

Program Management

Database ID 84_12

Year 2006

Of importance for the supply of rabies vaccine is the use of the intradermal route schedule which reduces the number of vaccine vials and thereby the cost of PEP by up to 80% (US\$ 5-10 for vaccine alone).

State of the art of new vaccines: research and development

WHO/IVB/06.01 Page 89

Database ID 64_10

Year 2002

Where rabies is a public health issue, control of rabies in dogs is an essential component. A combination of initiatives, including vaccination of dogs with minimum 80% coverage, is recommended. (Initiatives should include control of the dog population, vaccination of stray dogs using baits as well as traditional vaccination of owned dogs - page 119)

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 110

Vaccine Quality

Database ID 84_11

Year 2006

A number of cell-culture based rabies vaccines are being developed in China and India on Vero cells, human diploid cells (HDC), or duck embryo cells. These vaccines however have not yet been prequalified by WHO and may require further assessment in terms of safety and efficacy before they can be traded internationally.

State of the art of new vaccines: research and development

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Database ID 64_8

Year 2002

The potency of all cell-derived (rabies) vaccines is assessed using a National Institutes of Health test and the WHO requirement is a potency of at least 2.5 IU per intramuscular dose.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 114

Vaccine Handling

Database ID 64_15

Year 2002

Appropriate staff training to ensure correct storage, reconstitution and injection is essential for successful intradermal immunization (with rabies vaccine.) (Provided that a correct sterile technique is used, the remaining doses may be kept in the vial at 2-8 °C and used for another patient within 6 hours after reconstitution – page 117.)

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 110

Schedule

Database ID 93_11

Year 2007

Pre-exposure rabies vaccination requires IM doses of 1 ml or 0.5 ml, depending on the vaccine type, given on days 0, 7 and 28 (day 28 preferable, but administration may be advanced towards day 21 if time is limited).

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Database ID 84_10

Year 2006

This type of vaccine (inactivated rabies vaccine) is still unfortunately manufactured and used in South-East Asia, but the number of countries doing so has been decreasing during the past 10 years in accordance with the WHO recommendations to replace them by cell-cultured vaccines.

State of the art of new vaccines: research and development

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Rabies

Database ID 84_13

Year 2006

It is well known that rabies PEP [post-exposure prophylaxis] with vaccine alone is not always sufficient, especially in cases of severe exposure (category 3) where concomittant passive immunization with rabies immunoglobulins (RIG) is strongly recommended.

State of the art of new vaccines: research and development

WHO/IVB/06.01 Page 90

Database ID 64_1

Year 2002

Post-exposure treatment, including when necessary specific rabies immune globulin, is recommended for all cases of potential (rabies) infection.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 110

Database ID 64_3

Year 2002

The indication for post-exposure vaccination with or without rabies immune globulin depends on the type of contact with the rabid animal. Types of contact are: category I .touching or feeding animals, licks on the skin; category II .nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin; category III . Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks. For category I no treatment is required, whereas for category II immediate vaccination and for category III immediate vaccination and administration of rabies immune globulin are recommended in addition to immediate washing and flushing of all bite wounds and scratches. Depending on vaccine type, the post-exposure schedule prescribes intramuscular doses of 1 ml or 0.5 ml given as 4-5 doses over 4 weeks. For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or post-exposure treatment with cell-derived rabies vaccines, 2 intramuscular doses of a cell-derived vaccine separated by 3 days are sufficient. Rabies immune globulin treatment is not necessary in such cases. The same rules apply to persons vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 117

Database ID 64_4

Year 2002

Factors that should be taken into consideration when deciding whether or not to initiate (post-exposure rabies) treatment are the category of exposure, the presence of rabies in the area where the contact occurred or from which the animal came, and the animal species involved. Also, the vaccination status and clinical features of the animal involved, the type of vaccine used and the availability of the animal for observation must be considered, as should be, if available, the results of laboratory testing of the animal.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 119

Rabies

Database ID 64_9

Year 2002

Veterinary rabies vaccines should not be used for humans.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 118](#)

Database ID 64_11

Year 2002

Pre-exposure (rabies) vaccination may be performed with any of the modern cell-derived vaccines and is recommended for anyone at increased risk of exposure to rabies virus. Traditionally, this recommendation includes laboratory staff, veterinarians, animal handlers, wildlife officers with frequent exposure to potentially infected animals as well as visitors to highly rabies-enzootic areas who may be exposed to rabies hosts. However, according to age-stratified studies of incidence, those at greatest risk are probably children living in rabies-enzootic regions of the developing world.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 116](#)

Database ID 64_12

Year 2002

The pre-exposure (rabies vaccine) schedule requires intramuscular doses of 1 ml or 0.5 ml, depending on the vaccine type, given on days 0, 7 and 28. Major vaccine manufacturers recommend 1 booster dose after 1 year, and to ensure protection in persons at continued risk, booster vaccinations every 5 years, or ideally, at intervals dictated by regular testing for antirabies antibodies (titres >0.5 IU/ml required for protection). On the other hand, studies with the human diploid cell vaccine and the purified Vero cell rabies vaccine have shown that 10 years after a pre-exposure series followed by a single booster dose after 1 year, more than 96% of the vaccines still have neutralizing antibodies against rabies virus.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 117](#)

Vaccine Administration

Database ID 93_1

Year 2007

Following exposure to a suspected rabid animal, prevention of human rabies consists of prompt wound cleansing and administration of a modern CCV and, in cases of severe (category III) exposure, of rabies immunoglobulin (RIG).

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Database ID 93_2

Year 2007

it is strongly recommended that the production and use of NTVs for humans be discontinued and replaced by modern CCVs as soon as possible.

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Database ID 93_3

Year 2007

Pre-exposure immunization is recommended for anyone at increased risk of exposure to rabies virus, either by nature of their residence or occupation, or when travelling.

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Rabies

Database ID 93_5

Year 2007

Countries are encouraged to implement control programmes to ensure coordination between all public sectors involved in rabies control.

Weekly epidemiological record

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Database ID 93_10

Year 2007

Pre-exposure vaccination using any of the modern CCVs is recommended for anyone at increased risk of exposure to rabies virus. This recommendation includes laboratory staff, veterinarians, animal handlers, wildlife officers with frequent exposure to potentially infected animals, as well as visitors to areas with high risk of rabies.

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Database ID 93_12

Year 2007

For adults, the vaccine should always be administered in the deltoid area of the arm; for children aged <2 years, the anterolateral area of the thigh is recommended. Rabies vaccine should not be administered in the gluteal area, where the induction of an adequate immune response may be less reliable.

Weekly epidemiological record

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Rabies

Database ID 93_13

Year 2007

ID administration of 0.1 ml volumes on days 0, 7, and 28 (day 28 preferable, but administration may be advanced towards day 21 if time is limited) is an acceptable alternative to the standard IM route. However, ID administration is technically more demanding and requires appropriate staff training and qualified supervision.

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Database ID 93_14

Year 2007

Periodic booster injections are recommended only for people whose occupation puts them at continuous or frequent risk of rabies exposure. In such cases, a booster dose should be given at intervals ideally dictated by regular testing for antirabies antibodies. Potential laboratory exposures to high concentrations of rabies virus motivates testing as often as every 6 months; VNA titres of at least 0.5 IU/ml indicate protection. Where serological testing is unavailable, booster vaccination every 5 years may be an acceptable alternative.

Weekly epidemiological record

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The indication for post-exposure prophylaxis with or without RIG depends on the type of contact with the suspected rabid animal: Category I – touching or feeding animals, licks on the skin (i.e. no exposure);

Category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin;

Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, exposures to bats.

For category I exposures, no prophylaxis is required; whereas for category II, immediate vaccination, and for category III, immediate vaccination and administration of RIG are recommended. For categories II and III, thorough (for ~15 minutes) washing and flushing with soap/detergent and copious amounts of water of all bite wounds and scratches should be done immediately, or as early as possible.

Weekly epidemiological record

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Post-exposure prophylaxis can be discontinued if the suspect animal is proved by appropriate laboratory examination to be free of rabies, or, in the case of domestic dogs or cats, the animal remains healthy throughout a 10-day observation period.

Factors that should be taken into consideration when deciding whether or not to initiate post-exposure prophylaxis include the likelihood of the concerned animal being rabid, category of exposure (I–III), clinical features of the animal, as well as its availability for observation and laboratory testing. In most situations in developing countries, the vaccination status of the offending animal should not be taken into consideration to withhold prophylaxis.

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Intramuscular administration

The post-exposure vaccination schedule is based on IM doses of 1 ml or 0.5 ml, depending on the manufacturer. The recommended regimen consists of either a 5-dose or a 4-dose schedule.

- (i) The 5-dose regimen prescribes 1 dose injected into the deltoid muscle (or anterolateral thigh in children aged <2years) 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/thigh sites) followed by 1 dose on each of days 7 and 21.

Intradermal administration

Either the 8-site or the 2-site regimen should be used, as recommended by the respective vaccine manufacturer.

- (i) The 8-site ID regimen prescribes on day 0, injections of 0.1 ml given at 8 sites (1 in each upper arm, 1 in each lateral thigh, 1 on each side of the suprascapular region, and 1 on each side of the lower quadrant region of the abdomen); on day 7, 1 injection in each upper arm and each lateral thigh; and on each of days 30 and 90, 1 injection in one upper arm.8 The 1 dose on day 90 may be replaced by 2 ID injections on day 30.

- (ii) The 2-site ID regimen9 prescribes 1 injection of 0.1 ml at 2 sites on days 0, 3, 7 and 28.

For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or postexposure prophylaxis with a CCV, 2 IM or ID doses of such a vaccine administered on days 0 and 3 are sufficient. RIG is not necessary in such cases. The same rules apply to people vaccinated against rabies who have demonstrated VNA titres of at least 0.5 IU/ml. Vaccination cards carefully recording previous immunizations are invaluable for correct decision-making.

Rabies immunoglobulin for passive immunization

RIG should be administered in all category III exposures and in category II exposures involving immunodeficient individuals. Given its relatively slow clearance, human rabies immunoglobulin (HRIG) is the preferred product, particularly in cases of multiple severe exposures. However, HRIG is in short supply and available mainly in industrialized countries. Where HRIG is not available or affordable, purified equine immunoglobulin (ERIG) or F(ab')₂ products of ERIG should be used. Most of the new ERIG preparations are potent, highly purified, safe and considerably less expensive than HRIG. However, they are of heterologous origin and carry a small risk of hypersensitivity reactions.¹⁰ There are no scientific grounds for performing a skin test prior to administration of ERIG because testing does not predict reactions, and ERIG should be given whatever the result of the test. RIG for passive immunization should not be injected later than 7 days after the initiation of post-exposure vaccination. The dose for HRIG is 20 IU/kg body weight, and for ERIG and F(ab')₂ products 40 IU/kg body weight. All of the RIG, or as much as anatomically possible (cave compartment syndrome), should be administered into or around the wound site(s). Any remaining RIG should be injected IM at a site distant from the site of vaccine administration.

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Of importance for the supply of rabies vaccine is the use of the intradermal route schedule which reduces the number of vaccine vials and thereby the cost of PEP by up to 80% (US\$ 5-10 for vaccine alone).

State of the art of new vaccines: research and development

WHO/IVB/06.01 Page 89

Rabies

Database ID 64_5

Year 2002

If post-exposure (rabies) treatment must be given to immunocompromised individuals, HIV-positive persons, people under malaria chemoprophylaxis or people under anaesthesia, intramuscular vaccine and rabies immune globulin are mandatory and their antibody responses should be monitored serologically.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 119](#)

Database ID 64_14

Year 2002

In order to reduce the cost of post-exposure (rabies) treatment, intradermal multisite regimens using a fraction of the intramuscular volume per intradermal inoculation site have been developed. Only the cell-derived vaccines that meet the WHO requirements regarding safety, potency and efficacy for this application may be considered for intradermal use. (Where rabies poses a significant health problem and money and vaccines are in short supply, the use of the intradermal route for post-exposure treatment should be considered - page 110.)

For details on intradermal application of human rabies vaccines, see documents WHO/EMC/ZOO.96.6 and WHO/CDS/CSR/APH/2000.5).

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 117](#)

Contraindications

Database ID 93_6

Year 2007

Because rabies is a lethal disease, no contraindications to post-exposure prophylaxis following high-risk exposure exist. This also pertains to post-exposure rabies prophylaxis in infancy and pregnancy.

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Rabies

Database ID 93_7

Year 2007

For pre-exposure immunization, previous severe reaction to any of the vaccine components is a contraindication to further use of the same vaccine.

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Database ID 93_8

Year 2007

In immunocompromised individuals, including patients with HIV/AIDS, comprehensive wound management and local infiltration with RIG, in combination with a complete intramuscular CCV series, are of utmost importance for the successful prevention of rabies. In these situations, the VNA response should be determined 2–4 weeks following vaccination to assess the possible need for an additional dose of the vaccine.

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Database ID 93_9

Year 2007

People taking chloroquine for treatment or malaria prophylaxis can have a reduced response to ID rabies vaccination. These patients should receive the vaccine by the IM route.

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Database ID 64_6

Year 2002

There are no contraindications to any of these (cell-derived rabies) vaccines being used for post-exposure treatment. Should an allergic reaction occur, the modern vaccines of different cell substrate origin may replace each other. Pregnancy is not a contraindication to post-exposure treatment.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) Page 115

Research

Database ID 64_13

Year 2002

WHO encourages carefully designed studies on the feasibility and impact of incorporating modern rabies vaccines in the early immunization programmes of infants and children in communities where rabies is a major health problem.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 110](#)

Database ID 64_16

Year 2002

The feasibility and longterm outcome of intradermal pre-exposure (rabies) immunization of young children needs further assessment.

(Page 119): It is important to assess the efficacy of multisite intradermal (rabies vaccine) application in the absence of rabies immune globulin.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 110](#)

Introduction of Vaccines

Database ID 64_7

Year 2002

Rabies vaccines of nerve tissue origin may induce serious neurological complications. In addition, these vaccines require more injections because of inferior protective potency per dose. Therefore, nerve tissue vaccines should be replaced by modern, safe and efficacious vaccines. (Rabies vaccines of nerve tissue origin are not recommended for pre-exposure immunization - page 115) It is important to increase supply and accessibility of high-quality rabies vaccine and immune globulin among the poor segments of affected populations.

Rabies vaccines (WHO position paper)

Weekly Epid. Record (2002, 77: 109-119) [Page 110](#)
