2. Kweon MN. Shigellosis: the current status of vaccine development. *Curr Opin Infect Dis* 2008; **21:** 313–8.

Smallpox Vaccines

Vacunas de la viruela.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Smallpox Vaccine (Live)). A liquid or freeze-dried preparation of live vaccinia virus grown in the membranes of the chick embryo, in cell cultures, or in the skin of living animals. The cell culture medium may contain suitable antibacterials at the lowest effective concentration. Store at 2° to 8° and protect from light. The liquid vaccine should not be allowed to freeze.

USP 31 (Smallpox Vaccine). A suspension or solid containing a suitable strain of the living virus of vaccinia grown in the skin of bovine calves; it may contain a suitable preservative. The liquid vaccine should be stored below 0° and the dried vaccine at 2° to 8°.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Both first and second generation live smallpox vaccines have been associated with a high incidence of adverse effects. The most common adverse effects are injection site reactions, fatigue, fever, headache, malaise, myalgia, erythema, and generalised rash. Rarely there may be generalised vaccinial infection, or severe skin or CNS infection resulting in encephalitis, encephalomyelitis, encephalopathy, necrotising skin infection (progressive vaccinia, vaccinia necrosum), eczema vaccinatum, and erythema multiforme (including Stevens-Johnson syndrome). Fatalities have occurred, particularly from post-vaccination encephalitis and progressive vaccinia. Inadvertent contamination of other body sites (such as the face, mouth, nose, lips, and genitalia) from the site of vaccination also occurs frequently; autoinoculation of the eye (ocular vaccinia) may result in blindness. Benign and malignant lesions have also been reported at the vaccination site.

There have been reports of myocarditis or pericarditis or both, including some fatalities, associated with smallpox vaccination. Smallpox vaccination is not recommended for infants under 12 months of age, for persons with a history of eczema or other skin conditions, those who are immunocompromised, for pregnant women, or for women who breast feed. Household contacts of these groups should also not be vaccinated. Vaccination is best avoided in persons with known cardiac disease.

◊ References.

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3. Fulginiti VA, *et al.* Smallpox vaccination: a review, part II. Adverse events. *Clin Infect Dis* 2003; **37:** 251–71.
4. CDC. Update: adverse events following civilian smallpox vaccination—United States, 2003. *MMWR* 2004; **53:** 106–7. Correction. *ibid.*; 133. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5305a4.htm (accessed 06/11/07)
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6. Casey CG, *et al.* Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. *MMWR* 2006; **55** (RR-1): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5501.pdf (accessed 05/11/07)

Uses and Administration

After the global eradication of smallpox in 1980, vaccination against smallpox (using first generation vaccinia virus vaccine) has been indicated for those considered to be at high risk such as laboratory workers handling certain orthopoxviruses, and key emergency, healthcare, and military personnel who may have to respond to a bioterrorist release of smallpox. A second generation smallpox vaccine has been licensed in the USA for inclusion to the National Stockpile for vaccination of those considered to be at high risk for smallpox infection. Persons at high risk and who have received primary vaccination against smallpox, should be re-vaccinated every 10 years. Vaccination is not recommended for persons working with highly attenuated strains of orthopoxviruses.

WHO considers that mass vaccination against smallpox is currently not appropriate, although individuals who may be at risk of exposure to smallpox or those with confirmed infection may be vaccinated.

Recombinant vaccinia viruses are being investigated as vectors of foreign antigens, for example in a candidate AIDS vaccine (p.2203).

Vaccine development. Smallpox[1] is an acute contagious and sometimes fatal disease caused by variola virus, a member of the Poxviridae family and of the orthopoxvirus genus. There is substantial cross-protection between poxviruses of the same genus; the very effective first generation smallpox vaccine used in the global vaccination programme was created from an orthopoxvirus, vaccinia. In 1980 WHO declared smallpox to have been globally eradicated.

There has since been concern that smallpox may be used as a terrorist weapon (although WHO considers this risk to be extremely low in most countries). Therefore, research into safer vaccines against smallpox has continued. First generation vaccine was produced from vaccinia strains grown on the skin of live animals or calf lymph. Despite purification processes, the vaccine contained some bacteria, animal proteins, and adventitious animal viruses, and produced a high incidence of adverse effects, some of which were extremely serious (see Adverse Effects and Precautions, above). Second generation vaccines are single clones of vaccinia isolated from the set of genetically related viruses that made up the first generation ones; they are grown in tissue culture (rather than on animal skin or calf lymph) and are free of bacteria and adventitious animal viruses. A second generation vaccine has been found to be effective and is licensed in the USA for inclusion to the National Stockpile. However, this vaccine still has a high incidence of adverse effects. Third generation vaccines are in the early stages of development. They are being developed from vaccinia strains attenuated by serial passage on non-human tissue or by genetic manipulation, and are expected to be safer than either first or second generation vaccines. Interest has also been shown in monoclonal variola antibodies for passive immunisation.[1,2]

Stocks of smallpox (variola) virus are being kept in a few secure laboratories in the USA and Russia. Since the eradication of smallpox, WHO maintains a stockpile of smallpox vaccine, and recommends vaccination for people with occupational exposure to fully potent orthopoxviruses, such as certain laboratory and healthcare workers. Because of concern that smallpox may be used for bioterrorism, WHO and several countries have increased the number of doses kept in stock.[1] Policies for the use of smallpox vaccine, including bioterrorism preparedness, have been developed in many countries such as the USA[3,4] and UK[5,6] with some countries recommending vaccination for key emergency and military personnel.

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5. Health Protection Agency. Interim guidelines for action in the event of a deliberate release: smallpox (issued January 2008). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947373093 (accessed 15/07/08)
6. Department of Health. Guidelines for smallpox response and management in the post-eradication era (smallpox plan) (issued December 2003). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4070830 (accessed 15/07/08)

Preparations

Ph. Eur.: Smallpox Vaccine (Live);
USP 31: Smallpox Vaccine.

Proprietary Preparations (details are given in Part 3)
USA: ACAM2000; Dryvax.

Snake Venom Antisera

Antisuero contra el veneno de serpiente; Snake Antivenins; Snake Antivenoms.

ATC — J06AA03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Viper Venom Antiserum, European; Immunoserum Contra Venena Viperarum Europaearum). A preparation containing the specific antitoxic globulins that have the power of neutralising the venom of one or more species of viper (*Vipera ammodytes*, *V. aspis*, *V. berus*, or *V. ursinii*). The globulins are obtained by fractionation of the serum of animals that have been immunised against the venom or venoms. Each mL neutralises the venoms in not less than 100 mouse LD_{50} of *V. ammodytes*, 100 of *V. aspis*, 50 of *V. berus*, or 50 of *V. ursinii*. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that the only poisonous snake native to the British Isles is the adder or common viper, *Vipera berus*. In a geographical region where other species of snake (including elapids) are found, antisera able to neutralise the venoms of the species of snake indigenous to the region should be used. When the preparation is intended to neutralise the venom or venoms of one or more snakes other than vipers, the title Snake Venom Antiserum is used.

USP 31 (Antivenin (Crotalidae) Polyvalent). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against 4 species of pit vipers, *Crotalus atrox* (western diamondback), *Crotalus adamanteus*, *Crotalus durissus terrificus* (South American rattlesnake), and *Bothrops atrox* (South American fer de lance). One dose neutralises the venoms in not less than 180 mouse LD_{50} of *C. atrox*, 1320 of *C. durissus terrificus*, and 780 of *B. atrox*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

USP 31 (Antivenin (Micrurus Fulvius)). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against venom of *Micrurus fulvius* (eastern coral snake). One dose neutralises the venom in not less than 250 mouse LD_{50} of *M. fulvius*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Serum sickness is not uncommon and anaphylactic reactions may occur.

Anaphylaxis. Conjunctival or cutaneous hypersensitivity testing failed to predict early (anaphylactic) reactions to the antivenom given in a study of patients in Nigeria with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*) and in Thailand with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T. macrops*), the monocellate Thai cobra (*Naja kaouthia*), or the Malayan pit viper (*Calloselasma rhodostoma*). It was considered that conventional hypersensitivity testing has no predictive value for the occurrence of allergic reactions to antivenom and that it is not justifiable to delay treatment for 20 or 30 minutes to read the results of these tests. Although the rate at which antiserum can be given is more easily controlled by intravenous infusion, this method has serious practical disadvantages in the rural tropics where most cases of snake bite occur and an advantage of the intravenous push injection is that the person giving the antiserum must remain with the patient during the period when most severe anaphylactic reactions develop.

Pretreatment with low-dose subcutaneous adrenaline may reduce the incidence of anaphylaxis and other acute adverse reactions to the antiserum.[1] However, premedication with adrenaline, antihistamines, and corticosteroids, although widely practiced, is controversial. In one study,[2] prophylaxis with promethazine was ineffective in preventing anaphylaxis from antiserum against *Bothrops* envenomation.

1. Premawardhena AP, *et al.* Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ* 1999; **318:** 1041–3.
2. Fan HW, *et al.* Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; **318:** 1451–2.

Uses and Administration

Venomous snakes comprise the Viperidae (vipers), Elapidae (cobras, kraits, and mambas), and the Hydrophiidae (sea snakes).

The venom of snakes is a complex mixture chiefly of proteins, many of which have enzymatic activity, and may provoke local inflammatory reactions. The venom may have profound effects on tissue, blood vessels and other organs, blood cells, coagulation, and myotoxic or neurotoxic effects with sensory, motor, cardiac, renal, and respiratory involvement.

Snake venom antisera are the only specific treatment available for venomous snake bites, but can produce severe adverse reactions. They are generally only used if there are clear indications of systemic involvement, severe local involvement, or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. Adrenaline should be available in case of anaphylactic reactions to the antiserum; premedication with adrenaline, corticosteroids, and/or antihistamines is widely practiced but is regarded as controversial.

In Great Britain, the only indigenous poisonous snake is the adder, *Vipera berus*; its bite is rarely fatal but European Viper Venom Antiserum (or Zagreb antivenom) may sometimes be indicated as part of the overall treatment. The usual dose for adults and children is 10 mL by intravenous injection over 10 to 15 minutes or by intravenous infusion over 30 minutes after diluting in 5 mL/kg body-weight of sodium chloride 0.9%; the dose may be repeated after about 1 to 2 hours if symptoms of systemic envenoming persist.

In the USA, a polyvalent crotalidae antiserum against *Bothrops atrox*, *Crotalus adamanteus*, *C. atrox*, and *C. durissus terrificus*, and an antiserum against the North American coral snake, *Micrurus fulvius*, are available. In Australia, polyvalent antisera against the brown snake, death adder, taipan, and tiger snake, together with either the king brown snake or black snake, are available. A variety of polyvalent and monovalent antisera are also available as appropriate to the indigenous species of snakes in many other countries.