Updated WHO position paper on rabies vaccines

Geneva, Switzerland
August 2010
Introduction

- Replaces the position paper on rabies vaccines published in the *Weekly Epidemiological Record* in December 2007
- August 2010 paper incorporates recent developments in the field of human rabies vaccines, in particular with regard to immunization schedules
- Footnotes provide a limited number of core references
- Additional document with a more comprehensive list of references available
- Grading tables that assess the quality of scientific evidence for key conclusions also available
Background information

- Rabies is a viral zoonosis of mammals
- Rabid dogs are the dominant source of human infection
- Incubation period 1-3 months (<1 week to >1 year)
- In humans, the rabies virus causes acute invariably fatal encephalitis
- Each year, rabies causes an estimated 55,000 human deaths, many in children in rural Africa and Asia
- Rabies may be grossly underreported; without post-exposure prophylaxis it is estimated that approximately 327,000 persons would die from rabies each year
- In industrialized countries and most urbanized areas of Latin America human (dog-mediated) rabies is nearly eliminated due to vaccination of domestic dogs and other control measures
Cell-culture-based rabies vaccines (CCRVs)

- Most CCRVs are propagated in either human diploid cells (i.e. embryonic fibroblast cells), fetal rhesus diploid cells, Vero cells (i.e. kidney cells from African green monkey), primary Syrian hamster kidney cells, primary chick embryo cells, or in embryonated duck eggs.
- CCRVs are safe and efficacious and have been administered to millions of people worldwide.
- CCRVs can be administered intramuscularly (IM), but some are recommended also for vaccine-saving intradermal (ID) use.
**CCRV development**

- Following growth in the respective cell cultures, the viral harvest is concentrated, purified, inactivated and lyophilized. Some CCRVs use human albumin or processed gelatine as stabilizer. No thimerosal is added to most CCVS.

- Shelf-life: ≥3 years at +2°C to +8°C. Storage in darkness.

- Lyophilized CCRVs, once reconstituted with accompanying diluent, should be used immediately or within 6–8 hours.

- CCRVs should comply with the WHO recommended potency of ≥2.5 IU per single IM dose.
Intradermal administration

- Compared with the standard IM use of CCRVs, ID administration is equally safe and immunogenic.
- ID regimens require only 1–2 vials for post-exposure prophylaxis, reducing volume and direct costs by 60–80%.
- The same vaccine potency ID is used for both IM and ID.
- ID vaccines must be explicitly authorized for this route.
- ID regimens require sufficient staff training to ensure correct storage, reconstitution, and injection.
- ID regimens have been successfully introduced for post-exposure prophylaxis e.g. in India, the Philippines, Sri Lanka and Thailand.
Efficacy of CCRVs

- An appropriate CCRV-series induces adequate neutralizing antibody concentrations (≥0.5 IU/mL) in almost all healthy persons and so far, nobody with this antibody level before exposure has developed rabies.

- Prompt post-exposure vaccination combined with proper wound management and administration of rabies immunoglobulin is almost invariably effective in preventing rabies, even after high-risk exposure.

- Delays in starting or failure to complete correct prophylaxis may result in death, particularly following bites in highly innervated regions, such as the head, neck or hands, or following multiple wounds.
Duration of protection

- Long-lasting immunity against rabies depends on immunological memory, which can be demonstrated by a rapid (anamnestic) antibody response to a booster dose.
- Anamnestic responses following booster doses have been observed even 21 years after primary vaccination.
- Long-lasting immunity against rabies is achieved regardless of route of immunization (IM or ID) and follows pre-exposure as well as post-exposure immunization.
- Due to the long duration of protection, regular booster doses of the vaccine are not recommended following a completed pre-exposure or post-exposure series except for certain groups at continual, frequent or increased risk (see slide 15).
Adverse events/vaccine safety

- In general, CCRVs are shown to be safe and well tolerated
- However, in 35–45% of vaccinees, transient erythema, pain and/or swelling may occur at the injection site (ID>IM). Also, mild systemic reactions (transient fever, headache, dizziness and gastrointestinal symptoms) are observed in 5–15% of vaccinees
- Serious adverse events, mainly of allergic or neurological nature, rarely occur
- For pre-exposure prophylaxis (PrEP), previous severe reaction to vaccine components is a contraindication to further use; another CCV must be used to complete the PrEP series
- As rabies is a lethal disease, no contraindications apply to post-exposure prophylaxis following high-risk exposure
Rabies immunoglobulin

- Rabies immunoglobulin should be administered in all people with category III* exposure and to those with category II* exposure who are immunodeficient.

- Human rabies immunoglobulin (half-life is about 21 days) is the preferred product, but it is expensive and in short supply.

- Equine immunoglobulin or its F(ab´)2 products have a faster clearance, but are more widely available and considerably less expensive.

- Although most new equine immunoglobulin preparations are potent, highly purified, and safe, they are of heterologous origin, and an anaphylactic reaction occurs in about 1/45 000 cases.

*risk categories presented later
Economic considerations

- It is estimated that in Africa and Asia, deaths due to rabies could be responsible for 1.74 million disability-adjusted life years (DALYs) lost each year.

- The annual cost of rabies, including costs for post-exposure prophylaxis and rabies control in dogs, has been calculated at US$ 583.5 million.

- In 2005, the estimated global expenditure for rabies prevention exceeded US$ 1 billion.

- The frequency and costs of post-exposure prophylaxis are expected to rise dramatically in all countries where rabies is present in dogs, particularly where nerve-tissue vaccines are replaced by CCVs.
WHO position on the use of rabies vaccines (1)

Nerve tissue vaccines

- Production and use of nerve-tissue vaccines should be discontinued as soon as possible and replaced with CCVs

ID administration of CCVs

- CCVs for ID use should meet the same WHO requirements for production and control as for vaccines for IM administration only
- The immunogenicity and safety of vaccines for ID regimens should be demonstrated in appropriate clinical trials
- To be endorsed, new ID post-exposure regimens must have clear practical or economical advantages over existing IM regimens
- In countries where ID administration is approved for post-exposure prophylaxis, manufacturers of vaccines proved to be safe and efficacious by this route should clearly state that their vaccine can be used intradermally
WHO position on the use of rabies vaccines (2)

Pre-exposure prophylaxis (PrEP)

- PrEP is recommended for anyone at continual, frequent or increased risk of exposure to the rabies virus, either as a result of residence or occupation.
- Travellers with extensive outdoor exposure in rural high-risk areas with limited access to appropriate medical care should also be vaccinated, regardless of duration of stay.
- Children living in, or visiting, rabies-affected areas are at increased risk.
- WHO encourages the implementation of carefully designed studies on the feasibility, cost-effectiveness and long-term impact of incorporating CCVs into the immunization programmes of infants and children.
Administration of PrEP

- **IM administration** requires doses of 1 ml or 0.5 ml (volume depending on type of vaccine) given on days 0, 7 and 21 or 28

- For adults and children ≥2 years the IM vaccine is injected in the deltoid area of the arm; for children <2 years in the antero-lateral thigh. IM vaccines should not be given in the gluteal area

- **ID administration** of 0.1 ml on days 0, 7, and 21 or 28 is an acceptable alternative to the standard IM route

- To lead to significant savings, ID sessions should involve enough individuals to utilize all opened vials within 6–8 hours
WHO position on the use of rabies vaccines (4)

Booster injections of rabies vaccine

- Periodic booster doses are not required for individuals who have received a complete primary series of pre- or post-exposure prophylaxis with a CCV.

- Periodic booster injections are recommended as an extra precaution only for people whose occupation puts them at continual, frequent or increased risk of exposure (e.g. some laboratory workers and veterinarians).

- If available, antibody monitoring of personnel at risk is preferred to the administration of periodic boosters. Antibody testing should be done every 6-24 months, depending on the risk assessment. A booster would be recommended only if rabies virus neutralizing antibody titres fall to <0.5 IU/ml.
WHO position on the use of rabies vaccines (5)

Post-exposure prophylaxis (PEP)

The indication for PEP depends on the type of contact with the suspected rabid animal:

• category I – touching or feeding animals, licks on intact skin

• category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding

• category III – single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposures to bats

If possible, the rabies suspected animal should be kept under observation for at least 10 days, or be killed to obtain specimens for appropriate laboratory examination.
WHO position on rabies vaccines (6)

Post-exposure prophylaxis (PEP) contd.

- Category I exposures, no prophylaxis is required
- Category II, immediate vaccination
- Category III, immediate vaccination and administration of rabies immunoglobulin
- For categories II and III, thorough washing of all bite wounds and scratches should be done as early as possible
- Where available, an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound
- When impossible to complete PEP with the same CCV, another CCV should be used
PEP for category II and III exposures

- **IM administration** requires 1 ml or 0.5 ml (depending on type of vaccine) into the deltoid muscle (or anterolateral thigh in children aged <2 years)

- *(i) the 5-dose regimen* prescribes 1 dose on each of days 0, 3, 7, 14 and 28

- *(ii) the 4-dose regimen* prescribes 2 doses on day 0 (1 in each of the 2 deltoid or thigh sites) followed by 1 dose on each of days 7 and 21

- **An alternative regimen** for healthy, fully immunocompetent people who receive wound care plus high quality rabies immunoglobulin (RIG) plus WHO-prequalified rabies vaccines is 4 doses administered IM on days 0, 3, 7 and 14
WHO position on rabies vaccines (8)

PEP for category II and III exposures

*ID administration*

- The 2-site regimen prescribes ID injection of 0.1 ml at 2 sites (deltoid and thigh) on days 0, 3, 7 and 28

- This regimen may be used for people with category II and III exposures in countries where the ID route has been endorsed by national health authorities
WHO position on rabies vaccines (9)

PEP for previously-vaccinated individuals

- For rabies-exposed patients who have completed PrEP or PEP with a CCV, 1 dose delivered IM or ID on days 0 and 3 is sufficient. Rabies immunoglobulin is not indicated here.

- This 1-site 2-day ID or IM regimen also applies to people who have demonstrated rabies-virus neutralizing antibody titres of ≥0.5 IU/ml.

- As an alternative to this regimen, the patient may be offered a single-visit 4-site ID regimen consisting of 4 injections of 0.1 ml equally distributed over left and right deltoids or thighs.

- Vaccination cards recording previous immunizations are invaluable for making correct decisions.
WHO position on rabies vaccines (10)

Immunization of immunocompromised individuals

- In immunocompromised individuals including patients with HIV/AIDS, a complete series of 5 doses of IM CCV in combination with comprehensive wound management and local infiltration with human rabies immunoglobulin is required for patients with category II and III exposures.

- When feasible, the rabies-virus neutralizing antibody response should be determined 2–4 weeks following vaccination to assess possible need for an additional dose of the vaccine.
WHO position on rabies vaccines (11)

Rabies immunoglobulin (RIG) for passive immunization

- RIG is administered only once, and as soon as possible after the initiation of PEP (RIG is not indicated beyond the seventh day after the first vaccine dose)

- The dose of human RIG is 20 IU/kg body weight; for equine immunoglobulin and F(ab’)2 products, 40 IU/kg body weight

- All of the RIG, or as much as anatomically possible (avoid compartment syndrome), should be administered into or around the wound site or sites

- Remaining RIG, if any, should be injected IM at a site distant from the site of vaccine administration. Rabies immunoglobulin may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated
WHO position on rabies vaccines (12)

Coordinated efforts towards rabies control

- Eliminating rabies from dog populations significantly reduces human exposure to the disease

- Mass vaccination of dogs is the single most cost-effective intervention to control and eliminate canine rabies

- Successful rabies control also depends on measures such as
  - promoting responsible dog ownership
  - compulsory notification of rabies in humans and animals
  - ensuring the availability of reliable diagnostic procedures
  - conducting postmortem examinations to confirm the cause of death in people suspected to have been infected with rabies
  - coordination between those involved in rabies control