

Important rabies references

(mainly 2007-2002)

Zinsstag J, Schelling E, Roth F, Bonfoh B, de Savigny D, Tanner M. Human benefits of animal interventions for zoonosis control. Emerg Infect Dis. 2007 Apr;13(4):527-31.

Although industrialized countries have been able to contain recent outbreaks of zoonotic diseases, many resource-limited and transitioning countries have not been able to react adequately. The key for controlling zoonoses such as rabies, echinococcosis, and brucellosis is to focus on the animal reservoir. In this respect, ministries of health question whether the public health sector really benefits from interventions for livestock. Cross-sectoral assessments of interventions such as mass vaccination for brucellosis in Mongolia or vaccination of dogs for rabies in Chad consider human and animal health sectors from a societal economic perspective. Combining the total societal benefits, the intervention in the animal sector saves money and provides the economic argument, which opens new approaches for the control of zoonoses in resource-limited countries through contributions from multiple sectors.

Sudarshan MK, Madhusudana SN, Mahendra BJ, Rao NS, Ashwath Narayana DH, Abdul Rahman S, Meslin FX, Lobo D, Ravikumar K, Gangaboraiah. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. Int J Infect Dis. 2007 Jan;11(1):29-35.

OBJECTIVE: Human rabies has been endemic in India since time immemorial, and the true incidence of the disease and nationwide epidemiological factors have never been studied. The main objectives of the present study were to estimate the annual incidence of human rabies in India based on a community survey and to describe its salient epidemiological features. **METHODS:** The Association for Prevention and Control of Rabies in India (APCRI) conducted a national multi-center survey with the help of 21 medical schools during the period February-August 2003. This community-based survey covered a representative population of 10.8 million in mainland India. Hospital-based data were also obtained from the 22 infectious diseases hospitals. A separate survey of the islands of Andaman, Nicobar, and Lakshadweep, reported to be free from rabies, was also undertaken. **RESULTS:** The annual incidence of human rabies was estimated to be 17,137 (95% CI 14,109-20,165). Based on expert group advice, an additional 20% was added to this to include paralytic/atypical forms of rabies, providing an estimate of 20,565 or about 2 per 100,000 population. The majority of the victims were male, adult, from rural areas, and unvaccinated. The main animals responsible for bites were dogs (96.2%), most of which were stray. The most common bite sites were the extremities. The disease incubation period ranged from two weeks to six months. Hydrophobia was the predominant clinical feature. Many of the victims had resorted to indigenous forms of treatment following animal bite, and only about half of them had sought hospital attention. Approximately 10% of these patients had taken a partial course of either Semple or a cell culture vaccine. The islands of Andaman, Nicobar, and Lakshadweep were found to be free of rabies. **CONCLUSION:** Human rabies continues to be endemic in India except for the islands of Andaman, Nicobar, and Lakshadweep. Dogs continue to be the principal reservoir. The disease is taking its toll on adult men and children, the majority from rural areas, due to lack of awareness about proper post-exposure immunization. The keys to success in the further reduction of rabies in India lies in improved coverage with modern rabies vaccines, canine rabies control, and intensifying public education about the disease.

Rupprecht CE, Willoughby R, Slate D. Current and future trends in the prevention, treatment and control of rabies. *Expert Rev Anti Infect Ther.* 2006 Dec;4(6):1021-38.

Rabies remains a global zoonosis of major public health, agricultural and economic significance. Dogs are the major animal reservoirs in developing regions, wildlife maintain cycles of infection even in developed countries and new viral etiological agents continue to emerge. Nearly all human rabies cases are related directly to animal bite and thus, primary disease prevention requires minimization of suspected exposures. Once exposure occurs, modern prophylaxis entails immediate wound care, local infiltration of rabies immune globulin and parenteral administration of modern cell culture vaccines in multiple doses. Pre-exposure vaccination should occur in selected population groups at risk of occupational exposure. Historically, survival from fatal rabies by at least five human patients, vaccinated prior to the onset of clinical signs, signaled initial optimism as to the theoretical utility of medical intervention. Recently, the heroic recovery of an unvaccinated teenager from clinical rabies offers hope of future specific therapy. Canine rabies elimination is the key towards ultimate reduction of the disease burden, as first illustrated in developed countries. Implementation of oral vaccination in free-ranging carnivore hosts demonstrates the feasibility of disease abatement in particular wildlife populations, such as demonstrated in Europe and North America, with an enhanced need for application to developing countries in the Americas, Africa and Eurasia.

Willoughby RE Jr, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, Chusid MJ, Rupprecht CE. Survival after treatment of rabies with induction of coma. *N Engl J Med.* 2005 Jun 16;352(24):2508-14.

We report the survival of a 15-year-old girl in whom clinical rabies developed one month after she was bitten by a bat. Treatment included induction of coma while a native immune response matured; rabies vaccine was not administered. The patient was treated with ketamine, midazolam, ribavirin, and amantadine. Probable drug-related toxic effects included hemolysis, pancreatitis, acidosis, and hepatotoxicity. Lumbar puncture after eight days showed an increased level of rabies antibody, and sedation was tapered. Paresis and sensory denervation then resolved. The patient was removed from isolation after 31 days and discharged to her home after 76 days. At nearly five months after her initial hospitalization, she was alert and communicative, but with choreoathetosis, dysarthria, and an unsteady gait.

Jackson AC (2007) Human disease. In *Rabies, Second edn*, Jackson AC and Wunner AH (eds), Elsevier, Academic Press, London, pp. 309-40. (No summary available).

Knobel DL, Cleaveland S, Coleman PG, Fèvre EM, Meltzer MI, Miranda ME, Shaw A, Zinsstag J, Meslin FX. Re-evaluating the burden of rabies in Africa and Asia. *Bull World Health Organ.* 2005 May; 83(5):360-8.

OBJECTIVE: To quantify the public health and economic burden of endemic canine rabies in Africa and Asia. **METHODS:** Data from these regions were applied to a set of linked epidemiological and economic models. The human population at risk from endemic canine rabies was predicted using data on dog density, and human rabies deaths were estimated using a series of probability steps to determine the likelihood of clinical rabies developing in a person after being bitten by a dog suspected of having rabies. Model outputs on mortality and morbidity associated with rabies were used to calculate an improved disability-adjusted life year (DALY) score for the disease. The total societal cost incurred by the disease is presented. **FINDINGS:** Human mortality from endemic canine rabies was estimated to be 55 000 deaths per year (90% confidence interval (CI) = 24 000-93 000). Deaths due to rabies are responsible for 1.74 million DALYs lost each year (90% CI = 0.75-2.93). An additional 0.04 million DALYs are lost through morbidity and mortality following side-effects of nerve-tissue vaccines. The estimated annual cost of

rabies is USD 583.5 million (90% CI = USD 540.1-626.3 million). Patient-borne costs for post-exposure treatment form the bulk of expenditure, accounting for nearly half the total costs of rabies. **CONCLUSION:** Rabies remains an important yet neglected disease in Africa and Asia. Disparities in the affordability and accessibility of post-exposure treatment and risks of exposure to rabid dogs result in a skewed distribution of the disease burden across society, with the major impact falling on those living in poor rural communities, in particular children.

Warrell MJ, Warrell DA. Rabies and other lyssavirus diseases. Lancet. 2004 Mar 20;363(9413):959-69.

The full scale of the global burden of human rabies is unknown, owing to inadequate surveillance of this fatal disease. However, the terror of hydrophobia, a cardinal symptom of rabies encephalitis, is suffered by tens of thousands of people each year. The recent discovery of enzootic European bat lyssavirus infection in the UK is indicative of our expanding awareness of the Lyssavirus genus. The main mammalian vector species vary geographically, so the health problems created by the lyssaviruses and their management differ throughout the world. The methods by which these neurotropic viruses hijack neurophysiological mechanisms while evading immune surveillance is beginning to be unravelled by, for example, studies of molecular motor transport systems. Meanwhile, enormous challenges remain in the control of animal rabies and the provision of accessible, appropriate human prophylaxis worldwide.

Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine. 2007 Nov 1;25(44):7605-9.

Rabies remains a public health problem in many emerging countries. Virtually all is known that should enable us to eliminate this scourge by controlling the disease in canine populations and by diligent provision of WHO recommended post-exposure prophylaxis (PEP). Nevertheless, post-exposure prophylaxis failures do occur. Most common failures are due to deviations from WHO management recommendations and lack of essential biologicals. True failures, where all was done according to WHO recommendations, are fortunately extremely rare. Presented are seven such deaths. Other examples of common management deviations that resulted in deaths are also shown.

Madhusudana SN, Sanjay TV, Mahendra BJ, Sudarshan MK, Narayana DH, Giri A, Muhamuda K, Ravi V, Vakil HB, Malerczyk C. Comparison of safety and immunogenicity of purified chick embryo cell rabies vaccine (PCECV) and purified vero cell rabies vaccine (PVRV) using the Thai Red Cross intradermal regimen at a dose of 0.1 ML. Hum Vaccin. 2006 Sep-Oct;2(5):200-4.

Intradermal (ID) vaccination with modern cell culture rabies vaccines is a means to significantly reduce the cost of post-exposure prophylaxis as compared to intramuscular vaccination. In this study we evaluated the efficacy, immunogenicity and tolerability of PCECV and PVRV administered ID in doses of 0.1 mL per site according to the 2-site Thai Red Cross (TRC) regimen. Patients with WHO category III exposure to suspect or laboratory proven rabid animals were administered either PCECV (n = 58) or PVRV (n = 52) ID at a dose of 0.1 mL per site at two sites on days 0, 3 and 7 and at one site on days 30 and 90. Serum samples were withdrawn on days 0, 14, 30, 90 and 180 and rabies virus neutralizing antibody (RVNA) titers were determined by rapid fluorescent focus inhibition test (RFFIT). Patients who were exposed to laboratory confirmed rabid animals were followed up for one year after exposure. All 110 patients developed RVNA titers above 0.5 IU/mL by day 14. Adequate titers >0.5 IU/mL were maintained up to day 180. Both vaccines induced equivalent RVNA titers at all time points and were well tolerated.

Five subjects who were bitten by laboratory confirmed rabid dogs were alive and healthy one year after exposure. As demonstrated, PCECV and PVRV are both immunogenic, efficacious and well tolerated when administered in the TRC post-exposure prophylaxis regimen in ID doses of 0.1 mL as recommended by WHO guidelines. The use of PCECV in this regimen may prove more economical in developing countries like India.

Morris J, Crowcroft NS. Pre-exposure rabies booster vaccinations: a literature review. Dev Biol (Basel). 2006;125:205-15.

In Europe, more attention is turning towards human infection with European bat lyssaviruses (EBLVs). Following the death of a bat conservationist from EBLV in Scotland, in 2002, the Department of Health in the United Kingdom (UK) recommended that all bat workers receive prophylactic rabies vaccination. This systematic literature review aims to review the evidence base for current UK policy on rabies booster vaccination. Ten papers met the inclusion criteria and were reviewed. Most of the papers were prospective cohort studies with follow-up ending after the first booster vaccination. One year after a three dose intramuscular primary rabies vaccination course, 87.9-100 % of participants had a rabies antibody level $>$ or $=$ 0.5 IU/ml, before the first booster. It may, therefore, be prudent for the UK to reduce its current recommended interval, primary course to first booster, from two years to one year. More research, with longer follow-up, is required to enable recommendations on subsequent boosters to be made.

Ambrozaitis A, Laiskonis A, Balciuniene L, Banzhoff A, Malerczyk C. Rabies post-exposure prophylaxis vaccination with purified chick embryo cell vaccine (PCECV) and purified Vero cell rabies vaccine (PVRV) in a four-site intradermal schedule (4-0-2-0-1-1): an immunogenic, cost-effective and practical regimen. Vaccine. 2006 May 8;24(19):4116-21.

Currently, two intradermal (ID) regimens for rabies post-exposure prophylaxis (PEP) are recommended by WHO and used in countries where approved by national authorities: the Thai Red Cross (TRC) two-site ID regimen and the eight-site ID regimen. Besides these WHO recommended schedules, a new economical four-site ID regimen was evaluated that reduces the cost of PEP by up to 80%, when compared with the standard intramuscular Essen regimen, reduces the number of visits required for the patients when compared with the TRC regimen, and is more convenient than the eight-site regimen. To determine the immunogenicity of the ID four-site PEP regimen (4-0-2-0-1-1), 180 healthy volunteers were randomized to receive 0.1 mL volumes of PCECV or PVRV administered ID over both left and right shoulders and both deltoid regions on day 0, both deltoid regions on day 7 and over one deltoid region on days 30 and 90. Regardless of the vaccine, every subject developed rabies virus neutralizing antibody (RVNA) titers above 0.5 IU/mL by day 14, as determined by rapid fluorescent focus inhibition test (RFFIT) using a homologous test system. Two weeks after the last dose of vaccine, RVNA titers were all above 0.5 IU/mL (day 104). Geometric mean titers were similar throughout the study period. Both vaccines were well tolerated. These results demonstrate that a new four-site ID PEP regimen is a cost-effective and convenient alternative to IM (Essen or Zagreb) or ID (TRC or eight-site) regimens, especially using a 1 mL vial of vaccine (PCECV).

Khawplod P, Wilde H, Sirikwin S, Benjawongkulchai M, Limusanno S, Jaijaroensab W, Chiraguna N, Supich C, Wangroongsarb Y, Sitprija V. Revision of the Thai Red Cross intradermal rabies post-exposure regimen by eliminating the 90-day booster injection. Vaccine. 2006 Apr 12;24(16):3084-6.

The Thai Red Cross intradermal post-exposure rabies prophylaxis regimen (TRC-ID) is being used in Thailand, the Philippines, Sri Lanka and is making inroads in India. It consists of two injections of 0.1 mL of any World Health Organization recommended tissue culture rabies vaccine intradermally at two sites on days 0, 3, 7, followed by one injection on days 28 and 90. Two decades of experience had shown that approximately 11% of 187,000 possibly rabies exposed subjects who received the TRC-ID schedule, did not return for the 90-day booster. No rabies deaths had, however, been reported from this group. This stimulated two studies to determine whether the 90-day booster can be abolished. They demonstrated that, if the single 28-day 0.1 mL injection is increased to two at two sites, a comparable antibody response can be achieved and the 90-day booster can be omitted. The tissue culture rabies vaccine used in the preliminary study was purified chick embryo vaccine (PCEC Chiron) and for this study it was chromatography purified Vero cell vaccine (CPRV, Aventis-Pasteur). CPRV had been previously shown to be as immunogenic and effective as purified Vero cell rabies vaccine (PVRV).

Chhabra M, Ichhpujani RL, Bhardwaj M, Tiwari KN, Panda RC, Lal S. Safety and immunogenicity of the intradermal Thai red cross (2-2-2-0-1-1) post exposure vaccination regimen in the Indian population using purified chick embryo cell rabies vaccine. Indian J Med Microbiol. 2005 Jan;23(1):24-8.

PURPOSE: To test the immunogenicity of the WHO recommended "2-2-2-0-1-1" post-exposure rabies vaccination regimen in Indian subjects to determine the feasibility of replacing crude sheep brain nerve tissue rabies vaccine with modern tissue culture rabies vaccine at major anti-rabies treatment centers throughout India. **METHODS:** Purified chick embryo cell vaccine (PCECV) was administered in the dosage of 0.1 mL per site to 53 Indian subjects. **RESULTS:** All subjects produced rabies antibodies above 0.5 IU/mL by day 14 post-vaccination. Only minor adverse reactions including swelling (6.6%), erythema (5.4%) and pain (1.4%) were observed for which no treatment was required. **CONCLUSIONS:** This study demonstrated that PCECV is safe and highly immunogenic in Indian subjects when administered intradermally as 0.1 mL/site using the "2-2-2-0-1-1" post-exposure regimen.

1% of 187,000 possibly rabies exposed subjects who received the TRC-ID schedule, did not return for the 90-day booster. No rabies deaths had, however, been reported from this group. This stimulated two studies to determine whether the 90-day booster can be abolished. They demonstrated that, if the single 28-day 0.1 mL injection is increased to two at two sites, a comparable antibody response can be achieved and the 90-day booster can be omitted. The tissue culture rabies vaccine used in the preliminary study was purified chick embryo vaccine (PCEC Chiron) and for this study it was chromatography purified Vero cell vaccine (CPRV, Aventis-Pasteur). CPRV had been previously shown to be as immunogenic and effective as purified Vero cell rabies vaccine (PVRV).

Multi-centric study on the use of intradermal administration of tissue culture antirabies vaccines in India. National Institutes of Epidemiology. http://www.icmr.nic.in/annual/2004-05/nie/clinical_trials.pdf

Madhusudana SN, Sanjay TV, Mahendra BJ, Suja MS. Simulated post-exposure rabies vaccination with purified chick embryo cell vaccine using a modified Thai Red Cross regimen. Int J Infect Dis. 2004 May;8(3):175-9.

OBJECTIVES: Currently, two intradermal regimens for the administration of cell culture rabies vaccines are approved by the WHO for rabies post-exposure prophylaxis: the two

site Thai Red Cross regimen (TRC) and the eight site regimen. For the TRC regimen the volume of vaccine recommended per dose is 0.1 ml of purified Vero cell rabies vaccine (PVRV) and 0.2 ml of purified chick embryo cell vaccine (PCEC). The objective of the present study was to evaluate comparatively the immune response to PCEC and PVRV vaccines administered by the TRC regimen using a uniform dose of 0.1 ml of vaccine. METHODS: Forty-two subjects received TRC regimen (2-2-2-0-1-1) with 0.1 ml of PCEC vaccine and 38 subjects received the same regimen with PVRV. The rabies neutralizing antibody response in these subjects on days 10, 28, 90 and 180 was determined by the standard mouse neutralization test (MNT). RESULTS: There was adequate antibody response with both the vaccines and 100% seroconversion was observed by day 10. Furthermore, the antibody titers obtained with PCEC did not differ significantly from those obtained with PVRV on all days tested ($p > 0.05$). CONCLUSIONS: It can be concluded from the results that an adequate antibody response can be obtained with PCEC vaccine when administered by the TRC regimen even after reducing the quantity of vaccine from 0.2 ml to 0.1 ml per intradermal dose. The feasibility of using this regimen in true post-exposure cases needs to be further evaluated.

Kamoltham T, Singhsa J, Promsaranee U, Sonthon P, Mathean P, Thinyounyong W. Elimination of human rabies in a canine endemic province in Thailand: five-year programme. Bulletin of the World Health Organization 2003; 81:375-381.

A five-year project to prevent human deaths from rabies in Phetchabun Province, Thailand involved increasing accessibility of post-exposure treatment with the Thai Red Cross intradermal (2-2-2-0-1-1) regimen for humans exposed to potentially and confirmed rabid animals; intensifying documentation of post-exposure treatment; increasing educational awareness through advocacy in provincial schools, television programmes, and newspapers; reducing canine rabies by monitoring the dog population and implementing vaccination and sterilization programmes; increasing the cooperation between the Ministries of Public Health, Agriculture, and Education on a provincial level; and assessing the impact of the programme through intensified follow-up of patients exposed to suspected and laboratory-confirmed rabid animals. Between 1996 and 2001, 10 350 patients received post-exposure treatment; 7227 of these received the Thai Red Cross intradermal regimen. Fewer than 3% of exposed patients received rabies immunoglobulin. Seventy-three percent of all patients presented with WHO category III exposures. In a retrospective study, 188 patients exposed to laboratory-confirmed rabid animals were followed to determine their health status. Of these patients, 20 received the intramuscular Essen regimen and 168 the Thai Red Cross intradermal regimen (148 received 0.1 ml purified chick embryo cell rabies vaccine, 10 received 0.1 ml purified vero cell rabies vaccine, and 10 received 0.2 ml purified duck embryo cell rabies vaccine). All patients were alive one year after exposure. Two human deaths occurred in the first two years of the programme - neither patient had received vaccine or rabies immunoglobulin after exposure. No deaths occurred during the last three years of the programme, which indicated that the programme was successful.

Wilde H, Briggs DJ, Meslin FX, Hemachudha T, Sitprija V. Rabies update for travel medicine advisors. Clin Infect Dis. 2003 Jul 1;37(1): 96-100.

Rabies is a neglected disease in many developing countries. It is preventable, and the tools to prevent it are known. There is urgent need for more funding, for study of innovative dog population-control measures, and for sustainable canine immunization. Safe and effective tissue-culture rabies vaccines and human and equine rabies immunoglobulins (HRIG and ERIG) are not readily available in many regions where rabies is endemic. This and the continuing presence and spread of rabies have increased the risk for travelers, who cannot rely on being able to receive optimal postexposure treatment in many parts of the world. Alternatives to HRIG or ERIG are not available. Travelers who leave the safe environments of tourist hotels and buses in regions of Asia,

Russia, Africa, and Latin America where canine rabies is endemic may be at risk of life-threatening exposure to rabies.

Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S, Wasi C. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull World Health Organ. 2000;78(5):693-8.

Although the introduction of tissue culture vaccines for rabies has dramatically improved the immunogenicity and safety of rabies vaccines, they are often prohibitively expensive for developing countries. To examine whether smaller doses of these vaccines could be used, we tested the safety and immunogenicity of purified chick embryo cell vaccine (PCECV) on 211 patients in Thailand with World Health Organization (WHO) category II and III exposures to rabies. The patients presented at two Thai hospitals and were randomized into three groups. Patients in Group 1 received 0.1 ml PCECV intradermally at two sites on days 0, 3, 7, and at one site on days 30 and 90. Group 2 was treated similarly, except that purified Vero cell rabies vaccine (PVRV) was used instead of PCECV. Group 3 received 1.0 ml PCECV intramuscularly on days 0, 3, 7, 14, 30 and 90. After 0, 3, 7, 14, 30 and 90 days serum was collected from the subjects and the geometric mean titres (GMTs) of rabies virus neutralizing antibody determined. After 14 days the GMT of 59 patients vaccinated intradermally with PCECV was equivalent to that of patients who received PVRV. Adverse reactions were more frequent in patients who received vaccines intradermally, indicating the reactions were associated with the route of injection, rather than the vaccine *per se*. We conclude that PCECV is a safe and highly immunogenic vaccine for postexposure rabies vaccination when administered intradermally in 0.1-ml doses using the two-site method (2,2,2,0,1,1) recommended by WHO.

Chutivongse S, Wilde H, Supich C, Baer GM, Fishbein DB. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. Lancet. 1990 Apr 14; 335(8694):896-8.

The Thai Red Cross intradermal postexposure rabies treatment schedule was prospectively assessed in 100 Thai patients severely bitten by proven rabid animals. It consists of 0.1 ml of purified Vero cell rabies vaccine containing more than 2.5 IU of rabies antigen per 0.5 ml of reconstituted vaccine given intradermally at two sites on days 0, 3, and 7, followed by one 0.1 ml injection on days 30 and 90. The commercial vaccine used had an antigen content of 3.17 IU per 0.5 ml ampoule. Purified equine or human rabies immuno-globulin was also given on day 0 to patients with severe exposures. As much of the immunoglobulin as possible was infiltrated around the wounds. All patients were followed for 1 year post exposure. There were no deaths; the efficacy of the regimen was 100%. Antibody titre determination in a randomly selected subgroup showed seroconversion in all 10 patients.