World Health Organization
Global Vaccine Safety,
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
ANTHRAX VACCINES TO HUMANS

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The Vaccines

There are two main types of anthrax vaccine for human use:

- A *cell free filtrate* that contains antigenic proteins which are adsorbed or precipitated using an aluminium-based adjuvant and have been obtained from cultures of attenuated, avirulent strains of *Bacillus anthracis.* The principal active ingredient is the Protective Antigen (PA) component of the anthrax toxin complex. These vaccines include Anthrax Vaccine Adsorbed (AVA) and Anthrax Vaccine Precipitated (AVP).
    - AVA, adsorbed onto aluminium hydroxide, was first licensed in the USA in 1972 and is administered intramuscularly in 5 doses over a period of 18 months (Wright et al., 2010).
    - AVP, precipitated onto aluminium potassium phosphate, was first licensed in the UK in 1979 and is administered intramuscularly in 4 doses over a period of 8 months (32 weeks).

  For both, yearly boosters are required to maintain immunity. (Baillie et al., 1999; CAMR, 2003; Friedlander et al., 1999; Joellenbeck et al., 2002; Pittman, Gibbs et al., 2002; Turnbull, 1991; 2000; 2010; WHO, 1998; 2008);
- A *live attenuated vaccine* containing spores from attenuated strains of *B. anthracis*. The vaccine is administered as a two-dose regimen in the skin of the shoulder by scarification. Annual boosters are required. The Russian vaccine was first licensed in 1953 for administration by scarification, and by subcutaneous injection in 1959 (Shlyakhov et al., 1997; Turnbull, 1991; 2000; 2010; WHO, 1998; 2008) and is mentioned here mainly for historical reasons. Few data were published on adverse events following the Russian vaccine (Splino et al., 2005). A 1990 study, which included approximately 2,500 vaccine recipients reported no severe adverse events (Shlyakhov et al., 1997). In more than 30 years' experience, no instance of adverse effects were recorded (Shlyakhov et al., 1994). During some field trials over 6,000 individuals were vaccinated using both routes of administration and "closely followed". Less than 1% were reported to have experienced fever and/or mild local reactions.

Route of administration:
Recommendations for administration of human anthrax vaccines shifted in 2008 from subcutaneous to intramuscular. Subcutaneous application is still an option for AVA when medically indicated, such as in persons with coagulation disorders or receiving medications that affect coagulation. Both routes of administration are covered in this information sheet.

Types of vaccines

Types	Vaccines	Excipients
Cell free PA vaccines	Anthrax Vaccine Adsorbed (AVA) Nonencapsulated V770-NP1-R strain	Formaldehyde, benzethonium chloride adsorbed onto aluminium hydroxide
	Anthrax Vaccine Precipitated (AVP) Avirulent Sterne 34F2 strain cultures of B. anthracis.	Aluminium potassium sulphate, thiomersal and sodium chloride
Live vaccines	Russian vaccine Live spores from attenuated strain STI-1 of B. anthracis, (4 x 108 spores per dose).	Glycerol
	PR China vaccine A suspension of attenuated strain A16R of B. anthracis.	

Adverse events

Mild adverse events of PA vaccines

Local adverse events:
Mild injection-site reactions (ISR) including erythema or oedema <5 cm in diameter, localised pruritus and induration are very common following both vaccines.

- With AVA, they have been reported in up to 40% of vaccine recipients. Erythema or oedema of up to 12 cm in diameter occurred in up to 5%, while more extensive oedema including swellings of the lower arm, were reported in 1% of vaccinees.
- With AVP, there were similar rates of injection site reactions. In a study of 129 members of a military field hospital, 47% of vaccinees reported pain at the injection site (Hayes et al., 2000), and 18% of recipients reported some incapacity, preventing them from lifting or driving for 48 hours. A mild rash or swelling at the site of injection or even at the site of an earlier injection may occur, which may last for some days.

Local reactions occurred more often in women than in men, regardless of their severity (Brachman et al., 1962, CDC, 2000). In a re-analysis of the short term safety data obtained from vaccine trials performed from the 1960's the age-adjusted relative risk for ISR in women was 2.78 (95%CI: 2.29, 3.38) (McNeil et al., 2007).

For AVA, the intramuscular route of administration has been found significantly less reactogenic in both women and men (though the difference was less pronounced as compared to the subcutaneous route), with significantly reduced ISR recorded in a CDC sponsored multi-center clinical study (Marano et al., 2008).

Systemic adverse events:
Systemic adverse events are also commonly reported following both vaccines, irrespective of the route of administration. With AVA, these included myalgia (up to 31%), rash (up to 17%), headache and malaise (up to 17%), joint aches (up to 13%), nausea, vomiting and loss of appetite (up to 9%), chills (up to 6%) and fever (up to 5%), usually lasting a few days. The frequency of these events do not substantially vary between doses (Brachman et al., 1962; CDC, 2000; Gunzenhauser et al., 2001; Pittman, Gibbs et al., 2002; Pittman, Kim-Ahn et al., 2002). In a more recent study (Marano et al., 2008), systemic adverse events including fatigue, muscle ache, headache, and tender/painful axillary adenopathy were detected in fewer vaccinees (overall ranging from 0.3 to 11.9%) compared to previous studies. Mild systemic adverse events following AVP include flu-like symptoms in about 24% of vaccinees. Rarely, swollen glands, mild fever, rash, itching or other allergic reactions have been associated with the AVP vaccine (Hayes et al., 2000).

Severe adverse events PA vaccines

Severe adverse events reported after AVA mainly include allergic or inflammatory reactions at the injection site and anaphylaxis (CDC, 2000, Joellenbeck, 2002). The rate of anaphylaxis is reported to be 0.76 episodes per 100,000 doses (Joellenbeck et al., 2002). Infrequently reported single events included disorders of the nervous system, skin, subcutaneous tissue, musculoskeletal system, connective tissue and bones, none of which have been fatal (Joellenbeck et al., 2002). A case of hypersensitivity pneumonitis following anthrax vaccination has been described (Timmer et al., 2002). Marano et al. (2008) listed 9 severe adverse events involving 7 participants out of 1,005 enrollees in the study as possibly associated with AVA, but the complete unblinded analysis of such events is not yet available.

In a review of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) following AVA administered to 500,000 US military personnel that included individual case review, there was no evidence for an unusual reporting rate of any severe or unusual adverse events (Sever et al., 2004).

Other safety issues

Anthrax vaccine and Gulf War syndrome:
Speculation concerning a possible link between biological weapon vaccines and Gulf War veterans' illnesses was the result of a weak, but statistically significant association between self-reported multiple immunisations and self-reported illness in Gulf War veterans (Unwin et al., 1999). These findings have not been confirmed by other epidemiological studies, or by clinical assessment (Hotopf et al., 2000; Chalder et al., 2001; Sever et al 2002, Sever et al 2004, Wells et al 2006). In a study of 170,723 active duty US service members, hospitalizations due to any-cause, diseases of the blood and blood-forming organs, and diseases of the respiratory system were less likely to occur in those individuals who received an anthrax vaccine (Wells et al., 2006).

Summary of mild and severe adverse events after administration of human anthrax AVA (Pittman et al. 2002, Marano et al. 2008)

Description		Reported incidence after SC administration*		Reported incidence after IM administration*	
Mild	Local	Female	Male	Female	Male
	Tenderness	85%	63%	67%	49%
	Subcutaneous nodule	63%	24%	0%	0%
	Erythema	63%	22%	7%	6%
	Warmth	35%	6%	7%	4%
	Induration	38%	3%	2%	1%
	Pruritus	30%	6%	7%	3%
	Arm motion limitation	10%	8%	17%	3%
	Oedema	10%	2%	2%	0%
	Systemic				
	Headache	11%	9%	17%	7%
	Anorexia	0%	2%	9%	3%
	Malaise	9%	10%	7%	4%
	Myalgia	7%	3%	2%	6%
	Nausea	3%	2%	7%	3%
	Respiratory difficulty	1%	3%	2%	4%
	General pruritus	3%	2%	0%	0%
	Fever	1%	3%	0%	1%
Severe	Anaphylaxis	0.76 per 100,000		Case reports	
	Disorders of the nervous system, skin, subcutaneous tissue, musculoskeletal system, connective tissue and bone, hypersensitivity pneumonitis, invasive ductal carcinoma of the breast.	Case reports			

***where possible rates are disaggregated into female/male per 100**

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: **http://www.who.int/vaccine_safety/vaccrates/en/index.html**

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