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Shingles (herpes zoster)

The disease

Shingles (herpes zoster) is caused by the reactivation of a latent varicella zoster virus (VZV) infection, sometimes decades after the primary infection.

Primary VZV infection typically occurs during childhood and causes chickenpox (varicella); further information on this can be found in Chapter 34. Following primary VZV infection, the virus enters the sensory nerves and travels along the nerve to the sensory dorsal root ganglia and establishes a permanent latent infection. It is not known what causes reactivation of the latent virus, which leads to the clinical manifestations of shingles, but reactivation is usually associated with conditions that depress the immune system such as immunosuppressive therapy, HIV infection and/or old age. The incidence of shingles in England and Wales is estimated to be around 790 to 880 cases per 100,000 people per year for those aged 70 to 79 years (van Hoek *et al.*, 2009), see Figure 1. The risk and severity of shingles increases with age.

The first signs of shingles begin most commonly with abnormal skin sensations and pain in the affected area of skin (dermatome). Headache, photophobia, malaise and less commonly fever may occur as part of the prodromal phase. Within days or weeks, a unilateral vesicular (fluid filled blisters) rash typically appears in a dermatomal distribution. In immunocompromised individuals, a rash involving multiple dermatomes may occur. The affected area may be intensely painful with associated paraesthesia (tingling, pricking, or numbness of the skin), and intense itching is common (Gilden *et al.*, 1991). The rash typically lasts between two and four weeks.

Following the rash, persistent pain at the site, known as Post Herpetic Neuralgia (PHN), can develop and is seen more frequently in older people. Pain that persists for, or appears more than 90 days after the onset of rash (Oxman *et al.*, 2005) is a commonly accepted definition for PHN. On average, PHN lasts from three to six months, but can persist for longer. The severity of pain can vary and may be constant, intermittent or triggered by stimulation of the affected area, such as by wind on the face. (Katz *et al.*, 2004)

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Other complications of shingles depend on the nerves affected and include paresis (motor weakness), facial palsy and ‘herpes zoster ophthalmicus’, with involvement of the eye and associated dermatome, which may result in keratitis, corneal ulceration, conjunctivitis, retinitis, optic neuritis and/or glaucoma. (Shaikh S *et al.*, 2002; Pavan LD, 1995).

The reactivated virus can, in some cases, disseminate into the lungs, liver, gut, and brain, leading to pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Disseminated disease is more likely to occur in those who are severely immunocompromised, with a case fatality rate reported to be between 5 and 15%, and most deaths being attributable to pneumonia (Rogers *et al.*, 1995; Gnann *et al.*, 1991).

Individuals with active lesions, particularly if they are immunosuppressed, can transmit VZV to susceptible individuals to cause chickenpox and therefore at risk individuals who have had a significant exposure to shingles require post exposure management (see Chapter 34). There is no evidence that shingles can be acquired from another individual who has chickenpox.

History and epidemiology of the disease

Varicella infection is a prerequisite for the development of shingles. In temperate climates in the absence of a varicella vaccination programme, the lifetime risk for varicella infection is over 95% (Banz *et al.*, 2003).

Although shingles can occur at any age, incidence increases with age (see Figure 1) with an estimated lifetime risk of one in four, (Miller *et al.*, 1993). The increasing incidence with age is thought to be associated with age related immune senescence and decline in cell mediated immunity.

Age-specific incidence rates of shingles have been estimated using a number of different primary care derived data sources (van Hoek *et al.*, 2009)

Data from GP-based studies in England and Wales suggest that over 50,000 cases of shingles occur in older people aged 70 years and over annually. The severity of shingles generally increases with age and can lead to PHN (Figure 1) that can require hospitalisation. Studies have estimated ophthalmic zoster to occur in 10-20% of shingles cases (Opstelten *et al.*, 2002) with around 4% of the cases resulting in long-term sequelae, including pain (Bowsher, 1999).

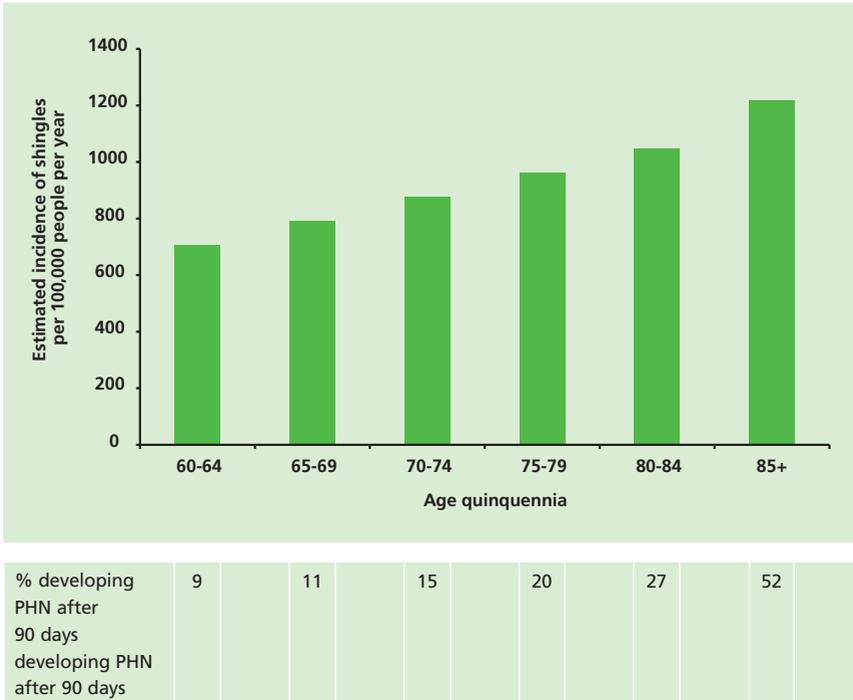


Figure 28a.1 Upper panel Estimated annual age-specific incidence of shingles per 100,000 per year in the immunocompetent population in England and Wales (population 2007).

Lower panel Estimated percentage developing PHN in the immunocompetent population in England and Wales (population 2007).

Data taken from van Hoek *et al.*, 2009.

It is estimated that, in people aged 70 years and over, around one in 1000 cases of shingles results in death (van Hoek *et al.*, 2009), although due to the nature of the population and risk of co-morbidities some deaths recorded as being shingles related may not be directly attributable to the disease.

The risk of shingles is also increased in individuals with certain conditions, including systemic lupus erythematosus, (Nagasawa *et al.*, 1990) rheumatoid arthritis, (Smitten *et al.*, 2007) and Wegener’s granulomatosis. (Wung *et al.*, 2005).

The shingles vaccination

Zostavax[®] is the only market authorised shingles vaccine available in the UK. It contains live, attenuated virus derived from the Oka/Merck strain of varicella zoster virus, at a significantly higher dose than the Varivax[®] varicella vaccine.

In a clinical trial, one dose of Zostavax[®] was assessed in 38,546 adults aged 60 years and over of whom 17,775 were aged 70 or over. The Zostavax[®] vaccine reduced the incidence of shingles by 51.3 and 38%, and the incidence of PHN by 66.5 and 66.8% in those aged 60 and 70 years and older respectively (Oxman *et al.*, 2005; Oxman *et al.*, 2008). The vaccine is well tolerated and is also immunogenic in individuals who have had a history of shingles prior to vaccination (Levin *et al.*, 2008).

In clinical trials with Zostavax[®], transmission of the vaccine virus has not been reported. However, experience with varicella vaccines which use a lower dose of the same virus strain suggests that transmission of vaccine virus occurs rarely between those vaccinees that develop a varicella-zoster virus (VZV)-like rash and susceptible close contacts (for example, a susceptible infant/grandchild). Transmission of vaccine virus from varicella vaccine recipients without VZV-like rash has not been confirmed. Therefore there remains a theoretical risk of transmitting the attenuated vaccine virus to a susceptible individual but this should be weighed against the reduced risk of developing natural shingles and potential transmission of natural virus (Zostavax SPC).

The duration of protection following a single dose of Zostavax is not known. In the original clinical trials the average follow up was 3.09 years although it is likely that the vaccine confers protection for longer, and follow up is continuing. The need for, or timing of, revaccination with Zostavax[®] has therefore not yet been determined.

Storage

The unconstituted 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 may be reduced unless the vaccine is stored at the correct temperature. Freezing may cause increased reactivity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

Zostavax® is available as a lyophilised preparation (an off-white compact crystalline plug) for reconstitution with a diluent (a clear colourless fluid). When reconstituted, Zostavax® is a semi-hazy to translucent, off-white to pale yellow liquid.

Zostavax® is supplied as a vial and a prefilled syringe, with two separate needles in the secondary packaging. Zostavax® is only available in single packs.

After reconstitution of the lyophilised suspension, the vaccine should be used immediately, but may be used up to 30 minutes following reconstitution.

Dosage and schedule

Adults should receive a single **0.65ml** dose of Zostavax®

The need for and timing of reinforcing doses have not yet been determined.

Administration

Zostavax® must be administered by **subcutaneous** injection preferably in the deltoid region of the upper arm. It should not be given by intramuscular injection as there is insufficient data on the effectiveness of the vaccine given by this route. The vaccine must not be given intravascularly. Further information on injection technique can be found in Chapter 4.

Zostavax® can be given at the same time as inactivated influenza vaccination. If given at the same time as influenza vaccination, care should be taken to ensure that the appropriate route of injection is used for all the vaccinations and to check there are no contraindications to administering a live vaccine to individuals in at risk groups presenting for seasonal influenza vaccination.

Zostavax® can be given at the same time as 23-valent pneumococcal polysaccharide vaccine for those who are eligible for both vaccines. Although a manufacturer-conducted trial showed inferior VZV antibody responses in those receiving zoster vaccine and PPV-23 concomitantly compared with those receiving the vaccines four weeks apart, there is no established correlation between antibody titres to VZV and protection from herpes zoster. Furthermore, a more recent observational study showed that herpes zoster vaccine was equally

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effective at preventing herpes zoster whether it was administered simultaneously or four weeks apart(Tseng *et al.*, 2011).

The vaccines should be given at separate sites, preferably in different limbs. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2006). The site at which each vaccine was given should be noted in the individual's records.

Travel vaccines containing live attenuated virus e.g. yellow fever, may be given to the age group recommended for shingles vaccination. If live vaccines are given simultaneously, then each vaccine virus will begin to replicate and an appropriate immune response is made to each vaccine. Several days after a live vaccine is given, natural interferon is produced in response to that vaccine. Therefore, if a second live vaccine is given during the time of this response, the interferon may prevent replication and attenuate the response to the second vaccine virus. Based on evidence that MMR vaccine can lead to an attenuation of the varicella vaccine response (Mullooly *et al.*, 2001), the recommended interval between live vaccines is currently four weeks. For this reason, if live vaccines cannot be administered simultaneously, a four-week interval is recommended to ensure adequate protection from the second vaccine.

Concurrent administration of Zostavax[®] and anti-viral medications known to be effective against VZV has not been evaluated, but drugs such as acyclovir are likely to reduce replication of the vaccine virus and therefore attenuate response.

Disposal (also refer to Chapter 3)

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in the technical memorandum 07-01 (Department of Health, 2006).

Recommendations for the use of the vaccine

The aim of the national shingles immunisation programme is to lower the incidence and severity of shingles in older people. It is recommended that it be routinely offered to people aged 70 years but it can be given to individuals up until the eightieth birthday.

The impact and cost effectiveness of vaccination is greatest in those aged 70 to 79 years of age, (van Hoek *et al.*, 2009) due to a combination of factors including:

- the burden of shingles disease within this age group (which increases with age),
- the estimated effectiveness of the vaccine within this age group (which decreases with age),
- the duration of protection of the vaccine, and
- the lack of knowledge about the effectiveness of a second dose of vaccine.

The course consists of a single dose of Zostavax®.

As Zostavax® can be administered concomitantly with inactivated influenza vaccine, the appointment for administration of the seasonal influenza vaccine is an appropriate opportunity to also provide Zostavax®, although any opportunity to provide the vaccine should be used.

Whilst the vaccine is authorised for use from age 50 years and is effective in this age group, the burden of shingles disease is generally not as severe when compared with older ages. Furthermore, given that the duration of protection is not known to last more than ten years and the need for a second dose is not known, the vaccine is not recommended to be offered routinely below 70 years of age. Administration after 80 years is less cost-effective due to the limited effectiveness of the vaccine beyond this age.

Zostavax is not indicated for prevention of primary VZV infection (chickenpox) and should not be used in children and adolescents.

Management of at risk individuals following significant exposure to herpes zoster

Transmission of VZV can occur following direct contact with herpes zoster lesions, resulting in chickenpox in contacts who are susceptible to VZV. Therefore individuals at high risk of severe complications from varicella infection should be assessed for the need for post exposure management with varicella zoster immunoglobulin (see Chapter 34 for further details).

Contraindications

The vaccine should not be given to a person who:

- has primary or acquired immunodeficiency state due to conditions such as:
 - acute and chronic leukaemias
 - lymphoma
 - other conditions affecting the bone marrow or lymphatic system
 - immunosuppression due to HIV/AIDS (see below)
 - cellular immune deficiencies
- is receiving immunosuppressive therapy (including high-dose corticosteroids); however, Zostavax® is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or in patients who are receiving corticosteroids as replacement therapy, e.g. for adrenal insufficiency
- has an active untreated TB infection
- is pregnant
- has had a confirmed anaphylactic reaction to a previous dose of varicella vaccine
- has had a confirmed anaphylactic reaction to any component of the vaccine, including neomycin or gelatin.

Therapy with low-doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6mercaptopurine (<1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are not considered sufficiently immunosuppressive and are not contraindications for administration of zoster vaccine.

Precautions

Immunisation of individuals who are acutely unwell should be postponed until they have recovered fully. This is to avoid confusing the diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

Zostavax® is not recommended for the treatment of shingles or post herpetic neuralgia (PHN). Individuals who have shingles or PHN should wait until symptoms have ceased before being considered for shingles immunisation. The natural boosting that occurs following an episode of shingles, however, makes the benefit of offering zoster vaccine immediately following recovery limited.

Ideally, shingles vaccine should be delayed until therapy with anti-viral drugs, such as aciclovir are completed as they may reduce response to the vaccine. The use of topical acyclovir is not a contraindication to vaccination. Further information on contraindications and special considerations for vaccination can be found in Chapter 6.

Pregnancy and breast-feeding

Zostavax is not indicated in women of childbearing age. Women who are pregnant should not receive Zostavax®.

Immunosuppression and HIV infection

The safety and efficacy of Zostavax® have not been established in adults who are known to be infected with HIV with or without evidence of immunosuppression (see contraindications). Immunosuppressed patients who require protection against shingles should seek advice from a specialist.

Inadvertent vaccination in immunosuppressed individuals

Immunosuppressed individuals who are inadvertently vaccinated with Zostavax should be urgently assessed to establish the degree of immunosuppression. As all individuals of this age group should be VZV antibody positive, varicella-zoster immunoglobulin is unlikely to be of benefit but prophylactic aciclovir may be considered in those for whom the attenuated vaccine virus poses a significant risk. Immunosuppressed individuals who develop a varicella rash following inadvertent vaccination can be offered prompt treatment with acyclovir.

Transmission

Post-marketing experience with varicella vaccines suggests that transmission of vaccine virus may occur rarely between those vaccinated who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from varicella vaccine recipients who do not develop a varicella-like rash has also been reported (Varivax® SPC).

As a precautionary measure, any person who develops a vesicular rash after receiving Zostavax® should avoid direct contact with a susceptible (chickenpox naïve) person until the rash is dry and crusted.

Inadvertent vaccination in individuals under 50 years of age

Zostavax[®] is licensed for use in individuals over 50 years of age. However, most adults below the age of 50 years are likely to be immune to varicella and therefore inadvertent vaccination with Zostavax[®] is unlikely to result in serious adverse reactions. Based on limited data from two clinical trials including VZV-seronegative or low seropositive adults aged 30 years and older, the rates of local and systemic reactions were similar to those reported by other subjects who received the vaccine as part of a clinical trial. No serious vaccine related reactions were reported.

Although Zostavax[®] is similar to the varicella vaccine, it has a significantly higher antigen content. Early trials in susceptible children used vaccine at doses approaching the range used in Zostavax[®] (Weibel *et al.*, 1984). The high dose formulation was well tolerated and efficacious. Inadvertent vaccination with Zostavax[®] in varicella naïve children is unlikely to result in serious adverse reactions and should count as a valid dose of varicella vaccine.

Adverse reactions

The safety of Zostavax[®] has been extensively evaluated in clinical trials; the most commonly reported side effects for Zostavax[®], occurring in at least one in ten people, were injection site reactions including erythema (redness), pain, swelling, and pruritis (itching). Other common reactions reported in at least one in 100 people were haematoma, induration and warmth at the injection site, pain in arm or leg and headache. Very rarely, a varicella (chickenpox) like-illness was reported, in fewer than one in 10,000 people.

A full list of side effects can be found in the Zostavax[®] summary of product characteristics.

Serious suspected adverse reactions to Zostavax[®] should be reported to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (www.mhra.gov.uk/yellowcard).

Supplies

Zostavax[®] vaccine is manufactured by Merck & Co. Inc., USA – one of the parent companies of Sanofi Pasteur MSD(Tel: 0800 085 5511).

In England, this vaccine should be ordered online via the ImmForm website (www.immform.dh.gov.uk) and it is distributed by Movianto UK (Tel: 01234 248631) as part of the national immunisation programme. Further information about ImmForm is available at <http://immunisation.dh.gov.uk/immform-helpletsheets/> or from the ImmForm helpdesk at helpdesk@immform.org.uk or Tel: 0844 376 0040

Centrally purchased vaccines for the national immunisation programme for the NHS can only be ordered via ImmForm and are provided free of charge to NHS organisations. Vaccines for private prescriptions, outbreaks, occupational health use or travel are NOT provided free of charge and should be ordered from the manufacturers.

To obtain supplies of Zostavax® for use outside of the routine programme contact Sanofi Pasteur MSD, direct on Tel: 0800 085 5511.

In Northern Ireland supplies of Zostavax® for the national immunisation programme, are supplied via designated Trust pharmacy departments. Details of these Trust pharmacy departments are available from the Regional Pharmaceutical Procurement Service (Tel 028 94 424346; Email rphs.admin@northerntrust.hscni.net).

In Scotland, supplies should be obtained from local vaccine-holding centres. Details of these are available from National Procurement (Tel. 0131 275 7587)

References

American Academy of Pediatrics (2006) Active Immunization. In: Pickering LK (ed.) *Red Book: 2006. Report of the Committee on Infectious Diseases*. 27th edition. Elk Grove Village, IL: American Academy of Pediatrics, pp. 9-54.

Banz K, Wagenpfeil S, Neiss A *et al.* (2003) The cost-effectiveness of routine childhood varicella vaccination in Germany. *Vaccine* 7;21(11-12):1256-67.

Brisson M, Edmunds WJ, Law B *et al.* (2001) Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect.* 127(2):305-14.

Bowsher D (1999) The lifetime occurrence of Herpes zoster and prevalence of post-herpetic neuralgia: a retrospective survey in an elderly population. *Eur J Pain* 3(4): 335-42.

Department of Health (2006) *Health Technical Memorandum 07-01: Safe Management of Healthcare Waste*. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063274. Accessed: Jan 2013.

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Fleming DM (1999) Weekly Returns Service of the Royal College of General Practitioners. *Commun Dis Public Health* **2**(2): 96-100.

Gauthier A, Breuer J, Carrington D *et al.* (2009) Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiol Infect* **137**(1): 38-47.

Gilden DH, Dueland AN, Cohrs R *et al.* (1991) Preherpetic neuralgia. *Neurology*. **41**(8):1215-8.

Gnann JW and Whitley RJ (1991) Natural history and treatment of varicella-zoster virus in high-risk populations. *J Hosp Infect* **18**:317-29.

Katz J, Cooper EM, Walther RR *et al.* (2004) Acute pain in herpes zoster and its impact on health-related quality of life. *Clin Infect Dis* **39**:342-8.

Levin MJ, Oxman MN, Zhang JH *et al.* (2008) Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis* **197**(6): 825-35.

McCormick A, Charlton J and Fleming D (1995) Assessing health needs in primary care. Morbidity study from general practice provides another source of information. *BMJ* **310**(6993): 1534.

Miller E, Marshall R and Vurdien J (1993) Epidemiology, outcome and control of varicella-zoster infection. *Rev Med Microbiol* **4**(4): 222-30.

Mullooly J and Black S (2001) Simultaneous administration of varicella vaccine and other recommended childhood vaccines – United States, 1995–9. *MMWR* **50**(47): 1058-61.

Nagasawa K, Yamauchi Y, Tada Y *et al.* (1990) High incidence of herpes zoster in patients with systemic lupus erythematosus: an immunological analysis. *Ann Rheumatic Dis* **49**:630-3.

Opstelten W, Mauritz JW, de Wit NJ *et al.* (2002) Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Fam Pract* **19**(5): 471-5.

Oxman MN and Levin MJ (2008) Vaccination against Herpes Zoster and Postherpetic Neuralgia. *J Infect Dis* **197** Suppl 2 S228-36.

Oxman MN, Levin MJ, Johnson GR *et al.* (2005) A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* **352**(22): 2271-84.

Pavan Langston D (1995) Herpes zoster ophthalmicus. *Neurology* **45**:50-1.

Ragozzino MW, Melton LJ, Kurland LT *et al.* (1982) Population-based study of herpes zoster and its sequelae. *Medicine* **61**:310-6.

Rogers SY, Irving W, Harris A *et al.* (1995). Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. *Bone Marrow Transplant* **15**:805-7.

Shaikh S, Ta CN (2002) Evaluation and management of herpes zoster ophthalmicus. *Am Fam Physician* **66**:1723-30.

Smitten AL, Choi HK, Hochberg MC *et al.* (2007) The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum* **57**:1431–8.

Tseng HF, Smith N, Sy LS and Jacobsen SJ (2011) Evaluation of the incidence of herpes zoster after concomitant administration of zoster vaccine and polysaccharide pneumococcal vaccine. *Vaccine* **29**(20):3628-32

van Hoek AJ, Gay N, Melegaro A *et al.* (2009) Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. *Vaccine* **27**(9): 1454-67.

Weibel RE, Neff BJ, Kuter BJ *et al.* (1984). Live attenuated varicella virus vaccine. Efficacy trial in healthy children. *N Eng J Med* **310**: 1409-15.

Wung PK, Holbrook JT, Hoffman GS *et al.* (2005) Herpes zoster in immunocompromised patients: incidence, timing, and risk factors. *Am J Med* **118**:1416.e9–e18.

Zostavax SPC Zostavax®: Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf

Accessed: Jan 2013.