34

Varicella

NOTIFIABLE IN NORTHERN IRELAND

The disease

Varicella (chickenpox) is an acute, highly infectious disease caused by the varicella zoster (VZ) virus that occurs most commonly in young children.

A mild prodromal illness consisting of one to two days of fever and malaise may precede the rash although it may be absent, particularly in young children in whom the rash can be the first symptom. Vesicles often begin to appear on the face and scalp, spreading to the trunk and abdomen but are sparse on the limbs. After three or four days, the vesicles dry with a granular scab and are usually followed by further crops. Vesicles may be so few as to be missed or so numerous that they become confluent, covering most of the body. Virus is plentiful in the nasopharynx in the first few days and in the vesicles before they dry up; the infectious period is from one to two days before the rash appears until the vesicles are dry. This may be prolonged in immunosuppressed patients. Early treatment with high-dose oral aciclovir and analogues or systemic aciclovir shortens the duration and number of vesicles (Balfour *et al.*, 1992; Dunkle *et al*., 1991).

Herpes zoster (shingles) is caused by the reactivation of an individual's varicella virus. Virus from lesions can be transmitted to susceptible individuals to cause chickenpox but there is no evidence that herpes zoster can be acquired from another individual with chickenpox. Although more common in the elderly, it can occur in children and is especially common in immunosuppressed individuals of any age. Vesicles appear in the dermatome, representing cranial or spinal ganglia where the virus has been dormant. The affected area may be intensely painful with associated paraesthesia.

Varicella is transmitted directly by personal contact or droplet spread. The incubation period is between one and three weeks. The secondary infection rate from household contact with a case of chickenpox can be as high as 90%. The infection is most common in children below the age of ten, in whom it usually causes mild disease.

The disease can be more serious in adults, particularly pregnant women and those who smoke, as they are at greater risk of fulminating varicella pneumonia. Pregnant women appear to be at greatest risk late in the second or early in the third trimester; of the nine deaths due to varicella in pregnancy in England and Wales between 1985 and 1998, seven occurred between 27 and 32 weeks' gestation (Enders and Miller, 2000). For neonates and immunosuppressed individuals, the risk of disseminated or haemorrhagic varicella is greatly increased.

Risks to the fetus and neonate from maternal chickenpox are related to the time of infection in the mother (Enders *et al*., 1994; Miller *et al*., 1990):

- **in the first 20 weeks of pregnancy –** congenital (fetal) varicella syndrome, which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring. The mortality rate is high. From the largest available prospective study, 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 (Enders *et al*., 1994). In this study, no cases of congenital varicella syndrome occurred among the 477 pregnancies in which maternal varicella occurred after 20 weeks' gestation.
- **in the second and third trimesters of pregnancy –** not at the time of infection, but a subsequent herpes zoster reactivation (or shingles) in utero in an otherwise healthy infant. Occasional cases of fetal damage comprising chorioretinal damage, microcephaly and skin scarring following maternal varicella between 20 and 28 weeks' gestation have been reported (Tan and Koren, 2005), but the risk is likely to be substantially lower than that of the typical congenital varicella syndrome which occurs after maternal varicella in the first 20 weeks' gestation.
- **a week before, to a week after delivery –** severe and even fatal disease in the neonate. Before the introduction of human varicella zoster immunoglobulin (VZIG) in the UK, half the deaths in infants under one year old occurred in those aged less than three weeks in whom infection would have been contracted either before or during birth or in the first week of life.

History and epidemiology of the disease

The incidence of varicella is seasonal and classically reaches a peak from March to May, although in recent years seasonality has been less marked. Since chickenpox is so common in childhood, 90% of adults raised in the UK are immune.

Herpes zoster is less common than chickenpox and the incidence is highest in older people. The incidence of shingles increases with age and prior to a vaccination programme around one in four adults will experience an attack in their lifetime (Miller *et al.*, 1993).

The varicella vaccination

Varicella vaccines are lyophilised preparations containing live, attenuated virus derived from the Oka strain of varicella zoster virus. Two vaccines are currently available: Varilrix® (GSK) and Varivax® (Merck Sharp & Dohme Ltd). On reconstitution, both preparations should be given as a 0.5ml dose. Data from the manufacturer of Varilrix® on interchangeability indicate that in children aged 9 months to 6 years, where necessary, a course can be completed effectively with a different vaccine.

Varivax® contains hydrolysed gelatin and both vaccines may contain traces of neomycin. The Summary of Product Characteristics (SPC) contain a full list of excipients for each vaccine.

Transmission of vaccine virus from immunocompetent vaccinees to susceptible close contacts has occasionally been documented but the risk is very low. Transmission in the absence of a post-vaccination rash has not been documented (Marin *et al.* 2019).

The two-dose vaccination schedule provides about 98% protection in children (Shapiro *et al.,* 2011) and about 75% protection in adolescents and adults (Annunziato and Gershon, 2000). In both age groups, most of the breakthrough infections are modified and vaccinated individuals who contract varicella have fewer lesions and less systemic upset than unvaccinated individuals.

Varicella immunoglobulin for iv administration (Varitect® CP)

Varicella-zoster immunoglobulin for i.v. administration (Varitect® CP) is produced by Biotest as a solution for intravenous infusion and is dispensed as 25 IU/ml. It is recommended that Varitect is administered as a single dose as post-exposure prophylaxis for eligible neonates.

Although Varitect® CP is licensed for use in Germany, it is not licensed in the UK. Clinicians are able to prescribe unlicensed medicines when it is in the best interest of the patient on the basis of available evidence, and the use of this product in neonates has been considered and recommended by the PHE/UKHSA convened expert working group:

https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles

Storage

The unreconstituted vaccine and its diluent should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature.

Presentation

Varicella vaccines are available as lyophilised preparations for reconstitution with a diluent.

- Varilrix®: before reconstitution, the powder is a slightly cream to yellowish or pinkish coloured cake and the solvent is a clear colourless liquid
- Varivax®: before reconstitution, the Varivax® vial contains a white to off-white powder and the pre-filled syringe contains a clear, colourless liquid solvent. The reconstituted vaccine is a clear, colourless to pale yellow liquid

After reconstitution, the Varivax® should be used within 30 minutes and Varilrix® should be used immediately.

Dosage and schedules

Varicella vaccination

Individuals should receive two doses to ensure optimal protection against varicella. Vaccine should not be administered to children less than 9 months.

Children from 9 to 12 months of age

Where vaccination is indicated between 9 and 12 months of age, a second dose is needed and should be given a minimum interval of 3 months after the first dose.

Children from 12 months to 12 years of age

For individuals from 12 months to 12 years of age, at least 4 weeks must elapse between the first and second dose.

Adolescents and adults from 13 years of age and above

Two doses with the second dose at least 6 weeks after the first dose but in no circumstances less than 4 weeks.

Varitect CP

It is recommended that a treatment dose of 50IU/kg (2ml/kg) is administered as a single dose as post-exposure prophylaxis for eligible neonates.

Administration

Varilrix® and Varivax® can be administered by either intramuscular or deep subcutaneous injection. The preferred injection sites are the anterolateral area of the thigh in younger children and the deltoid area in older children, adolescents, and adults.

Varicella vaccine can, and ideally should (see below), be given at the same time as other live vaccines such as MMR. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

Varitect® CP should be given by slow intravenous infusion (0.1ml/kg BW/hr for the first 10 minutes and then slowly increased to a maximum for 1ml/kg BW/hr for the rest of the infusion). Treatment should be started as soon as possible after exposure, preferably within 96 hours, and no longer than 10 days after exposure.

Interchangeability

A single dose of either Varilrix® or Varivax® may be administered to those who have already received a single dose of another varicella-containing vaccine.

Administration with other vaccines

Either varicella vaccine product can be given at the same time as other vaccines such as MMR, DTaP/ IPV, Hib/MenC, PCV, hepatitis B and Men B. If varicella vaccine cannot be given at the same time as an inactivated vaccine, it can be given at any interval before or after. If varicella vaccine cannot be administered on the same day as MMR, then a 4 week minimum interval should be observed between the vaccines. For all other live vaccines e.g LAIV no deferral is required.

Disposal

For information on disposal of equipment used for vaccination, including used vials, ampoules, syringes or partially discharged vaccines please see Chapter 3.

Recommendations for the use of the vaccine

Pre-exposure vaccination

There is no universal varicella vaccine programme in the UK, and the aim of varicella immunisation is to protect those who are at most risk of serious illness from exposure. This is done by immunising specific individuals who are in regular or close contact with those at risk. Since 2003, this recommendation includes vaccinating non-immune healthcare workers who themselves will derive benefit as they will be protected from contact with infectious patients. Varicella vaccine is also recommended for healthy susceptible close household contacts of immunocompromised patients.

Non-immune groups recommended to receive pre-exposure vaccination

Healthcare workers

Chickenpox is a risk to susceptible healthcare staff who may pass it on to vulnerable patients. Therefore any healthcare workers who have patient contact, for example those working in general practice and hospitals such as cleaners on wards, catering staff, ambulance staff, receptionists in general practice, as well as medical and nursing staff, whether employed directly or through contract should be protected.

Those with a reliable history of chickenpox or herpes zoster or those with two documented doses of varicella containing vaccine or a positive VZ IgG can be considered protected. Healthcare workers with a negative or uncertain history of chickenpox or herpes zoster should be serologically tested and vaccine offered only to those without VZ antibody.

Healthcare workers should be told at the time of vaccination that they may experience a local rash around the site of injection or a more generalised rash in the month after vaccination. In either case, they should report to their occupational health department for assessment before commencing work. If the rash is generalised and consistent with a vaccine-associated rash (papular or vesicular), the healthcare worker should avoid patient contact until all the lesions have crusted. Healthcare workers with localised vaccine rashes that can be covered with a bandage and/or clothing should be allowed to continue working unless in contact with immunocompromised or pregnant patients. In the latter situation, an individual risk assessment should be made.

Post-vaccination serological testing is no longer recommended.

Samples from rashes following vaccine should be sent for analysis to the UKHSA Virus Reference Department). Instructions and forms for samples are available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/344576/E11_Varicella_Zoster_Virus.pdf

Laboratory staff

Vaccination should be offered to individuals who may be exposed to varicella virus in the course of their work, in virology laboratories and clinical infectious disease units.

Contacts of immunocompromised patients

Varicella vaccine is not currently recommended for routine use in children. However, it is recommended for healthy susceptible contacts of immunocompromised patients where continuing close contact is unavoidable (e.g. siblings of a leukaemic child, or a child whose parent or sibling is undergoing chemotherapy; see above).

Advice on vaccination of susceptible individuals prior to commencing immunosuppressive treatment

Based on clinical discretion, varicella vaccination may be considered for seronegative individuals who are planning to receive immunosuppressive treatment if there is sufficient time to complete the two dose course.

Management of at-risk individuals following significant exposure to chickenpox or herpes zoster

The aim of post-exposure management is to protect individuals at high risk of suffering from severe varicella. Antiviral treatment is the recommended post-exposure prophylaxis for all at risk individuals (https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles), with the addition of VZ immunnoglobulin

(Varitect® CP or IVIG) for neonates exposed to maternal infection within 1 week of delivery. Varitect® CP should only be offered to those susceptible individuals who are unable to take oral antivirals, i.e. due to malabsorption or renal toxicity, or aged less than 4 weeks.

Further guidance can be found at: https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles

Effectiveness of post exposure prophylaxis

Neonates

About half of neonates exposed to maternal varicella became infected despite varicella immunoglobulin prophylaxis (Miller *et al*., 1990). In up to two-thirds of these infants, infections were mild or asymptomatic but rare fatal cases have been reported despite immunoglobulin prophylaxis in those with onset of maternal chickenpox in the period four days before to two days after delivery. Post-exposure prophylaxis with intravenous aciclovir and i.v. Varitect® CP is recommended for infants in this exposure category.

Immunosuppressed contacts and pregnant women

Oral aciclovir (or valaciclovir) is now the post exposure treatment of choice for all immunosuppressed contacts and pregnant women.

Historically, hyperimmune varicella zoster immunoglobulin (VZIG) was used as post-exposure treatment. However, efficacy of aciclovir for post exposure prophylaxis in immunocompromised individuals has been evaluated in a small number of retrospective studies. The findings from these have varied from reporting no breakthrough varicella infections following aciclovir while others report a rate of 3–22% (Bate *et al*., 2018). In a retrospective observational study evaluating the effectiveness of aciclovir post exposure prophylaxis in 141 contacts exposed to varicella in a paediatric setting between 2000 and 2007 in a Japanese hospital, the rate of secondary infection was 2.1% in all contacts and 3.1% for immunocompromised contacts (Shinjoh *et al,*, 2009). This compares with a secondary infection rate of 18% in those not receiving any post exposure prophylaxis (RR 8.5 (95%CI: 1.6-45.9)).

In a recent UK observational study (PEPtalk3) of 105 immunosuppressed children with underlying haematology or oncology diagnoses exposed to VZV and requiring PEP, 87 were treated with antivirals (aciclovir or valaciclovir) compared to 18 children who received VZIG. Five children (of 84) who received aciclovir developed break through infections (6.0%) (3 mild and 2 moderate severity) compared with 2 children (11.1%) who received VZIG (1 mild and 1 moderate severity). Although the results were not significantly different (risk difference: -5.2% (95% CI -20.5% to 10.2%), p=0.60), treatment with anti-virals was no worse than VZIG prophylaxis (Cuerden *et al.,* 2022).

The rationale for the use of VZ prophylaxis in pregnant women is twofold: reduction in severity of maternal disease and reduction of risk of fetal infection for women contracting varicella in the first 20 weeks of pregnancy. In late pregnancy, PEP may also reduce the risk of neonatal infection. The risk of fatal varicella is estimated to be about five times higher in pregnant than non-pregnant adults with fatal cases concentrated late in the second or early in the third trimester (Enders and Miller, 2000).

In the absence of PEP, the risk of developing varicella in susceptible contacts is high with 13 of 18 (72%) of seronegative pregnant women developing varicella following a significant exposure (Trotta *et al* 2018)

In an UKHSA study comparing aciclovir with VZIG prophylaxis in pregnancy there were less cases of chickenpox in the aciclovir arm, although the difference was not statistically significant (Sile *et al.,* 2022).

There is little if any available data on the efficacy of aciclovir in preventing congenital varicella infection and prevention of transplacental infection of the foetus following potential exposures in the first 19 weeks of pregnancy. Use of antivirals in this situation is less clear, not least because the optimal timing and duration of treatment are unknown.

Management of healthcare workers exposed to VZ virus infection, and post exposure prophylaxis

Vaccinated healthcare workers or those with a definite history of chickenpox or zoster and having a significant exposure to VZ virus (as above and including those dressing localised zoster lesions on non-exposed areas of the body) should be considered protected and be allowed to continue working. As there is a remote risk that they may develop chickenpox, they should be advised to report to their occupational health department for assessment before having patient contact if they feel unwell or develop a fever or rash.

Unvaccinated healthcare workers without a definite history of chickenpox or zoster and having a significant exposure to VZ virus (see above) should either be excluded from contact with high-risk patients from eight to 21 days after exposure, or should be advised to report to their occupational health department before having patient contact if they feel unwell or develop a fever or rash.

There is some evidence that varicella vaccine administered within three days of exposure may be effective in preventing chickenpox (Ferson, 2001). (Both vaccines are licensed for post-exposure prophylaxis.) In any case, irrespective of the interval since exposure, vaccine should be offered to reduce the risk of the healthcare workers exposing patients to VZ virus in the future (see above).

Management of healthcare workers with herpes zoster

Healthcare workers with localised herpes zoster on a part of the body that can be covered with a bandage and/or clothing should 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.

Contraindications

The vaccine should not be given to:

- immunosuppressed patients. For patients who require protection against chickenpox, seek advice from a specialist
- women who are pregnant. Pregnancy should be avoided for one month following the last dose of varicella vaccine (see below)

or to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccine
- a confirmed anaphylactic reaction to any component of the vaccine, including neomycin or gelatin

Precautions

Unless protection is needed urgently, immunisation should be postponed in acutely unwell individuals until they have recovered fully. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

Pregnancy and breast-feeding

Women who are pregnant should not receive varicella vaccine and pregnancy should be avoided for one month following the last dose.

Studies have shown that the vaccine virus is not transferred to the infant through breast milk (Bohlke *et al*., 2003) and therefore breast-feeding women can be vaccinated if indicated.

Inadvertent vaccination in pregnancy

Surveillance of cases of inadvertent vaccination in pregnancy in the US has not identified any specific risk to the fetus. Follow-up between March 1995 to March 2012 of over 900 women in the US who were vaccinated with Oka/Merck strain (Varivax®) while pregnant has identified no cases of congenital varicella in any liveborn infant (Marin *et al.* 2014; Willis ED *et al.* 2022). In addition, the rate of occurrence of congenital anomalies was similar to that reported in the general population. However, it is nevertheless important to record such cases and to document the outcome of pregnancy. Surveillance of inadvertent vaccination in pregnancy is undertaken by the Immunisation and Vaccine Preventable Diseases Division of UKHSA (formerly known as PHE) to whom such cases should be reported using the form at https://www.gov.uk/guidance/vaccination-in-pregnancy-vip. Any such cases in Scotland should be reported to the local NHS Health Protection Team for collation on a national basis via Public Health Scotland (PHS) using the UKHSA form (https://www.gov.uk/guidance/vaccination-in-pregnancy-vip) and in Wales cases should be reported to Public Health Wales (Tel: 01443 824160)

These will, in turn, contribute to the UK figures via UKHSA.

Immunosuppression and HIV infection

Current varicella vaccines are contraindicated in immunosuppressed patients. However, vaccination is recommended for healthy susceptible contacts of immunosuppressed patients where continuing contact is unavoidable (e.g. siblings of a leukaemic child, or a child whose parents or sibling is undergoing chemotherapy; see above).

For patients who require protection against chickenpox, seek advice from a specialist.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA; http://www.bhiva.org/vaccination-guidelines.aspx) and the Children's HIV Association of UK and Ireland (CHIVA; http://www.chiva.org.uk/guidelines/immunisation/)

Use of salicylates

Aspirin and systemic salicylates should not be given to children under 16 years of age, except under medical supervision, because of the risk of Reye's syndrome, which has been reported in children treated with aspirin during natural varicella infection. However there is no need to avoid salicylates before or after receiving a varicella-containing vaccine, if

needed. The benefit is likely to outweigh any possible risk of Reye's syndrome after vaccination. In addition there are no reports of an association between Reye's syndrome and varicella vaccination (https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/varicella-chickenpox).

Adverse reactions

Varicella vaccines are well tolerated. Extensive clinical and post-marketing safety surveillance data from the US (for the Oka/Merck strain, Varivax® and the Oka strain used by GSK in Varilrix®) show the most commonly reported reactions are at the injection site (pain, redness and swelling). Generalised symptoms, such as fever and rash, can also occur but less frequently. Management of these reactions in healthcare workers is detailed below.

Up to 10% of adults and 5% of children develop a vaccine-associated rash, either localised at the injection site or generalised, within one month of immunisation (Annunziato and Gershon, 2000). Varicella vaccine rashes may be papular or vesicular. Illness associated with the vaccine can be treated with aciclovir. It is important to determine whether the rash is due to the vaccine virus or to coincidental wild-type chickenpox. Samples from rashes following vaccine should be sent for analysis to the UKHSA Virus Reference Department at Colindale. Further information is available at:

https://www.gov.uk/government/publications/varicella-zoster-virus-referral-form

The vaccine virus strain can establish latent infection and reactivate to cause herpes zoster in immunocompetent individuals, but the risk is substantially lower than with wild varicella infection. Cases of zoster occurring in a vaccinee should be investigated and samples should be sent to the UKHSA Virus Reference Department, as above.

Transmission of vaccine virus from immunocompetent vaccinees to susceptible close contacts has occasionally been documented but the risk is very low. If a localised rash develops then the lesions should be covered to further reduce the risk of transmission. If the rash is disseminated, then the risk is higher, and immunosuppressed contacts should be treated with acyclovir. Transmission in the absence of a post-vaccination rash has not been documented (Marin *et al.* 2019).

All suspected reactions in children and severe suspected reactions in adults should be reported to the Medicines and Healthcare product Regulatory Agency using the Yellow Card scheme (https://yellowcard.mhra.gov.uk/).

Safety of Varitect® CP

Varitect® CP appears to be well tolerated. Very rarely anaphylactoid reactions occur in individuals with hypogammaglobulinaemia who have IgA antibodies, or in those who have had an atypical reaction to blood transfusion.

No cases of blood-borne infection acquired through immunoglobulin preparations designed for intramuscular use have been documented in any country.

Treatment

Varicella vaccines have no place in the treatment of severe disease, and treatment is generally with intravenous and oral anti-virals, although Varitect® CP is licensed in Germany as adjunct therapy for severe or complicated VZ infections especially in immunocompromised patients

Supplies

Vaccines

- Varivax® is manufactured by MSD. MSD vaccines are distributed by Alliance Healthcare (Tel: 0330 100 0448. Email: customerservice@alliance-healthcare.co.uk)
- Varilrix® – manufactured by GSK (Tel: 01992 467 272)

Varitect® CP

England: Varitect® CP is issued through the UKHSA Rabies and Immunoglobulin Service (tel: 0300 128 1020), after an appropriate risk assessment.

Wales: available following consultation with local consultant microbiologist

Northern Ireland: advice via Regional Virus Laboratory, BHSCT Royal Hospitals Site on 07889 086 946 or BHSCT Royal Pharmacy Department through switchboard at 0289 024 0503.

Scotland: available from local hospital pharmacy departments. Details of these are available from Procurement, Commission and Facilities of NHS National Service Scotland (Tel: 0131 275 6725).

Varitect® CP is issued free of charge for neonates who meet the criteria given above. Clinicians who wish to issue Varitect® CP for patients not meeting these criteria should approach the manufacturer directly to purchase a dose.

No licensed VZIG preparations for intramuscular use are available in the UK.

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