV vaccine (refer to 4.9.11 Adverse events in 4.9 Measles).

### 4.22.12 Public health management of varicella

Varicella is a notifiable disease in most states and territories in Australia.

Further instructions about the public health management of varicella, including management of cases of varicella and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

**Zoster Immunoglobulin-VF (human)** – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to the varicella-zoster virus. Single vials contain 200 IU of varicella-zoster antibody, with the actual volume stated on the label on the vial. Also contains glycine.

High-titre zoster immunoglobulin (ZIG) is available from the Australian Red Cross Blood Service on a restricted basis for the prevention of varicella in high-risk subjects who report a significant exposure to varicella or HZ. ZIG has no proven use in the treatment of established varicella or zoster infection. ZIG is highly efficacious, but is often in short supply. Normal human immunoglobulin (NHIG) can be used for the prevention of varicella if ZIG is unavailable. Post-exposure prophylaxis using varicella vaccine may also be indicated, if vaccination is not contraindicated (refer below). Zoster immunoglobulin should only be given by IM injection.
‘Significant exposure’ to VZV is defined as living in the same household as a person with active varicella or HZ, or direct face-to-face contact with a person with varicella or HZ for at least 5 minutes, or being in the same room for at least 1 hour. In the case of varicella infection, the period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred. Transmission from a person with localised zoster is less likely than from a person with varicella.4

Immunocompetent varicella contacts should be tested for varicella-zoster antibodies.

ZIG must be given early in the incubation period (within 96 hours of exposure), but may have some efficacy if administered out to as late as 10 days post exposure. ZIG is able to prevent or ameliorate varicella in infants <1 month of age, in children who are being treated with immunosuppressive therapy, and in pregnant women. Persons with primary or acquired diseases associated with cellular immune deficiency and those receiving immunosuppressive therapy should be tested for varicella-zoster antibodies following contact with a person with confirmed varicella. However, testing should not delay ZIG administration after initial exposure to a case.84-86

ZIG administration (preferably within 96 hours and up to 10 days after exposure) is required for the following groups and should not be delayed by testing (if indicated below):

- Pregnant women who are presumed to be susceptible to varicella infection. If practicable, they should be tested for varicella-zoster antibodies before ZIG is given.3
- Neonates whose mothers develop primary VZV infection (chickenpox) from 7 or fewer days before delivery to 2 days after delivery. ZIG must be given, as the neonatal mortality without ZIG is up to 30% in this setting.1,7 ZIG must be given as early as possible in the incubation period.
- Neonates exposed to varicella in the 1st month of life, if the mother has no personal history of infection with VZV and is seronegative.27 ZIG should be given, due to the increased risk of severe varicella in newborns of seronegative women.
- Premature infants (born at <28 weeks gestation or whose birth weight is <1000 g) exposed to VZV while still hospitalised should be given ZIG regardless of maternal history of varicella.
- Patients suffering from primary or acquired diseases associated with cellular immune deficiency, and those receiving immunosuppressive therapy.85,86

Note: If an immunocompromised VZV contact is shown to have recent evidence of detectable antibodies, it is not necessary to give ZIG, as its administration will not significantly increase varicella-zoster antibody titres in those who are already antibody positive. Note that varicella-zoster antibodies detected in patients who have been transfused or who have received intravenous immunoglobulin or ZIG in the previous 3 months may be passively acquired and transient.

The dose schedule recommended for ZIG administration is shown in Table 4.22.2.

Table 4.22.2: Zoster immunoglobulin-VF (ZIG) dose based on weight

<table>
<thead>
<tr>
<th>Weight of patient (kg)</th>
<th>Dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>200</td>
</tr>
<tr>
<td>11–30</td>
<td>400</td>
</tr>
<tr>
<td>&gt;30</td>
<td>600</td>
</tr>
</tbody>
</table>

A dose of ZIG may be repeated if a 2nd exposure occurs more than 3 weeks after the 1st dose of ZIG. However, testing for varicella antibodies is also recommended (refer above). NHIG can be used for the prevention of varicella if ZIG is unavailable (refer to Part 5 Passive immunisation). Persons receiving monthly high-dose intravenous NHIG are likely to be protected and probably do not require ZIG if the last dose of NHIG was given 3 weeks or less before exposure.

Vaccination for post-exposure prophylaxis

If VV is not contraindicated, it can be offered to non-immune age-eligible children and adults who have a significant exposure to varicella or HZ and wish to be protected against primary infection with VZV (refer to ‘Post-exposure vaccination’ in 4.22.7 Recommendations above).51-55 Vaccination has the added benefit of reducing the likelihood of varicella infection, particularly moderate to severe disease, following exposure, and also provides long-term protection. Vaccination of exposed persons during outbreaks has also been shown to prevent further cases and to control outbreaks.55 If MMR vaccination is also indicated, MMRV vaccine can be used in children <14 years of age, although MMRV vaccine is not routinely recommended as the 1st dose of MMR-containing vaccine in children aged <4 years (refer to 4.22.7 Recommendations above).

Post-exposure vaccination should be administered within 5 days, and preferably within 3 days, after exposure.51-55

4.22.13 Variations from product information

Varilrix and Varivax Refrigerated are registered for use as 2 doses of 0.5 mL (1–2 months apart) in adolescents ≥13 years of age and adults. The ATAGI instead recommends a single dose of varicella vaccine for children <14 years of age and 2 doses of varicella vaccine in those aged ≥14 years.

In adults and adolescents where 2 doses of varicella vaccine are required, the product information for Varilrix states that the 2nd dose should be given at least 6 weeks after the 1st dose. The ATAGI recommends instead that the 2nd dose may be given at least 4 weeks after the 1st dose.

The product information for both monovalent varicella vaccines and both MMRV vaccines recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination. The ATAGI instead recommends avoiding pregnancy for 28 days after vaccination.87

The product information for Priorix-tetra and ProQuad states that persons with a history of anaphylactic or anaphylactoid reactions to egg should not be vaccinated. The ATAGI recommends instead that either Priorix-tetra or ProQuad can be given in this situation.68

The product information for Priorix-tetra states that it should be given by SC injection. The ATAGI recommends that it may also be given by IM injection.

The product information for ProQuad states that this vaccine is indicated for vaccination in individuals 12 months through 12 years of age. The product information for Priorix-tetra states that this vaccine can be used in persons from 9 months of age. The ATAGI recommends instead that both MMRV vaccines can be given to persons up to 14 years of age. The ATAGI also recommends that MMRV vaccine should not be used routinely as the 1st dose of MMR-containing vaccine in children aged <4 years.

The product information for all varicella-containing vaccines states that salicylates should be avoided for 6 weeks after vaccination, as Reye syndrome has been reported following the use of salicylates during natural varicella infection. The ATAGI recommends instead that non-immune persons receiving long-term salicylate therapy can receive varicella-containing vaccine, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination.

The product information for Varivax Refrigerated recommends delaying vaccination for 5 months after receipt of NHIG by IM injection or blood transfusion. The ATAGI recommends instead that varicella-containing vaccines should not be given for at least 3 months after receipt of immunoglobulin-containing blood products according to the intervals contained in Table 3.3.6 Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination.

The dosage of ZIG recommended in the product information differs from that in Table 4.22.2, which has been revised in order to minimise wastage of ZIG.

References

A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


