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Varicella-Zoster

OUTBREAK NOTIFIABLE

Introduction

Infection with the varicella-zoster virus (VZV) causes two distinct clinical syndromes, chickenpox and shingles (zoster). Primary infection results in varicella, an acute exanthematous disease of childhood. The virus becomes latent in the cells of the dorsal root or cranial nerve ganglia and may reactivate after a latent period, which may be several decades. Reactivation results in the clinical syndrome of zoster.

Epidemiology

In Ireland, the incidence of varicella is seasonal, reaching a peak from January to April. The incubation period is from 14 to 16 days (range 10-21). This may be prolonged up to 28 days in immunocompromised patients and in individuals who have received specific varicella-zoster immunoglobulin (VZIG). VZV enters through the respiratory tract and conjunctiva. Transmission is by inhalation of respiratory droplets, by direct contact with vesicular fluid, or less commonly by contact with fomites. In Ireland ICGP/HPSC sentinel data from 2000-2005 demonstrated that 54% of chicken pox cases occur in children under 5 years of age while 17% of cases occur over age 15 years.

Cases of chickenpox are highly infectious from 2 days before the appearance of the rash until all of the lesions have crusted, typically a total of 7 days. This period may be prolonged in immunosuppressed individuals. In the family setting the secondary attack rate ranges from 60-90% for susceptible hosts.

Zoster is transmissible to non-immune contacts as chickenpox, but is less infectious than chickenpox. Transmission is by direct or indirect contact including inhalation from non-intact vesicles. The period of infectivity, typically 5 days, is from the appearance of the lesions until all lesions have crusted. In some clinical circumstances, the viral load and/or viral

shedding may be increased with increased risk of transmission. Examples are disseminated zoster, exposed lesions (e.g. ophthalmic zoster) or immunosuppressed patients with localised zoster on any part of the body. In the Irish ICGP/HPSC sentinel data 60% of zoster cases occurred in those over 45 years of age, and 9% in those aged under 15 years.

Effects of varicella

Varicella is typically a benign infection of childhood characterised by a generalised, pruritic vesicular rash. Complications of varicella are uncommon in childhood and include superinfection usually with the Group A streptococcus, skin scarring, encephalitis, pneumonia, hepatitis and coagulopathy. The risk of complications varies with age and is higher in infants under 1 year and in persons over 15 years of age. In the USA, the fatality rate of varicella is approximately 1 per 100,000 cases among children aged 1-14 years; this increases to 25.2 per 100,000 cases in adults aged 30-49 years.

Maternal infection in pregnancy carries a greater risk of severe varicella pneumonia in the mother especially late in the second trimester and early in the third trimester. Risks to the foetus and neonate are related to the time of infection in the mother.

In the first 20 weeks of pregnancy maternal infection can result in the congenital (foetal) varicella syndrome, which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring. The mortality rate is high. The incidence has been estimated to be less than 1% in the first 12 weeks and around 2% between 13 and 20 weeks of pregnancy. A prospective study published in 1994 found no cases of congenital varicella syndrome among the 477 pregnancies in which maternal varicella occurred after 20 weeks gestation.

In the second or third trimester of pregnancy, infection can cause herpes zoster in an otherwise healthy infant. Occasional case reports of foetal damage comprising chorioretinal damage, microcephaly and skin scarring following maternal varicella between 20 and 28 weeks gestation have been published. The risk is likely to be substantially lower than that of the typical congenital varicella syndrome that occurs after maternal varicella in the first 20 weeks' gestation.

In contrast, **maternal infection in the period from 7 days before to 7 days after delivery is associated with risk of neonatal infection, the highest risk has been associated with maternal infection in the 5 days before to 2 days after delivery.**

Other groups at increased risk of severe complications or disseminated infection include immunocompromised patients, especially those who have leukaemia or other disorders in which there is depressed cell-mediated immunity, and transplant recipients.

Effects of zoster

Zoster is usually a unilateral vesicular eruption in the distribution of a single dermatome. Severe pain in the affected area and/or parasthesia is common and may occur prior to the onset of the rash. Post-herpetic neuralgia may be severe and is more common in the elderly. Zoster is typically found in conditions in which cell-mediated immunity is suppressed such as immunosuppressive therapy or HIV infection. Zoster is rare in childhood but can follow intrauterine exposure, congenital or neonatal varicella. Zoster is transmissible to susceptible individuals as chickenpox. There is no evidence that maternal zoster poses a risk to the foetus or neonate.

Passive immunisation: Varicella-zoster immunoglobulin (VZIG)

Two products which are licensed in Europe (but not in Ireland) can be obtained if required for post exposure prophylaxis, One is an intravenous preparation of varicella-zoster immunoglobulin (IV VZIG), Varitect® CP and the other product, Human varicella–zoster immunoglobulin (VZIG) specific is produced by Bio Products Laboratory (BPL) and is administered via the intramuscular (IM) route. Either product may be used for post exposure prophylaxis but the IM product is generally easier to administer in older children or adults rather than in neonates due to volume.

These products are prepared from pooled plasma of donors with a history of recent chickenpox or herpes zoster, or from those who on screening are found to have high titres of V-Z antibody. These products contain specific antibodies (mainly IgG) against varicella-zoster virus. They must be stored at 2-8°C and protected from light. Both products should be used immediately when ampoules or bottles have been opened and any unused solution discarded.

The timing of administration of the VZIG product depends on the product used. Ideally both products should be given as soon as possible after exposure, ideally within 96 hours of exposure, but the intramuscular product is licensed for use up to 10 days maximum after exposure (or 7 days in individuals with immunocompromising conditions).

The administration of VZIG does not always prevent infection. However, it will typically attenuate the illness. Severe varicella may still occur despite

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VZIG prophylaxis in high-risk groups including immunosuppressed individuals, adults and neonates.

Indications

Recommendations for VZIG prophylaxis

VZIG prophylaxis is recommended for individuals who fulfil all of the following three criteria:

- a Significant exposure (see below) to:**
- (i) Chickenpox
- or
- (ii) Disseminated zoster or extensive exposed lesions in immunocompetent individuals
- or
- (iii) Localised or disseminated zoster in immunosuppressed patients.

PLUS

- b A clinical condition which increases the risk of severe varicella (see below).**

PLUS

- c No antibodies to varicella-zoster virus (see below).**

a. Explanation of significant exposure

As a guideline, significant exposure includes the following:

- Household contact
- Contact in the same room* for a significant period of time (usually 1 hour or more†)
- Face-to-face contact such as when having a conversation (usually 5 minutes or more)

*An example of 'same room' is a classroom or 2-4 bedded hospital bay. This does not usually include a large hospital ward. However, because airborne transmission at a distance has occasionally been reported in large open wards, in this instance the necessity of giving VZIG to all susceptible high-risk contacts should be considered on a case-to-case basis, particularly in paediatric wards where the degree of contact may be difficult to define.

†Experts differ in opinion about the duration of face to face contact that warrants VZIG. However, the contact should be non-transient. Some experts suggest a contact of 5 minutes or more and other define contact as 1 hour or more.

VZIG should normally be restricted to patients exposed to a case of chickenpox or disseminated zoster between 48 hours before onset of rash until crusting of lesions. In the case of exposure to localised open zoster (e.g. ophthalmic zoster) the relevant time period for exposure is day of onset of rash until crusting of lesions.

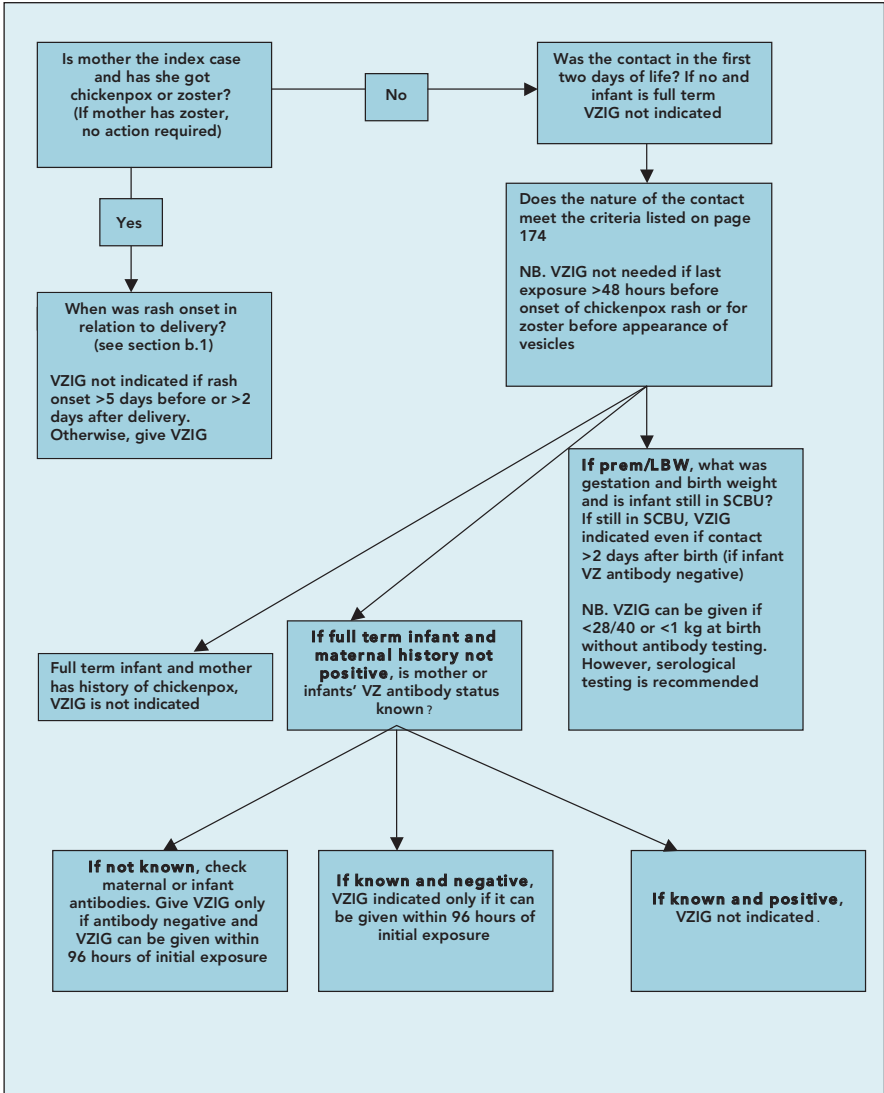
Zoster in an unexposed localised site (e.g. thoracolumbar area) in an immunocompetent patient has a low risk of transmission and contacts do not require VZIG therapy.

b. Description of clinical conditions that increase the risk of severe varicella

(1) Neonates

- Infants whose mothers develop chickenpox (but not zoster) around the time of delivery are at increased risk of severe varicella. The risk is greatest for neonates whose mothers develop varicella 5 days before delivery or 2 days after delivery, but VZIG may be beneficial for infants of mothers who develop varicella 7 days before or 7 days after delivery. Approximately half of these infants may develop varicella despite immunoprophylaxis, but the disease is usually modified. All infants in this group should be carefully monitored; hospitalisation and i.v. acyclovir treatment may occasionally be required.
- VZIG is not usually recommended for full-term healthy infants exposed post-natally to varicella, including infants of mothers who develop varicella more than 7 days after delivery
- In the event of significant exposure in a neonatal intensive care unit (NICU), or special care baby unit (SCBU),
 - VZIG is recommended for infants of non-immune mothers.
 - Infants born before 28 weeks or whose birth weight is less than 1,000 g may not possess VZ antibody despite a positive maternal history or titre and should receive VZIG in the event of significant exposure.

Figure 17.1 VZIG algorithm for neonates (see modification)

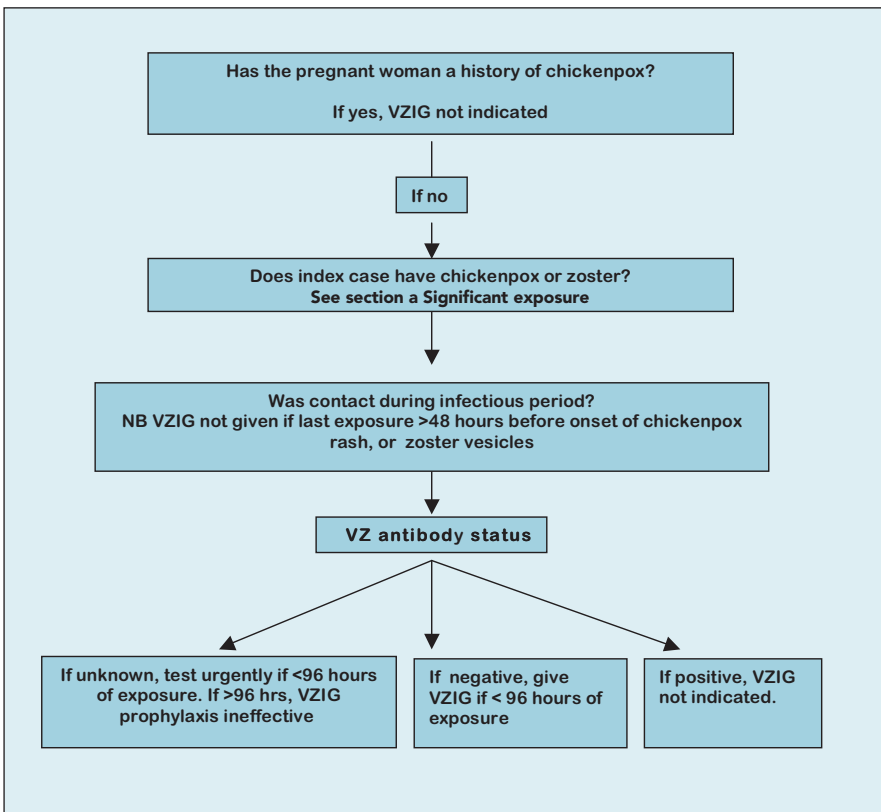


(2) Pregnant women

It is generally recommended that non-immune women who have been significantly exposed to varicella at any stage of pregnancy should be offered VZIG as soon as possible and ideally within 96 hours of the contact. VZIG BPL product for IM administration can be administered up to within 10 days post exposure.

The primary aim of VZIG immunoprophylaxis is to modify the illness in the mother, but severe maternal varicella may still occur despite prophylaxis. There is little evidence that VZIG will prevent the congenital varicella syndrome following significant exposure of a non-immune mother in the first 20 weeks. Management of varicella in pregnancy should be discussed urgently with an obstetrician/microbiologist/ID consultant and consideration given to the use of acyclovir.

Figure 17.2 VZIG algorithm for pregnant women



(3) Immunosuppressed patients

Immunosuppressed patients in whom VZIG is recommended include:

- Patients being treated with chemotherapy or generalized radiotherapy, or within 6 months of completing such treatments
- Patients who have received an organ transplant and are currently receiving immunosuppressive treatment
- Patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer where the patient has developed graft-versus-host disease. Further advice can be found in current guidance produced by the European Group for Blood and Marrow Transplantation (www.ebmt.org)
- Children who within the previous 3 months have received prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg/day for at least one week, or 1 mg/kg/day for one month. For adults, an equivalent dose is harder to define but immunosuppression may be present in those who have received a dose of around 40 mg prednisolone per day for more than one week in the previous 3 months
- Patients on lower doses of steroids, given in combination with cytotoxic drugs
- Patients with evidence of impaired cell mediated immunity, e.g. severe primary immunodeficiency or those with symptomatic HIV infection. There is no evidence of any increased risk of severe varicella in asymptomatic HIV-positive individuals with normal CD4 counts; hence VZIG is not indicated in this group
- Patients with immunoglobulin deficiencies who are receiving replacement therapy with intravenous normal immunoglobulin do not require VZIG.

Whenever possible, immunosuppressed contacts should be tested irrespective of their history of chickenpox. However, VZIG administration should not be delayed past 7 days ideally after initial contact while and antibody test is done. Under these circumstances VZIG should be given on the basis of a negative history of chickenpox. If the patient has a history of chickenpox wait for the antibody results. Those with a positive history in whom VZ is not detected by a sensitive assay should be given VZIG.

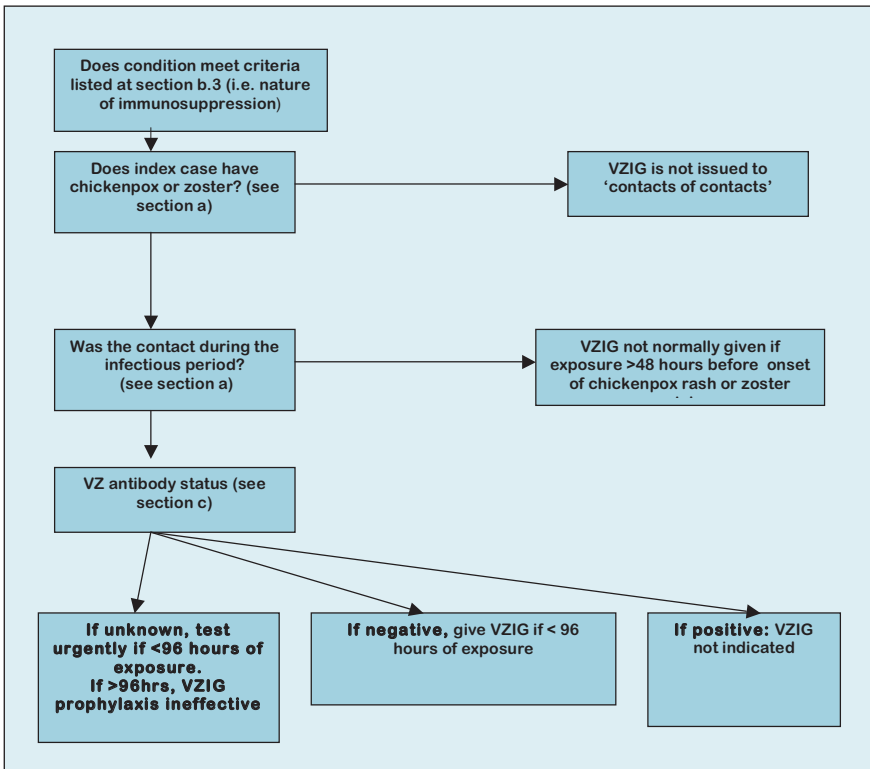
c. Description of conditions where there are no antibodies to varicella-zoster virus

Normal immunocompetent contacts with a definite history of chickenpox are immune; serology or immunoprophylaxis are not necessary and they can be reassured.

The majority of adults and a substantial proportion of children without a definite history of chickenpox are VZ antibody positive. In all individuals without a definite history or of unknown status who are being considered for VZIG, a serum sample should be tested for VZ antibody; only those without antibody require immunoprophylaxis. However, immunosuppressed contacts should be tested for VZ antibody regardless of history of chickenpox. When antibody is not detected, VZIG is indicated. To arrange urgent testing for VZ antibody local laboratories should be contacted. Testing will rarely be required outside normal working hours.

VZ antibody detected in patients who have been transfused, or who have received intravenous immunoglobulin in the previous 3 months, may have been passively acquired. Although VZIG is not indicated if antibody from other blood products is detectable, re-testing in the event of a subsequent exposure is required, as the patient may have become antibody negative.

Figure 17.3 VZIG algorithm for immunocompromised patients exposed to varicella



VZIG products for post exposure prophylaxis

1. Intramuscular VZIG (Bio Products Laboratory, BPL)

This product is licensed in Europe for post exposure prophylaxis of varicella (previously defined)

This product is dispensed in vials of: 250mg (minimum 100 i.u./ml) supplied by BPL and ideally should be given within 96 hours of exposure but can be given within 10 days of exposure.

Recommended dose for prevention of chickenpox:

Dosage is ≥ 15 I.U/kg body weight

Alternative dose levels for treatment are as follows

0 – 5 Years	250mg (1 vial)	} By slow intramuscular injection
6 – 10 Years	500mg (2 vials)	
11 – 14 Years	750mg (3 vials)	
15 years and older	1000mg (4 vials)	

The correct volume of solution to give a dose of 250 mg is overprinted on the label.

Give second dose if further exposure occurs and three weeks have lapsed since first dose.

Administration

VZIG IM product should be administered via the intramuscular route.

The usual recommended sites:

- for adults are the buttock, thigh or deltoid;
- for infants, the lateral aspect of the thigh is preferable.

If a large volume is required (> 2 ml for children or > 5 ml for adults) is required, it is recommended to administer this in divided doses at different sites.

If Intramuscular administration is contra-indicated (bleeding disorders) the injection can be administered subcutaneously. However it should be noted that there are not efficacy data to support administration by this route.

Note: For small infants in NICU, the intravenous VZIG product (outlined below) may be the preferred option due to volume required and small muscle mass in these infants.

Procurement

The VZIG BPL product can be obtained from BPL directly. Contact details of BPL can be found at <http://www.bpl.co.uk/worldwide-contacts/contact-us/>

Or Tel: +44 (0) 20 8957 2200 and Email: info@bpl.co.uk

Please see product information for more detail.

2. Intravenous VZIG (Varitect® CP supplied by Intrapharma)

This product is licensed in Europe for post exposure prophylaxis of varicella (previously defined)

Varitect® CP is a ready for-use solution for intravenous administration provided in glass containers: Vial with 5 ml (125 IU), vial with 20 ml (500 IU)

Recommended dose for prevention of chickenpox:

1 ml (25 IU) per kg body weight.

In repeated exposure, e. g. household contact, higher doses are preferable. For post- exposure prophylaxis, Varitect® CP should be administered as soon as possible and not later than 96 hours after exposure.

Administration

During the infusion the rate of 20 drops per minutes (corresponding to 1 ml per minute) must not be exceeded. (see product insert)

The solution must be inspected for particulate matter and discolouration prior to administration; cloudy or discoloured solutions or those that have deposits must not be used. Varitect® CP should be brought to room or body temperature before administration.

Special warnings and special precautions for use

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate outlined in the product insert must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. In case of adverse reactions, either the rate of administration must be reduced or the infusion stopped until symptoms disappear. Patients should be monitored for the first hour post infusion. Please see product insert for more information and read carefully before administration.

Patients with gammaglobulin deficiencies who are receiving replacement therapy with intravenous normal immunoglobulin, do not require VZIG

Procurement

Varitect® CP can be obtained by contacting Intrapharma. Contact details are available at <http://www.united-drug.ie/intrapharma.php>, Telephone: +353 (1) 452 0388

Please see product information for more detail.

Adverse reactions to VZIG

Nausea, chills, fever, headache, vomiting, allergic reactions, arthralgia and mild back pain may occasionally occur. The efficacy of live attenuated virus vaccines may be impaired for at least 6 weeks and possibly up to 3 months.

Active immunisation: Varicella Vaccine

Varicella zoster vaccine is a live attenuated viral vaccine, derived from the Oka strain of VZV.

Indications

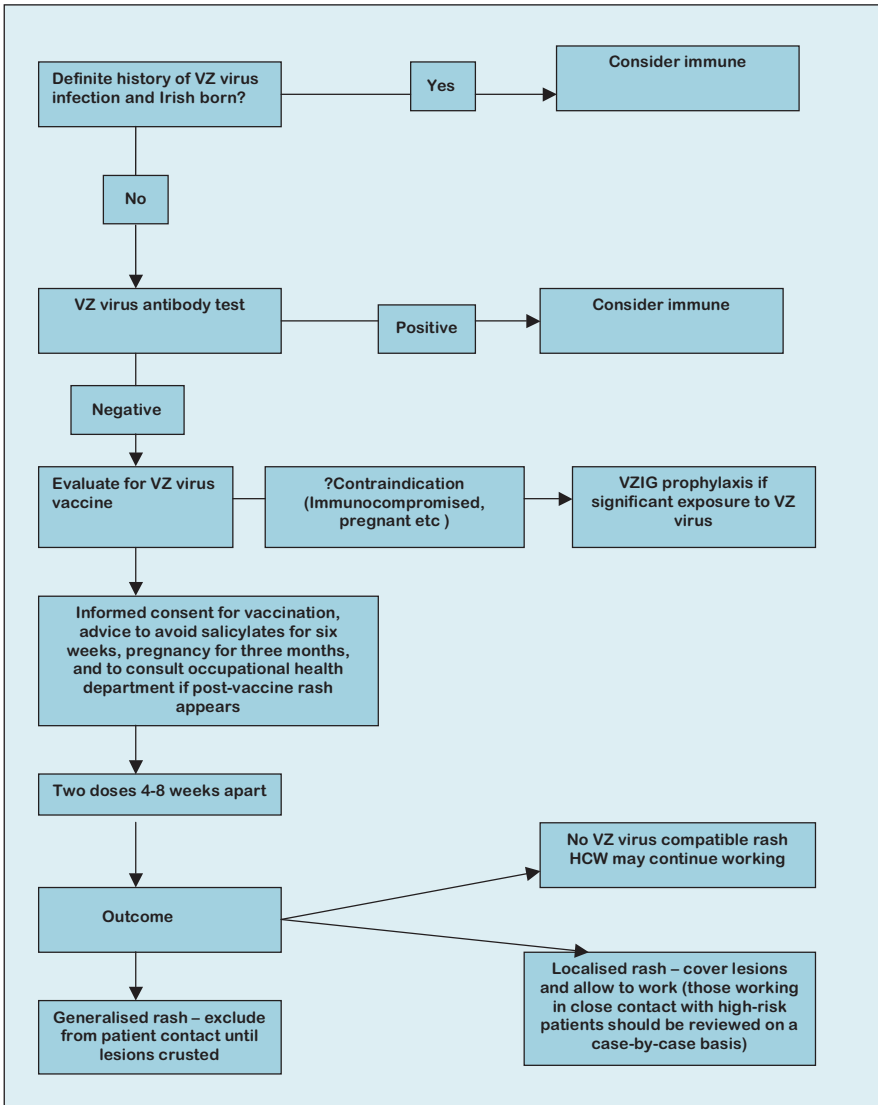
Recommendations for use of the vaccine

Two doses at least 4 weeks apart are required in both children and adults in the following risk groups:

- Non-immune health-care workers. HCWs without a definite history of chickenpox, proof of immunity or vaccination status, particularly those working with haematology, oncology, obstetrical, general paediatric or neonatal patients should be routinely screened for VZ antibody.
A history of chickenpox is a less reliable predictor of immunity in individuals born and raised overseas, and therefore routine testing should be considered in this group of HCWs. In addition, HCWs from outside Ireland and Western Europe are less likely to be immune.
Vaccination should be offered to non-immune staff.
- Laboratory staff who may be exposed to varicella virus in the course of their work
- Healthy susceptible close household contacts of immunocompromised patients
- Children with asymptomatic or mildly symptomatic HIV infection with age specific CD4+ T-lymphocyte percentage more than 25% should be considered for varicella vaccination. Two doses with a 3-month interval are required

- Under specialist hospital supervision and protocols certain categories of immunocompromised patients may be vaccinated, e.g. cases of lymphocytic leukaemia in remission and organ transplant recipients
- Children in residential units for physical disability
- All women of childbearing age without a history of varicella infection should have their immunity checked. Women with

Figure 17.4 Procedure for vaccinating health-care workers



negative serology should be vaccinated prior to pregnancy, if no contraindications exist. Pregnancy should be avoided for 3 months following the last dose of varicella vaccine. Alternatively, on completion of their pregnancy women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the health-care facility. The second dose should be administered 4-8 weeks later.

Contraindications

- Anaphylactic reaction to a preceding dose or any of the constituents including neomycin or gelatin.
- Immunosuppression due to leukaemia, lymphoma, generalized malignancy, immunodeficiency disease or immunosuppressive therapy should not be vaccinated (see above for exceptions under hospital supervision).
- Pregnancy. Pregnancy should be avoided for 3 months following the last dose of varicella vaccine. Inadvertent vaccination during pregnancy should be reported to the immunisation division in HPSC where surveillance of these events is being established.

Precautions

- Recent (less than 11 months) receipt of antibody containing blood product (specific interval depends on product See Chapter 1).
- Acute severe febrile illness, defer until recovery.
- Vaccine recipients should avoid salicylates for 6 weeks after vaccination (because of the association between aspirin use and Reye syndrome following chickenpox although this has not been reported following the vaccine)
- Persons known to have active untreated tuberculosis, although there is no evidence that either varicella or VZV exacerbates tuberculosis.

Persons whose immunosuppressive therapy with steroids has been discontinued for a month (3 months for chemotherapy) can be vaccinated.

The following are NOT contraindications

- Pregnancy of recipient's mother or other close or household contact
- Immunodeficient family member or household contact*

- Treatment with low dose (less than 2 mg/kg/day) alternate-day, topical, replacement, or aerosolised steroid preparations
- Asymptomatic or mildly symptomatic HIV infection
- Humoral immunodeficiency (e.g. agammaglobulinemia)
- Breast feeding. A study has shown no evidence of transmission of vaccine virus in breast milk. Non-immune breast-feeding mothers should be given varicella vaccine.

* If a vaccinee experiences a presumed vaccine-related rash 7-25 days after vaccination, avoid direct contact with immunocompromised persons for the duration of the rash, if possible.

Assessing immunity post vaccination is not recommended.

Testing for varicella immunity following two doses of vaccine is not recommended because 99% of persons have adequate response following the second dose. Moreover, available commercial assays are not sensitive enough to detect antibody following vaccination in all instances.

Presentation and storage

Varicella vaccine is available as lyophilised preparations for reconstitution with a diluent. VZV is less stable than other live virus vaccines and the storage temperature requirements are critical. The unreconstituted vaccine and its diluent should be stored in the original packaging at +2°C to +8°C and protected from light. After reconstitution the vaccine should be used immediately. **Discard any vaccine unused after 30 minutes. Varicella vaccines do not contain thiomersal or any other preservatives.**

The vaccine should be administered by Intramuscular (I.M.) or deep subcutaneous injection (SC).

Immunogenicity and vaccine efficacy

After one dose of vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titres. Vaccine efficacy is estimated to be 70-90% against infection, and 90-100% against moderate or severe disease.

As 10-30% of children who have received 1 dose of the vaccine are not fully protected, 2 doses are now advised for all ages. Vaccine efficacy is lower (~75%) in those aged 13 years and older. Immunity appears to be long lasting, probably permanent in the majority of vaccinees. However, approximately 1% of vaccinees per year have developed breakthrough infections. Breakthrough infection is significantly milder, with fewer

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lesions many of which are maculopapular rather than vesicular. The incidence of breakthrough infections is less in those receiving 2 doses

Post-exposure prophylaxis

Data from the USA and Japan indicate that varicella vaccine is effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days of exposure. Post-exposure vaccine prophylaxis is indicated for those listed in the risk groups for vaccination, but who have not yet been vaccinated or had the disease (subject to the listed precautions and contraindications).

Adverse reactions

Local reactions (pain redness or swelling) occur in 7-30% of vaccinees. Fever over 39°C occurs in 15% of children and 10% of adolescents and adults.

A localised or generalised maculopapular or papulovesicular rash may develop. Most varicelliform rashes that occur within 2 weeks after vaccination are due to wild type varicella-zoster virus with median onset 8 days after vaccination (range 1-24 days), while rashes caused by vaccine strain occur at a median of 21 days after vaccination (range 5-42 days). About 50% of vaccinated leukaemic patients develop a rash after the first dose and some may need antiviral therapy.

Transmission of vaccine virus from a vaccinated person can occur but the risk is very low and primarily occurs in the presence of a post-vaccination rash.

Zoster in vaccinated children has rarely been reported, and is usually a mild illness without complications.

Management of hospital exposure

Non-immune staff who have had a significant exposure to VZV (see above) should be excluded from contact with high-risk patients from 8-21 days after exposure.

HCWs with localised herpes zoster on a part of the body that can be covered with a bandage and/or clothing may be allowed to continue working unless they are in contact with high-risk patients, in which case an individual risk assessment should be carried out.

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