

References for Rabies Vaccine: WHO Position Paper, April 2018 References with abstracts cited in the position paper in the order of appearance.

**1 Weekly epidemiological record No. 32, 2010, pp. 309-320**

No abstract available

**2 Hampson K. et al. Estimating the Global Burden of Endemic Canine Rabies. PLoS Negl Trop Dis. 2015 Apr 16;9(4):e0003709.**

**BACKGROUND:**

Rabies is a notoriously underreported and neglected disease of low-income countries. This study aims to estimate the public health and economic burden of rabies circulating in domestic dog populations, globally and on a country-by-country basis, allowing an objective assessment of how much this preventable disease costs endemic countries.

**METHODOLOGY/PRINCIPAL FINDINGS:**

We established relationships between rabies mortality and rabies prevention and control measures, which we incorporated into a model framework. We used data derived from extensive literature searches and questionnaires on disease incidence, control interventions and preventative measures within this framework to estimate the disease burden. The burden of rabies impacts on public health sector budgets, local communities and livestock economies, with the highest risk of rabies in the poorest regions of the world. This study estimates that globally canine rabies causes approximately 59,000 (95% Confidence Intervals: 25-159,000) human deaths, over 3.7 million (95% CIs: 1.6-10.4 million) disability-adjusted life years (DALYs) and 8.6 billion USD (95% CIs: 2.9-21.5 billion) economic losses annually. The largest component of the economic burden is due to premature death (55%), followed by direct costs of post-exposure prophylaxis (PEP, 20%) and lost income whilst seeking PEP (15.5%), with only limited costs to the veterinary sector due to dog vaccination (1.5%), and additional costs to communities from livestock losses (6%).

**CONCLUSIONS/SIGNIFICANCE:**

This study demonstrates that investment in dog vaccination, the single most effective way of reducing the disease burden, has been inadequate and that the availability and affordability of PEP needs improving. Collaborative investments by medical and veterinary sectors could dramatically reduce the current large, and unnecessary, burden of rabies on affected communities. Improved surveillance is needed to reduce uncertainty in burden estimates and to monitor the impacts of control efforts.

**3 Tarantola A. Four Thousand Years of Concepts Relating to Rabies in Animals and Humans, Its Prevention and Its Cure. Trop Med Infect Dis. 2017; 2, 5.**

**Abstract:** The epitome of the One Health paradigm—and of its shortcomings—rabies has been known to humankind for at least 4000 years. We review the evolution through history of concepts leading to our current understanding of rabies in dogs and humans and its prevention, as transmitted by accessible and surviving written texts. The tools and concepts currently available to control rabies were developed at the end of the 19th Century, including the first live, attenuated vaccine ever developed for humans and the first post-exposure prophylaxis (PEP) regimen. No progress, however, has been made in etiologic treatment, leaving clinicians who provide care to animals or patients with symptomatic rabies as powerless today as their colleagues in Mesopotamia, 40 centuries ago. Rabies remains to date the most lethal infectious disease known to humans. Widespread access to timely, effective, and affordable PEP in rural areas of developing countries is urgently needed.

**4 WHO fact sheet on rabies.** Available at <http://www.who.int/mediacentre/factsheets/fs099/en/>, accessed March 2018.

No abstract available

5 Birhane MG et al. Rabies surveillance in the United States during 2015. *J Am Vet Med Assoc.* 2017; 250(10): p. 1117-1130.

**OBJECTIVE** To describe rabies and rabies-related events occurring during 2015 in the United States. **DESIGN** Observational study based on passive surveillance data. **ANIMALS** All animals submitted for rabies testing in the United States during 2015. **PROCEDURES** State and territorial public health programs provided data on animals submitted for rabies testing in 2015. Data were analyzed temporally and geographically to assess trends in domestic and sylvatic animal rabies cases. **RESULTS** During 2015, 50 states and Puerto Rico reported 5,508 rabid animals to the CDC, representing an 8.7% decrease from the 6,033 rabid animals reported in 2014. Of the 5,508 cases of animal rabies, 5,088 (92.4%) involved wildlife. Relative contributions by the major animal groups were as follows: 1,704 (30.9%) bats, 1,619 (29.4%) raccoons, 1,365 (24.8%) skunks, 325 (5.9%) foxes, 244 (4.4%) cats, 85 (1.5%) cattle, and 67 (1.2%) dogs. There was a 4.1% decrease in the number of samples submitted for testing in 2015, compared with the number submitted in 2014. Three human rabies deaths were reported in 2015, compared with only 1 in 2014. A 65-year-old man in Massachusetts was bitten by a rabid dog while abroad. A 77-year-old woman in Wyoming had contact with a bat. A 54-year-old man in Puerto Rico was bitten by a mongoose. The only connection among these 3 cases was that none received postexposure prophylaxis. **CONCLUSIONS AND CLINICAL RELEVANCE** Laboratory testing of animals suspected to be rabid remains a critical public health function and continues to be a cost-effective method to directly influence human rabies postexposure prophylaxis recommendations.

**6 Rupprecht CE et al. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 7th ed. Philadelphia: Elsevier Saunders. 2017. pp. 918–942.**

No abstract available

**7 Rupprecht CE et al. Current Status and Development of Vaccines and Other Biologics for Human Rabies Prevention. Expert Rev Vaccines. 2016 Jun;15(6):731-49.**

Rabies is a neglected viral zoonosis with the highest case fatality of any infectious disease. Pasteur's historical accomplishments during the late 19(th) century began the process of human vaccine development, continuing to evolve into the 21(st) century. Over the past 35 years, great improvements occurred in the production of potent tissue culture vaccines and the gradual removal from the market of unsafe nerve tissue products. Timely and appropriate administration of modern biologics virtually assures survivorship, even after severe exposures. Nevertheless, in the developing world, if not provided for free nationally, the cost of a single course of human prophylaxis exceeds the average monthly wage of the common worker. Beyond traditional approaches, recombinant, sub-unit and other novel methods are underway to improve the availability of safe, effective and more affordable rabies biologics.

**8 WHO Expert Consultation on Rabies, third report: WHO Technical Series Report, Geneva 2018 (in press) ISBN available soon.**

No abstract available

**9 Shim E et al. Evaluating the cost-effectiveness of rabies post-exposure prophylaxis: a case study in Tanzania. Vaccine. 2009; 27(51), pp.7167-7172.**

Although fatal if untreated, human rabies can be prevented through post-exposure prophylaxis (PEP), which involves a course of vaccination and immunoglobulin administered immediately after exposure. However, high costs and frequent lack of rabies vaccine and immunoglobulin lead to about 55,000 deaths per year worldwide. Using data from a detailed study of rabies in Tanzania, we calculate a cost-effectiveness ratio for PEP when the WHO-recommended Essen regimen, a 5-dose intramuscular vaccination schedule, is adopted. Our analyses indicate a cost-effectiveness ratio for PEP of \$27/quality-adjusted life year (QALY) from a health care perspective and \$32/QALY from a societal perspective in Tanzania. From both perspectives, it is "very cost-effective" to administer PEP to patients bitten by an animal suspected to be rabid. Moreover, PEP remains "very cost-effective" provided that at least 1% of doses are administered to people who were actually exposed to rabies.

**10 Hemachudha T et al. Human rabies: neuropathogenesis, diagnosis and management. Lancet Neurol. 2013, 12(5):498–513.**

Rabies is an almost invariably fatal disease that can present as classic furious rabies or paralytic rabies. Recovery has been reported in only a few patients, most of whom were infected with bat rabies virus variants, and has been associated with promptness of host immune response and

spontaneous (immune) virus clearance. Viral mechanisms that have evolved to minimise damage to the CNS but enable the virus to spread might explain why survivors have overall good functional recovery. The shorter survival of patients with furious rabies compared with those with paralytic rabies closely corresponds to the greater amount of virus and lower immune response in the CNS of patients with the furious form. Rabies virus is present in the CNS long before symptom onset: subclinical anterior horn cell dysfunction and abnormal brain MRI in patients with furious rabies are evident days before brain symptoms develop. How the virus produces its devastating effects and how it selectively impairs behaviour in patients with furious rabies and the peripheral nerves of patients with paralytic rabies is beginning to be understood. However, to develop a pragmatic treatment strategy, a thorough understanding of the neuropathogenetic mechanisms is needed.

**11 Aguèmon CT et al. Rabies transmission risks during peripartum—Two cases and a review of the literature. *Vaccine*. 2016 Apr 4;34(15):1752-7.**

We report two cases of probable rabies in near-term/at-term pregnant women in sub-Saharan Africa and Asia. One baby was delivered by caesarean section and the other one vaginally. Both received post-exposure prophylaxis (PEP), including RIG and vaccine and both are alive and healthy, at 9 and 24 months, respectively. We found 14 other published cases of infants born from rabid mothers. One confirmed case of rabies transmission occurred. The other children born from rabid mothers, with or without caesarean section, did not acquire rabies, and were still healthy at the time of reporting, with or without post-exposure prophylaxis. Mother-to-child transmission of rabies is possible, but rare, because rabies virus is not present in blood and exposure of the baby's mucosa to maternal infectious fluids and tissue seems limited. A conservative approach should however, be adopted, and rabies PEP, including RIG, be administered as soon as possible to babies born from probably rabid mothers. Whether cesarean-section clearly provides prevention remains unclear. Rabies can be prevented in pregnant women by PEP administration. Rabies cell-culture vaccines are safe and effective and can be administered to pregnant and lactating women, as well as newborns. Efforts must focus on raising rabies awareness in the general population, as well as in healthcare workers.

**12 Winkler WG et al. Airborne rabies transmission in a laboratory worker, *JAMA*. 1973; vol. 226 (pg. 1219-21)**

A 56-year-old man died of rabies 21 days after exposure to a "fixed" strain of rabies virus. Rabies virus was recovered from the brain by cultural techniques and demonstrated in neural tissue by electron microscopy. Infection apparently resulted from inhalation of an aerosol generated in a biological laboratory during the manufacture of animal rabies vaccine. The victim had received preexposure vaccination against rabies 13 years earlier but had not developed demonstrable serum antibodies.

**13 Constantine DG. Rabies transmission by air in bat caves. *Public Health Service Publication no. 1617*. 1967; Atlanta Centers for Disease Control and Prevention.**

No abstract available.

**14 Johnson N et al. Airborne transmission of lyssaviruses. J Med Microbiol. 2006 Jun;55(Pt 6):785-90.**

In 2002, a Scottish bat conservationist developed a rabies-like disease and subsequently died. This was caused by infection with European bat lyssavirus 2 (EBLV-2), a virus closely related to Rabies virus (RABV). The source of this infection and the means of transmission have not yet been confirmed. In this study, the hypothesis that lyssaviruses, particularly RABV and the bat variant EBLV-2, might be transmitted via the airborne route was tested. Mice were challenged via direct introduction of lyssavirus into the nasal passages. Two hours after intranasal challenge with a mouse-adapted strain of RABV (Challenge Virus Standard), viral RNA was detectable in the tongue, lungs and stomach. All of the mice challenged by direct intranasal inoculation developed disease signs by 7 days post-infection. Two out of five mice challenged by direct intranasal inoculation of EBLV-2 developed disease between 16 and 19 days post-infection. In addition, a simple apparatus was evaluated in which mice could be exposed experimentally to infectious doses of lyssavirus from an aerosol. Using this approach, mice challenged with RABV, but not those challenged with EBLV-2, were highly susceptible to infection by inhalation. These data support the hypothesis that lyssaviruses, and RABV in particular, can be spread by airborne transmission in a dose-dependent manner. This could present a particular hazard to personnel exposed to aerosols of infectious RABV following accidental release in a laboratory environment.

**15 The International Committee on Taxonomy of Viruses. Rhabdoviridae. Available at [https://talk.ictvonline.org/ictv-reports/ictv\\_9th\\_report/negative-sense-rna-viruses-2011/w/negrna\\_viruses/201/rhabdoviridae](https://talk.ictvonline.org/ictv-reports/ictv_9th_report/negative-sense-rna-viruses-2011/w/negrna_viruses/201/rhabdoviridae), accessed December 2017.**

No abstract available.

**16 WHO. The immunological basis for immunization series: module 17: rabies vaccines. 2017.**

Available at

**[http://www.who.int/immunization/documents/policies/WHO\\_IVB\\_ISBN9789241513371/en](http://www.who.int/immunization/documents/policies/WHO_IVB_ISBN9789241513371/en), accessed February 2018.**

No abstract available.

**17 Fooks AR et al. Current status of rabies and prospects for elimination. Lancet. 2014; 384(9951): p. 1389-99.**

Rabies is one of the most deadly infectious diseases, with a case-fatality rate approaching 100%. The disease is established on all continents apart from Antarctica; most cases are reported in Africa and Asia, with thousands of deaths recorded annually. However, the estimated annual figure of almost 60,000 human rabies fatalities is probably an underestimate. Almost all cases of human rabies result from bites from infected dogs. Therefore, the most cost-effective approach to elimination of the

global burden of human rabies is to control canine rabies rather than expansion of the availability of human prophylaxis. Mass vaccination campaigns with parenteral vaccines, and advances in oral vaccines for wildlife, have allowed the elimination of rabies in terrestrial carnivores in several countries worldwide. The subsequent reduction in cases of human rabies in such regions advocates the multidisciplinary One Health approach to rabies control through the mass vaccination of dogs and control of canine populations.

**18 Jackson AC. Human Rabies: a 2016 Update. Curr Infect Dis Rep. 2017 May 10;18(11).**

Rabies is a zoonotic disease that is usually transmitted to humans by animal bites. Dogs are the most important vector worldwide. There are encephalitic and paralytic forms of the disease. There are differences in the clinical features of the disease acquired from dogs and bats. Neuroimaging is non-specific. Confirmatory diagnostic laboratory tests for rabies include detection of neutralizing anti-rabies virus antibodies in serum or cerebrospinal fluid and rabies virus antigen or RNA in tissues or fluids. Rabies is preventable after recognized exposures with wound cleansing and administration of rabies vaccine and rabies immune globulin. Rabies is virtually always fatal after clinical disease develops, and there have only been rare survivors. The Milwaukee protocol, which includes therapeutic coma, has been shown to be ineffective and should no longer be used. The development of novel therapeutic approaches may depend on a better understanding of basic mechanisms underlying the disease.

**19 WHO fact sheet. Available at <http://www.who.int/mediacentre/factsheets/fs099/en/>, accessed March 2018.**

No abstract available.

**20 Kaplan MM et al. Studies on the local treatment of wounds for the prevention of rabies. Bull World Health Organ.1962;26:765-75. 6:765-75.**

This paper reports on laboratory studies made in guinea-pigs on puncture wounds infected with fixed rabies virus and treated one hour later with various substances, the purpose being to review the experience of previous workers and to explore new approaches to the problem of local treatment of wounds inflicted by rabid animals.

Among the measures affording greater or lesser protection were: nitric acid cauterization; direct application of benzalkonium chloride to the wound or its infiltration, as well as that of methylbenzethonium chloride, proximal to the wound; repeated swabbing and flushing with 20% soap solution or benzalkonium chloride; local inoculation of procaine anaesthetics; infiltration of the leg wound, or inoculation of the opposite leg, with antirabies gamma-globulin; and infiltration of the wound with interferon prepared in guinea-pig tissue cultures.

Protection was not afforded by flushing with 20% soap solution alone; topical application of aqueous or tincture preparations of iodine or thiomersal; inoculation of phenoxybenzamine, physostigmine

or diphenhydramine hydrochloride; or infiltration of the wound with interferon prepared on monkey kidney tissue cultures.

The authors conclude that, at the present time, very vigorous cleansing of the wound with 20% soap solution or 2% benzalkonium chloride, local infiltration of the wound with antirabies serum and—to minimize pain—the use of procaine in saline are indicated in the local treatment of wounds for the prevention of rabies.

**21 Franka R et al. Rabies virus pathogenesis in relationship to intervention with inactivated and attenuated rabies vaccines. Vaccine. 2009 Nov 27;27(51):7149-55.**

Despite progress in vaccine development in the past century the mechanisms behind immune responses elicited by rabies biologics or via natural infection remain largely unknown. In this study, we compared protection elicited by standard, early, or delayed prophylaxis with a reduced number of vaccine doses using inactivated and live-attenuated vaccines. Two-month-old Syrian hamsters, 4-week-old ICR mice or adult rhesus macaques were inoculated with canine rabies virus variants. Thereafter, prophylaxis was initiated 6h, 1, 2, 3, 4, 5, 6 or 7 days post-exposure (p.e.). One or several doses of inactivated (HDCV), or reverse genetically attenuated (live), or gamma-irradiated (inactivated)-ERAG333 vaccines were administered intramuscularly. The dynamics of virus spread were measured over time in the rodent models. Rabies virus reached the spinal cord at day 4 and brain at day 6 p.e. All hamsters succumbed in groups in which live ERAG333 was delayed until days 5 and 6 p.e. However, 78%, 44%, 56% and 22% of hamsters survived when one dose of live ERAG333 was administered 6h, 1, 2, 3, and 4 days p.e., respectively. Similarly, 67% survived when inactivated ERAG333 was administered at 24h p.e. All hamsters succumbed when standard prophylaxis (the Essen regimen) was delayed until days 3-6, but 67% and 33% of hamsters survived when PEP began 1 or 2 days p.e., respectively. Macaques were protected by one dose of attenuated ERAG333 at 24h p.e. The highly attenuated (live) and inactivated ERAG333 vaccines elicited potent protective immune responses, even when prophylaxis initiation was delayed. When 2-5 doses of commercial vaccine and HRIG were administered according to the Essen scheme, 89-100% of the animals survived. Reduced vaccine schedules provided efficacious intervention, regardless of the total number of vaccine doses administered.

**22 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 biologics. 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.

**23 OIE. Terrestrial Animal Health Code Chapter 7.7 . 26th Edition, 2017. Available at <http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/> , accessed March 2018.**

No abstract available.

**24 Coleman P.G. Immunization coverage required to prevent outbreaks of dog rabies. Vaccine. 1996; 14(3): p. 185-186.**

WHO recommends that 70% of dogs in a population should be immunized to eliminate or prevent outbreaks of rabies. This critical percentage (pc) has been established empirically from observations on the relationship between vaccination coverage and rabies incidence in dog populations around the world. Here, by contrast, we estimate pc by using epidemic theory, together with data available from four outbreaks in urban and rural areas of the USA, Mexico, Malaysia and Indonesia. From the rate of increase of cases at the beginning of these epidemics, we obtain estimates of the basic case reproduction number of infection,  $R_0$ , in the range 1.62-2.33, implying that pc lies between 39% and 57%. The errors attached to these estimates of pc suggest that the recommended coverage of 70% would prevent a major outbreak of rabies on no fewer than 96.5% of occasions.

**25 Mindekem R, Lechenne MS, Naissengar KS, Oussiguéré A, Kebkiba B, Moto DD, Alfaroukh IO, Ouedraogo LT, Salifou S, Zinsstag J. Cost Description and Comparative Cost Efficiency of Post-Exposure Prophylaxis and Canine Mass Vaccination against Rabies in N'Djamena, Chad. Front Vet Sci. 2017 Apr 3;4:38.**

Rabies claims approximately 59,000 human lives annually and is a potential risk to 3.3 billion people in over 100 countries worldwide. Despite being fatal in almost 100% of cases, human rabies can be prevented by vaccinating dogs, the most common vector, and the timely administration of post-exposure prophylaxis (PEP) to exposed victims. For the control and prevention of human rabies in N'Djamena, the capital city of Chad, a free mass vaccination campaign for dogs was organized in 2012 and 2013. The campaigns were monitored by parallel studies on the incidence of canine rabies based on diagnostic testing of suspect animals and the incidence of human bite exposure recorded at selected health facilities. Based on the cost description of the campaign and the need for PEP registered in health centers, three cost scenarios were compared: cumulative cost-efficiency of (1) PEP alone, (2) dog mass vaccination and PEP, (3) dog mass vaccination, PEP, and maximal communication between human health and veterinary workers (One Health communication). Assuming ideal One Health communication, the cumulative prospective cost of dog vaccination and PEP break even with the cumulative prospective cost of PEP alone in the 10th year from the start of the calculation (2012). The cost efficiency expressed in cost per human exposure averted is much higher with canine vaccination and One Health communication than with PEP alone. As shown in other studies, our cost-effectiveness analysis highlights that canine vaccination is financially the best option for animal rabies control and rabies prevention in humans. This study also provides evidence of the beneficial effect of One Health communication. Only with close communication between the human and animal health sectors will the decrease in animal rabies incidence be translated into a



decline for PEP. An efficiently applied One Health concept would largely reduce the cost of PEP in resource poor countries and should be implemented for zoonosis control in general.

**27 WHO. 0 by 30 our catalytic response. Available at [http://www.who.int/rabies/United\\_against\\_Rabies/en/](http://www.who.int/rabies/United_against_Rabies/en/) , accessed December 2017.**

No abstract available.

**28 United Nations: Sustainable Development Goals. <https://sustainabledevelopment.un.org/?menu=1300>, accessed December 2017.**

No abstract available.

**29 WHO recommendations for inactivated rabies vaccine for human use produced in cell substrates and embryonated eggs, Annex 2, WHO TRS No. 941, 2007. Available at <http://who.int/biologicals/publications/trs/areas/vaccines/rabies/Annex%20%20inactivated%20rabies%20vaccine.pdf?ua=1>, accessed December 2017.**

No abstract available.

**30 WHO. International Standard: Sixth International Standard for Rabies vaccine, NIBSC code: 07/162 <http://www.nibsc.org/documents/ifu/07-162.pdf> , accessed December 2017.**

No abstract available.

**31 Denis M et al. An overview of the immunogenicity and effectiveness of current human rabies vaccines administered by intradermal route. Submitted**

Pre- as well as post-exposure prophylaxis plays an important role in controlling the number of deaths associated with human rabies. Rabies vaccines, classically injected intramuscularly, are now widely administered by intradermal (ID) route. A WHO guideline requests a minimum potency of 2.5 IU per intramuscular (IM) dose of rabies vaccine. No similar requirement has been issued for the ID dose, which consists of a fraction of the IM dose. Concerns were raised that ID vaccination may sometimes involve an insufficient amount of antigen.

To address this question, a first literature search focused on the immunogenicity of rabies vaccines given by ID route. It The search strategy identified 299 338 publications in the period 1997-20172018, of which 38 40 studies were included in our analyses. A second search investigating the effectiveness of ID vaccination resulted in 227 368 hits for the period 2007-20172018, of which 11 13 suitable publications were retained.

The immunogenicity of current rabies vaccines was analyzed in 3 different ways: proportion of subjects reaching the antibody threshold of 0.5 IU/ml after ID vaccination, relationship between potency and immunogenicity of the vaccine given intra-dermally, and comparison of antibody responses after IM or ID vaccination. Overall, vaccines administered by ID route were found highly immunogenic, irrespective of their potency. Post-exposure prophylaxis by ID route appeared as least as immunogenic as that administered by IM regimens. By contrast, ID pre-exposure prophylaxis trended towards lower antibody titers than IM vaccination, but the observation was not associated with any clinical relevance.

Vaccine effectiveness was assessed by investigating survival after exposure. Data from approximately 36000 patients who sought rabies post-exposure prophylaxis did not indicate that current vaccines administered by ID route lack efficacy.

These results support current recommendations in terms of intradermal vaccination against rabies.

**32 Weekly Epidemiological Record. No. 32, 2010, pp. 309-320**

**33 Hampson K. et al. Modelling to inform prophylaxis regimens to prevent human rabies. Submitted.**

**BACKGROUND:** The Strategic Advisory Group of Experts (SAGE) Working Group on rabies vaccines and immunoglobulins was established in 2016 to develop practical and feasible recommendations for prevention of human rabies. To support the SAGE agenda we developed models to compare the relative costs and potential benefits of rabies prevention strategies.

**METHODS:** We examined different postexposure prophylaxis (PEP) regimens, protocols for administration of rabies Immunoglobulin (RIG) and inclusion of rabies Pre-Exposure Prophylaxis (PrEP) within the Expanded Programme on Immunization (EPI). For different PEP regimens, clinic throughputs and consumables for vaccine administration, we evaluated the cost per patient treated, costs to patients and potential to treat more patients given limited vaccine availability.

**RESULTS:** We found that intradermal vaccination reduces the volume of vaccine used in all settings, is less costly and has potential to mitigate vaccine shortages. Specifically, the 1-week ID regimen was the most cost-effective PEP regimen, even in settings with low numbers of bite patients presenting to clinics. We found advantages of administering RIG to the wound(s) only, using considerably less product than when the remaining dose is injected intramuscularly distant to the wound(s). We found that PrEP as part of the EPI programme would be substantially more expensive than other measures to prevent human rabies, such as PEP and dog vaccination.

**CONCLUSIONS:** These modeling insights inform WHO recommendations for use of human rabies vaccines and biologicals. Specifically, the 1-week ID regimen should be recommended as it is less costly and treats many more patients when vaccine is in short supply. If available, RIG should be administered at the wound only. PrEP is highly unlikely to be an efficient use of resources and should therefore only be considered in extreme circumstances, where the incidence of rabies exposures is high.

**34 Sudarshan MK et al. Boosting effect of purified chick embryo cell rabies vaccine using the intradermal route in persons previously immunized by the intramuscular route or vice versa. Natl Med J India. 2006 Jul-Aug;19(4):192-4.**

**BACKGROUND:** At present, in the event of re-exposure to rabies, 2 booster doses are recommended for people who have been previously vaccinated with cell culture rabies vaccines by the conventional intramuscular route. As the intradermal route of vaccination is likely to be introduced in the future, we investigated the immune response to a cell culture rabies vaccine after crossing over from the intramuscular to the intradermal route and vice versa.

**METHODS:** Twenty healthy adult volunteers who had received a primary course of rabies vaccination with purified chick embryo cell rabies vaccine by either the intramuscular (n = 10) or intradermal (n = 10) route received booster vaccination with the same vaccine by the alternative route. The regimen used was 0.1 ml of vaccine by the intradermal route at two sites (deltoid area) for the intramuscular group, or 1 ml of vaccine by the intramuscular route (deltoid muscle) to the intradermal group on days 0 and 3.

**RESULTS:** There was a 15-fold rise in the rabies virus neutralizing antibody response both by the intradermal and intramuscular routes of booster vaccination ( $p < 0.0001$ ). Thus, the change of route of purified chick embryo cell booster vaccination did not alter the anamnestic immune response to the vaccine. No side-effects were observed after vaccination with either of the routes.

**CONCLUSION:** Purified chick embryo cell vaccine was found to be safe and immunologically efficacious following booster vaccination after cross-over from the intradermal to the intramuscular route and vice versa.

**35 Ravish H et al. Assessing safety and immunogenicity of post-exposure prophylaxis following interchangeability of rabies vaccines in humans. Hum Vaccin Immunother. 2014; 10:5, 1354-1358.**

Rabies post exposure prophylaxis with cell culture vaccines by either intramuscular route or intradermal route spans over a period of one month. World Health Organization recommends completing post exposure prophylaxis against rabies with the same cell culture or embryonated egg rabies vaccine and with same route of administration and any deviation from this shall be an exception. In the present study, the safety and immunogenicity of rabies post-exposure prophylaxis was studied prospectively in 90 animal bite cases that had interchangeability of rabies vaccines either by route of administration or brand/type and such changes had occurred due to logistical/financial problems. Among them, 47 had change in route of administration from intramuscular to intradermal or vice versa and 43 had change in the brand/type of cell culture rabies vaccine. All of them had category III rabies exposure and received equine rabies immunoglobulin along with the rabies vaccine. None of the study subjects had any adverse reactions. The rabies virus neutralizing antibody titers was assessed by rapid fluorescent focus inhibition test and all the vaccinees had titers  $\geq 0.5$  IU per mL on day 14 which is considered as adequate for protection against rabies. Thus, the present study showed that, rabies post-exposure prophylaxis was safe and immunogenic despite changes in the route of administration and brand/type of rabies vaccine.

**36 WHO. WHO Prequalified Vaccines. 2017. Available at [https://extranet.who.int/gavi/PQ\\_Web/Default.aspx?nav=1](https://extranet.who.int/gavi/PQ_Web/Default.aspx?nav=1), accessed January 2018**

No abstract available.

**38 WHO. Guidance Note: Vaccine Diluents (2015 revision). Available at [http://apps.who.int/iris/bitstream/10665/192741/1/WHO\\_IVB\\_15.08\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/192741/1/WHO_IVB_15.08_eng.pdf), accessed December 2017.**

No abstract available.

**39 WHO. WHO policy statement: Multi-dose vial policy (MDVP)-Revision 2014. 2014; Report No. WHO/IVB/14.07.**

No abstract available.

**40 Tarantola A et al. Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in cambodia, 2003-2014. Submitted.**

**41 Tarantola A et al. Rabies Post-exposure Prophylaxis (PEP) Noncompletion After Dog Bites: Estimating the Unseen to Meet the Needs of the Underserved. Am J Epidemiol. 2017 Aug 23 ; (Epub ahead of print).**

Postexposure prophylaxis (PEP) prevents human rabies and is accessible in Cambodia principally in Phnom Penh, the capital. Timely, affordable access to PEP is a challenge for the mainly rural population. We aimed to identify districts independently associated with PEP noncompletion to position frontline vaccination centers. We analyzed the 2009-2013 database at the Rabies Prevention Center at the Institut Pasteur du Cambodge, Phnom Penh. Logistic regressions identified nongeographic determinants of PEP noncompletion as well as the districts that were independently associated with noncompletion after adjustment for these determinants. The influence of distance by road was estimated using a boosted regression-trees model. We computed a population attributable fraction (rabies index (RI)) for each district and developed a map of this RI distribution. A cartographic analysis based on the statistic developed by Getis and Ord identified clusters of high-RI districts. Factors independently associated with noncompletion were patients' district of residence, male sex, age 15-49 years, initial visit during rice harvest, the dog's status (culled or disappeared), and a prescribed PEP protocol requiring more than 3 PEP sessions (4 or 5). Four clusters of high-RI districts were identified using this analytical strategy, which is applicable to many vaccination or other health services. Positioning frontline PEP centers in these districts could significantly widen access to timely and adequate PEP.

**42 Shantavasinkul P et al. Post-exposure Rabies Prophylaxis Completed in 1 Week: Preliminary Study. Clin Infect Dis. 2010 Jan 1;50(1):56–60.**

Background. Patients exposed to a rabid animal often travel long distances to receive postexposure prophylaxis (PEP), which requires 4 or 5 visits. Reducing the number of clinic visits would not only reduce costs for the patient but may also help increase compliance to receive complete PEP. We made an effort to develop PEP completed in 1 week. Methods. We administered the 4-site intradermal injections of 0.1 mL of purified Vero cell rabies vaccine to the deltoids and thighs on days 0, 3, and 7, with and without equine rabies immunoglobulin (40 IU/kg). A control group received the World Health Organization–approved and widely used Thai Red Cross regimen (2-site intradermal injections on days 0, 3, and 7 and 1 injection on days 28 and 90) with equine rabies immunoglobulin. We then determined rabies neutralizing antibody (NAb) up to day 360. Results. Geometric mean titers for subjects receiving the 4-site intradermal regimen, with or without equine rabies immunoglobulin, had significantly higher NAb values than did the control group on day 14 and 28 ( $P < .001$ ). All subjects in all groups had a NAb value 0.5 IU/mL on days 14 and 28. The percentages of subjects who had a NAb value 0.5 IU/mL from days 0 through 360 were not significantly different among the 3 groups. Conclusions. After any PEP regimen, World Health Organization recommendations require a NAb value 0.5 IU/mL on days 14 and 28. The 1-week PEP regimen, therefore, appears promising. It increased immunogenicity over the 2-site intradermal schedule, and it is convenient and can be used in small clinics, because it consumes almost the entire supplied vaccine ampoule volume

**43 Narayana A et al. Comparison of safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen/schedule (4-4-4-0-0) in animal bite cases. Hum Vaccines Immunother. 2015;11(7):1748–53.**

The currently advocated rabies post-exposure prophylaxis regimens are of one month duration with reduced patient compliance. WHO recommended research on shortened vaccination regimens which have a practical and economic advantage over the existing regimens. Hence, the present study was undertaken to assess the safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen (4-4-4-0-0) in animal bite cases. This study was a comparative, open label, phase III, randomized clinical trial conducted at Anti rabies clinic, KIMS Hospital, Bangalore, India. The study was registered in Clinical Trials Registry of India (CTRI) bearing the registration number CTRI/2012/12/003230. Ninety subjects with category II/III animal bites/exposures were enrolled. Equine rabies immunoglobulin was administered to all category III exposures. 0.1 mL of either purified chick embryo cell vaccine (Rabipur) or purified verocell rabies vaccine (Verorab) was administered intradermally into 4 sites on days 0, 3 and 7 to all the study subjects. Serum of subjects collected on day 0, 14, 90 and 365 were analyzed for rabies virus neutralizing antibody (RVNA) concentration. The incidence of ADR in Rabipur and Verorab group was 2.96% and 1.14% respectively. In Rabipur group, geometric mean concentration (95% confidence interval) of RVNA was 14.5 (13.50, 15.57), 11.78 (11.27, 12.31) and 5.95 (5.50, 6.44) IU/mL on days 14, 90 and 365 respectively; In Verorab group geometric mean concentration (95% confidence interval) of RVNA was 14.43 (13.41, 15.53), 11.93 (11.47, 12.40) and 5.67 (5.29, 6.08) IU/mL on days 14, 90 and 365 respectively. In conclusion, Rabipur and Verorab were found to be

safe, immunogenic and comparable with each other, when administered using one week, 4 site intradermal regimen (4-4-4-0-0) in animal bite cases.

**44 Warrell MJ et al. A simplified 4-site economical ID post-exposure rabies vaccine regimen/schedule: a randomised controlled comparison with standard methods. PLoS Negl Trop Dis. 2008 Apr 23; 2(4):e224.**

**BACKGROUND:** The need for economical rabies post-exposure prophylaxis (PEP) is increasing in developing countries. Implementation of the two currently approved economical intradermal (ID) vaccine regimens is restricted due to confusion over different vaccines, regimens and dosages, lack of confidence in intradermal technique, and pharmaceutical regulations. We therefore compared a simplified 4-site economical PEP regimen with standard methods.

**METHODS:** Two hundred and fifty-four volunteers were randomly allocated to a single blind controlled trial. Each received purified vero cell rabies vaccine by one of four PEP regimens: the currently accepted 2-site ID; the 8-site regimen using 0.05 ml per ID site; a new 4-site ID regimen (on day 0, approximately 0.1 ml at 4 ID sites, using the whole 0.5 ml ampoule of vaccine; on day 7, 0.1 ml ID at 2 sites and at one site on days 28 and 90); or the standard 5-dose intramuscular regimen. All ID regimens required the same total amount of vaccine, 60% less than the intramuscular method. Neutralising antibody responses were measured five times over a year in 229 people, for whom complete data were available.

**FINDINGS:** All ID regimens showed similar immunogenicity. The intramuscular regimen gave the lowest geometric mean antibody titres. Using the rapid fluorescent focus inhibition test, some sera had unexpectedly high antibody levels that were not attributable to previous vaccination. The results were confirmed using the fluorescent antibody virus neutralisation method.

**CONCLUSIONS:** This 4-site PEP regimen proved as immunogenic as current regimens, and has the advantages of requiring fewer clinic visits, being more practicable, and having a wider margin of safety, especially in inexperienced hands, than the 2-site regimen. It is more convenient than the 8-site method, and can be used economically with vaccines formulated in 1.0 or 0.5 ml ampoules. The 4-site regimen now meets all requirements of immunogenicity for PEP and can be introduced without further studies.

**45 WHO. Rabies Working Group Report, SAGE meeting October 2017. Available at [http://www.who.int/immunization/sage/meetings/2017/october/1\\_Background\\_paper\\_WG\\_RA\\_BIES\\_final.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RA_BIES_final.pdf?ua=1), accessed February 2018.**

No abstract available.

**46 Robertson K et al. Seroconversion following incomplete human rabies post-exposure prophylaxis. Vaccine. 2010 Sep 7;28(39):6523-6.**

In August 2008, CDC and the Puerto Rico Department of Health conducted a serosurvey of patients who had discontinued rabies postexposure prophylaxis (PEP) prior to completing a schedule of five vaccine doses. The objective was to determine whether further vaccination of these patients was needed based on serum rabies neutralizing antibody levels. Eighteen patients consented to serology using the rapid fluorescent focus inhibition test. The World Health Organization's cutoff value of 0.5 IU/mL was used as the basis for recommending PEP continuance, while complete virus neutralization at the 1:5 dilution indicated seroconversion per current Advisory Committee for Immunization Practices recommendations. Serum samples were collected a median of 147 days (range 24-215) after receipt of the last vaccine dose. Ten patients were recommended for PEP continuance for titers below 0.5 IU/mL; however, of 11 patients, 33% of 2-dose, 100% of 3-dose, and 100% of 4-dose patients exhibited seroconversion. These findings corroborate previous studies that suggest a less than five-dose rabies vaccine regimen elicits adequate immunogenicity against rabies.

**47 Kessels JA.et al. Rabies Pre-Exposure Prophylaxis Use in High Risk Populations. Bull World Health Organ. 2017 Mar 1;95(3):210-219C.**

**Objective**

To review the safety and immunogenicity of pre-exposure rabies prophylaxis (including accelerated schedules, co-administration with other vaccines and booster doses), its cost-effectiveness and recommendations for use, particularly in high-risk settings.

**Methods**

We searched the PubMed, Centre for Agriculture and Biosciences International, Cochrane Library and Web of Science databases for papers on pre-exposure rabies prophylaxis published between 2007 and 29 January 2016. We reviewed field data from pre-exposure prophylaxis campaigns in Peru and the Philippines.

**Findings**

Pre-exposure rabies prophylaxis was safe and immunogenic in children and adults, also when co-administered with routine childhood vaccinations and the Japanese encephalitis vaccine. The evidence available indicates that shorter regimens and regimens involving fewer doses are safe and immunogenic and that booster intervals could be extended up to 10 years. The few studies on cost suggest that, at current vaccine and delivery costs, pre-exposure prophylaxis campaigns would not be cost-effective in most situations. Although pre-exposure prophylaxis has been advocated for high-risk populations, only Peru and the Philippines have implemented appropriate national programmes. In the future, accelerated regimens and novel vaccines could simplify delivery and increase affordability.

**Conclusion**

Pre-exposure rabies prophylaxis is safe and immunogenic and should be considered: (i) where access to postexposure prophylaxis is limited or delayed; (ii) where the risk of exposure is high and may go unrecognized; and (iii) where controlling rabies in the animal reservoir is difficult. Pre-exposure

prophylaxis should not distract from canine vaccination efforts, provision of postexposure prophylaxis or education to increase rabies awareness in local communities.

**48 Soentjens P et al. Pre-exposure intradermal rabies vaccination: a randomized trial in healthy adults on shortening the schedule from 28 to 7 days. Submitted.**

**BACKGROUND:** The current three- to four-week pre-exposure rabies vaccination schedules are rather cumbersome. Shorter effective schedules would be welcome.

**METHODS:** We conducted a randomized, open-label non-inferiority trial in 500 healthy adults, that compared the safety and immunogenicity of a shortened two visits 7-day intradermal (ID) primary vaccination (two doses of 0.1 ml ID of the Human Diploid Cell culture rabies Vaccine [HDCV] at day 0 and day 7) versus a standard three visits 28-day schedule (three single dose of 0.1 ml ID at day 0, 7 and 28). One to three years later, a single dose of 0.1 ml ID of HDCV was given as booster injection to evaluate the anamnestic antibody response (boostability). The primary endpoint for immunogenicity was the percentage of subjects with a protective antibody level (measured by Rabies Fluorescent Focus Inhibition Test (RFFIT) above 0.5 IU/ml seven days after boosting. Secondary endpoints were the proportion of participants with an antibody level above 10.0 IU/ml (considered as providing long lasting protection) and the geometric mean titers (GMT) of rabies virus neutralization antibodies on day 0, day 35, booster injection on day 365 to 1095 and 7 days after booster injection. Local and systemic adverse events were assessed after primary and booster vaccination.

**RESULTS:** All subjects in both arms had a rabies antibody titer > 0.5 IU/mL on day 7 after the booster injection. Long-lasting protection was observed in 96% of the participants of the shortened schedule arm compared to 83% in the standard schedule arm (Difference of 13). Subjects exposed to the shortened schedule had a GMT of 37 IU/ml (95% confidence interval [CI] 33 - 42) after booster injection, versus 25 IU/ml (95% CI 22 - 29) for the standard schedule ( $p < 0.001$ ). Local reactions on the injection site after primary vaccination were mild and transient and seen in 51.8% of the participants in the standard schedule versus 43.4% of the shortened arm ( $p = 0.07$ ). They were observed in 38.8% and 48.8% ( $p = 0.03$ ) of participants after the booster injection respectively.

**CONCLUSION:** In healthy adults, ID administration of twice a fractional 0.1 ml dose of HDCV over two visits in 7 days was as safe as, and not inferior to, the standard ID schedule. Proportion of participants with long lasting protection and anamnestic antibody response after booster injection were even higher in the shortened schedule.

**49 Wieten RW et al. Rabies vaccinations: are abbreviated intradermal schedules the future? Clin Infect Dis. 2013; 56(3), pp.414-419.**

Rabies is a deadly disease, and current preexposure vaccination schedules are lengthy and expensive. We identified nine studies investigating abbreviated schedules. Although initial responses were lower, accelerated adequate immune responses were elicited after booster vaccinations. Lower-dose (and therefore cheaper) vaccination schedules may constitute a valid alternative to current vaccination schedules.



**50 Jonker EFF et al. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study J Travel Med. 2017 Sep 1;24(5).**

**BACKGROUND:** The current standard 3-dose intramuscular rabies PrEP schedule suffers from a number of disadvantages that severely limit accessibility and availability. The cost of is often prohibitive, it requires 3 visits to the clinic, and there are regular vaccine shortages.

**METHODS:** Volunteers ( N = 30) were randomly assigned to 4 study arms: 1 standard dose intramuscular (IM) dose of PVRV (purified Vero cell rabies vaccine, Verorab), and 1/5th, 2/5th or 3/5th- fractional intradermal (ID) dose of PVRV in a single visit. All subjects received a simulated rabies post-exposure prophylaxis (D0, D3) 1 year later. Rabies virus neutralizing antibodies (RVNA) were determined by virus neutralization microtest (FAVN) on D0, D7, D28, Y1 and Y1 + D7.

**RESULTS:** 28 out of 30 subjects (93%) seroconverted 1 month after primary vaccination; 1 subject in the 1-dose IM arm and 1 in the 1/5th-fractional dose ID arm did not. After 1 year, 22 out of 30 subjects (73%) no longer had RVNA above 0.5 IU/ml, with no discernible difference between study groups. After 1 year, all 30 subjects mounted a booster response within 7 days after simulated PEP, with the highest titers found in the single dose IM group ( P < 0.03).

**CONCLUSIONS:** This dose finding study demonstrates that priming with a single dose of rabies vaccine was sufficient to induce an adequate anamnestic antibody response to rabies PEP in all subjects 1 year later, even in those in whom the RVNA threshold of 0.5 IU/ml was not reached after priming.

**51 Soentjens P et al. Statistical report RCT2: Boostability for rabies in last-minute travellers: One Day Rabies Pre-exposure Intradermal Vaccination followed by one day Post-exposure intradermal Vaccination. Registered randomised clinical trial EudraCT 2014-00183612, Available at: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001836-12/BE> , accessed December 2017.**

No abstract available.

**52 Mansfield KL et al. Rabies pre-exposure prophylaxis elicits long-lasting immunity in humans. Vaccine. 2016 Nov 21;34(48):5959-5967.**

Despite the availability of safe and effective human vaccines, rabies remains a global threat, with an estimated 60,000 human deaths annually attributed to rabies. Pre-exposure prophylaxis against rabies infection is recommended for travelers to countries where rabies is endemic, and also for those with a higher risk of exposure. In this study, the rabies-specific neutralising antibody responses in a cohort of rabies-vaccinated recipients over a period of twenty years have been assessed. In particular, the antibody response to primary vaccinations and boosters, and the waning of antibody post primary vaccination and post booster were investigated. The significance of gender, age at

vaccination, vaccine manufacturer and vaccination intervals were also evaluated. These data confirm that rabies vaccination can elicit a neutralising antibody response that can remain at detectable levels for a number of years, without additional booster vaccinations. The antibody response following both primary vaccination and booster was significantly influenced by the gender of the subject ( $p=0.002$  and  $0.03$  respectively), with supportive data that suggests an effect by the make of vaccine administered following primary vaccination, with significantly higher VNA titres observed for one vaccine manufactured prior to 2006 ( $p<0.001$ ) in a small subset of recipients ( $n=5$ ). Additionally, the decay rate was demonstrated through the overall decline in antibody titre for all individuals, which was a 37% and 27% reduction per 2-fold change in time following primary and booster vaccination respectively. Individuals within older age groups demonstrated a significantly faster decline in antibody titre following the primary vaccination course ( $p=0.012$ ). Rate of decline in antibody titre was also significantly influenced by the vaccine make following primary course ( $p<0.001$ ). The assessment of neutralising antibody titre decline has also provided an insight into the most appropriate timing for booster administration, and enabled the prediction of long term titres from post-vaccination antibody titres.

**53 WHO. Adverse events following immunization (AEFI). Geneva, 2017. Available at [http://www.who.int/vaccine\\_safety/initiative/detection/AEFI/en/](http://www.who.int/vaccine_safety/initiative/detection/AEFI/en/), accessed December 2017.**

No abstract available.

**54 Fooks AR et al. Development of a multivalent paediatric human vaccine for rabies virus in combination with Measles-Mumps-Rubella (MMR). Vaccine. 2014 Apr 11;32(18):2020-1.**

No abstract available.

**55 de Martino M. Dismantling the Taboo against Vaccines in Pregnancy. Int J Mol Sci. 2016 Jun 7;17(6).**

Vaccinating pregnant women in order to protect them, the fetus, and the child has become universal in no way at all. Prejudice in health professionals add to fears of women and their families. Both these feelings are not supported by even the smallest scientific data. Harmlessness for the mother and the child has been observed for seasonal, pandemic, or quadrivalent influenza, mono, combined polysaccharide or conjugated meningococcal or pneumococcal, tetanus toxoid, acellular pertussis, human papillomavirus, cholera, hepatitis A, Japanese encephalitis, rabies, anthrax, smallpox, yellow fever, mumps, measles and rubella combined, typhoid fever, inactivated or attenuated polio vaccines, and Bacillus Calm  tte Gu  rin vaccines. Instead, the beneficial effects of influenza vaccine for the mother and the child as well as of pertussis vaccine for the child have been demonstrated. Obstetrician-gynecologists, general practitioners, and midwives must incorporate vaccination into their standard clinical care. Strong communication strategies effective at reducing parental vaccine hesitancy and approval of regulatory agencies for use of vaccines during pregnancy are needed. It must be clear that the lack of pre-licensure studies in pregnant women and, consequently, the lack

of a statement about the use of the vaccine in pregnant women does not preclude its use in pregnancy.

**56 Crowcroft NS et al. The prevention and management of rabies. BMJ. 2015 Jan 14; 350:g7827.**

No abstract available.

**57 Dixit R et al. Benefits of using heterologous polyclonal antibodies and potential applications to new and undertreated infectious pathogens. Vaccine. 2016; 34(9), pp.1152-1161.**

Passive immunotherapy using polyclonal antibodies (immunoglobulins) has been used for over a century in the treatment and post-exposure prophylaxis of various infections and toxins. Heterologous polyclonal antibodies are obtained from animals hyperimmunised with a pathogen or toxin. The aims of this review are to examine the history of animal polyclonal antibody therapy use, their development into safe and effective products and the potential application to humans for emerging and neglected infectious diseases. A literature search of OVID Medline and OVID Embase databases was undertaken to identify articles on the safety, efficacy and ongoing development of polyclonal antibodies. The search contained database-specific MeSH and Emtree terms in combination with pertinent text-words: polyclonal antibodies and rare/neglected diseases, antivenins, immunoglobulins, serum sickness, anaphylaxis, drug safety, post marketing surveillance, rabies, human influenza, Dengue, West Nile, Nipah, Hendra, Marburg, MERS, Hemorrhagic Fever Virus, and Crimean-Congo. No language limits were applied. The final search was completed on 20.06.2015. Of 1960 articles, title searches excluded many irrelevant articles, yielding 303 articles read in full. Of these, 179 are referenced in this study. Serum therapy was first used in the 1890s against diphtheria. Early preparation techniques yielded products contaminated with reactogenic animal proteins. The introduction of enzymatic digestion, and purification techniques substantially improved their safety profile. The removal of the Fc fragment of antibodies further reduces hypersensitivity reactions. Clinical studies have demonstrated the efficacy of polyclonal antibodies against various infections, toxins and venoms. Products are being developed against infections for which prophylactic and therapeutic options are currently limited, such as avian influenza, Ebola and other zoonotic viruses. Polyclonal antibodies have been successfully applied to rabies, envenomation and intoxication. Polyclonal production provides an exciting opportunity to revolutionise the prognosis of both longstanding neglected tropical diseases as well as emerging infectious threats to humans.

**58 Simani OE et al. Effect of HIV-1 exposure and antiretroviral treatment strategies in HIV-infected children on immunogenicity of vaccines during infancy. AIDS. 2014; 28(4), pp.531-541.**

Introduction: We studied the effect of maternal HIV-exposure and timing of antiretroviral treatment (ART) in HIV-infected infants on antibody responses to combined diphtheria-toxoid–tetanus-toxoid–whole cell pertussis and Haemophilus influenzae type b conjugate vaccine (HibCV) and monovalent hepatitis B vaccine (HBV).

**Methods:** HIV-uninfected infants born to HIV-infected (HEU) or HIV-uninfected (HUU) mothers were enrolled in parallel with HIV-infected children with CD4+  $\geq 25\%$ , who were randomized to initiate ART immediately upon confirmation of HIV-infection (ART-Immed) or when clinically and/or immunologically indicated (ART-Def). Infants received three doses of diphtheria-toxoid–tetanus-toxoid –wP-HibC/HBV at 7.3, 11.4 and 15.4 weeks of age. Antibody to diphtheria-toxoid, tetanus-toxoid, pertussis toxin, filamentous hemagglutinin (FHA) and hepatitis B surface antigen (HBsAg) were measured by Luminex multiplex-immunoassay and polyribosyl-ribitol phosphate (PRP) antibodies by standard ELISA and bactericidal assay.

**Results:** Prevaccination antibody geometric mean concentrations (GMCs) were higher in HUU than HEU infants for tetanus-toxoid, but lower for HBsAg, diphtheria-toxoid and FHA. Postvaccination GMCs and proportion with seroprotective antibody levels or sero-conversion rates were similar between HUU and HEU infants for all vaccines. Postvaccination GMCs were higher in HUU for tetanus-toxoid, diphtheria-toxoid, HBsAg and FHA than ART-Immed infants; and for tetanus-toxoid, HBsAg and pertussis-toxoid than ART-Def infants. Nevertheless, there was no difference in proportion of HUU and HIV-infected infants who developed sero-protective vaccine-specific antibody levels postvaccination. The timing of ART initiation generally did not affect immune responses to vaccines between HIV-infected groups.

**Conclusion:** Vaccination with DTwP-HibCV/HBV of HEU and HIV-infected infants initiated on early-ART confers similar immunity compared with HUU children.

**59 Thisyakorn U et al. Immunologic and virologic evaluation of HIV-1-infected children after rabies vaccination. Vaccine. 2001 Jan 8;19(11-12):1534-7.**

**BACKGROUND:** One-third of Thai children experience a dog bite by the time they are 15 years old, and HIV-1 infection in children is also not uncommon. Previous study has shown that rabies vaccination of HIV-1-infected children may not result in a satisfactory antibody response when CD4+ T cells are less than 15%. The objective of this prospective clinical study is to evaluate the immunologic response and effect on viral load after rabies vaccination in HIV-infected children.

**METHODS:** Thirteen HIV-1-infected children were vaccinated with the intramuscular rabies pre-exposure regimen using human diploid cell rabies vaccine (HDCV) on days 0, 7 and 28. CD4+ and CD8+ lymphocyte counts were performed on days 0, 7 and 28. Plasma viral loads were determined on days 0, 7, 14, 60, 90, 180 and 360.

**RESULTS:** There were no significant change in serial measurements of CD4+/CD8+ lymphocytes during a period of 1 month and in plasma viral load during 1 year. There was no associated clinical deterioration or any adverse reactions attributable to vaccine.

**CONCLUSIONS:** Rabies vaccination in HIV-1-infected children appears to be safe but did not significantly change the levels of plasma HIV RNA, CD4+ and CD8+ cell counts.

**60 Farquhar C et al. Immune responses to measles and tetanus vaccines among Kenyan human immunodeficiency virus type 1 (HIV-1)-infected children pre- and post-highly active antiretroviral therapy and revaccination. Pediatr Infect Dis J. 2009 Apr;28(4):295-9.**

No abstract available.

**61 Pappaioanou, M. et al. 1986. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *New England Journal of Medicine*, 314(5), pp.280-284.**

We conducted a randomized controlled trial to evaluate the antibody response of freshman veterinary students to intradermal human diploid-cell rabies vaccine administered concurrently with chloroquine, a drug frequently used for chemoprophylaxis against malaria. Fifty-one students who had not been vaccinated against rabies were enrolled: 26 received 300 mg of chloroquine base per week (the recommended dose for malaria prophylaxis); 25 did not receive chloroquine and served as controls. All subjects received 0.1 ml of rabies vaccine intradermally on days 0, 7, and 28. Chloroquine was administered weekly to the treatment group, beginning nine days before the first dose of vaccine and continuing until day 48. The mean rabies-neutralizing antibody titer for the chloroquine group was significantly lower than that for the control group on each day of testing--i.e., day 28 ( $P = 0.0094$ ), day 49 ( $P = 0.0008$ ), and day 105 ( $P = 0.0002$ )--although both groups had neutralizing antibody titers on days 49 and 105, according to the criteria of the Centers for Disease Control. The blood concentrations of chloroquine and desethylchloroquine (the major metabolite of chloroquine, which also has antimalarial properties) were negatively associated with log antibody titers. These results indicate that chloroquine taken in the dose recommended for malaria prophylaxis can reduce the antibody response to primary immunization with intradermal human diploid-cell rabies vaccine.

**62 Bernard KW et al. Pre-exposure rabies immunization with human diploid cell vaccine: decreased antibody responses in persons immunized in developing countries. *Am J Trop Med Hyg*. 1985 May;34(3):633-47.**

In November 1982, a U.S. Peace Corps volunteer in Kenya completed pre-exposure rabies prophylaxis with a standard 3 dose intradermal (ID) series of human diploid cell rabies vaccine (HDCV). In May 1983, she was bitten by a dog and died of rabies 3 months later. An initial investigation revealed that the patient, as well as 9 of 11 others immunized at the same time, had no rabies antibody titers (less than 1:5). We therefore instituted investigations into the immunogenicity of pre-exposure HDCV both in the United States and in developing countries. A serosurvey revealed unexpectedly low rabies titers in both Peace Corps volunteers and others immunized in developing countries. Antibody titers measured 2-3 weeks after ID immunization were compared in 9 groups totaling 271 persons in the United States and Kenya. There was no statistically significant difference in antibody titers in the 6 U.S. groups immunized from 1980-1984 ( $P$  greater than 0.15); however, groups immunized in the United States had significantly higher titers than a group of Kenyan nationals ( $P$  less than or equal to 0.0001), and the Kenyans had significantly higher titers than 2 Peace Corps groups immunized in Kenya ( $P$  less than or equal to 0.0001). No single hypothesis proposed (laboratory error, vaccine potency, vaccination technique, or specific immune suppression) accounted for the observed differences. Although we cannot fully explain the poor response to HDCV, it is probably due to multiple factors. We conclude that persons immunized with ID pre-

exposure HDCV in developing countries should have rabies antibody titers determined to ensure their seroconversion; for persons immunized in the United States, such titers need not be routinely determined.

**63 Madhusudana SN et al. Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies: Results of in vitro and in vivo studies. Hum Vaccin Immunother. 2013; 9(9): 1914-1917.**

Passive immunization is a crucial parameter for prevention of human rabies. Presently as World Health Organization (WHO) strongly advocates local infiltration of rabies immunoglobulin in and around the bite wound, we feel that there is no basis for calculating the dose of immunoglobulin based on body weight. Keeping this in view we conducted both in vitro and in vivo studies to know whether the dose of immunoglobulin can be reduced and still obtain complete neutralization of the virus. In vitro neutralization studies were conducted using CVS strain of virus and BHK 21 cells. In vivo experiments were conducted in 4 weeks old Swiss albino mice by initial challenge with CVS followed by infiltration with increasing dilutions of either human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). In vitro studies showed that a dose of 100 FFD 50 of CVS was neutralized by increasing dilution of both HRIG and ERIG and 100% neutralization was observed with HRIG and ERIG in as low quantities as 0.025 IU. In mice studies there was 100% survival of mice infiltrated with 0.025 IU of both HRIG and ERIG compared with 100% mortality in mice infiltrated with normal saline. These results suggest that it is possible to reduce the dose of rabies immunoglobulins by at least 16 times the presently advocated dose. These findings needs to be further evaluated using larger animal models and street viruses prevalent in nature but cannot serve as recommendations for use of RIG for passive immunization in humans

**64 Saesow N et al. Diffusion and fate of intramuscularly injected human rabies immune globulin. Acta Trop. 2000 ; 76: 289-292.**

The importance of rabies immune globulin (RIG) in postexposure rabies treatment is well known and it has been emphasized that the local injection into the animal bite sites is crucial. This preliminary study used a radioisotope tracer that allows following the fate of human rabies immune globulin (HRIG) injected intramuscularly. There was significant retention and local diffusion of the immune globulin at the injection site and significant radiotracer could still be detected at the site 24 h later.

**65 Wilde H et al. Worldwide rabies deaths prevention – A focus on the current inadequacies in postexposure prophylaxis of animal bite victims. Vaccine. 2015; 17: 1-3.**

The World Health Organization reports that over 60,000 humans die of rabies annually, worldwide. Most occur in remote regions of developing countries. Almost all victims received no postexposure rabies prophylaxis (PEP). There are no facilities or health personnel able to provide it in many areas where the disease is prevalent. A first approach to correct this problem would be by extending provision of modern PEP to areas where human rabies is most prevalent.

**66 Bharti OK et al. Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG. Hum Vaccin Immunother. 2017; 13(4), pp.762-765.**

An increasing number of dog bite victims were being presented to public hospitals in Himachal Pradesh in 2014 amidst virtual non availability of any rabies immunoglobulin (RIG). Only a small quantity of equine rabies immunoglobulin (eRIG) was available from the government owned Central Research Institute (CRI) Kasauli. This available eRIG was used in 269 patients as an emergency response and only for local infiltration of severe bite wounds by suspected rabid dogs. This was followed by rabies vaccination, using the WHO approved intra-dermal Thai Red Cross Society vaccination schedule. A subgroup of 26 patients were later identified who had been severely bitten by laboratory confirmed rabid dogs. They were followed for more than one year and all were found to be alive.

**67 Bharti OK et al. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: An alternative cost-effective approach for passive immunization against rabies. Hum Vaccin Immunother. 2016; 12(3), pp.837-842.**

Presently the dose of rabies immunoglobulin (RIG) which is an integral part of rabies post exposure prophylaxis (PEP) is calculated based on body weight though the recommendation is to infiltrate the wound(s). This practice demands large quantities of RIG which may be unaffordable to many patients. In this background, we conducted this study to know if the quantity and cost of RIG can be reduced by restricting passive immunization to local infiltration alone and avoiding systemic intramuscular administration based on the available scientific evidence. Two hundred and sixty nine category III patients bitten by suspect or confirmed rabid dogs/animals were infiltrated with equine rabies immunoglobulin (ERIGs) in and around the wound. The quantity of ERIG used was proportionate to the size and number of wounds irrespective of their body weight. They were followed with a regular course of rabies vaccination by intra-dermal route. As against 363 vials of RIGs required for all these cases as per current recommendation based on body weight, they required only 42 vials of 5ml RIG. Minimum dose of RIGs given was 0.25 ml and maximum dose given was 8 ml. On an average 1.26 ml of RIGs was required per patient that costs Rs. 150 (\$3). All the patients were followed for 9 months and they were healthy and normal at the end of observation period. With local infiltration, that required small quantities of RIG, the RIGs could be made available to all patients in times of short supply in the market. A total of 30 (11%) serum samples of patients were tested for rabies virus neutralizing antibodies by the rapid fluorescent focus inhibition test (RFFIT) and all showed antibody titers  $>0.5$  IU/mL by day 14. In no case the dose was higher than that required based on body weight and no immunosuppression resulted. To conclude, this pilot study shows that local infiltration of RIG need to be considered in times of non-availability in the market or unaffordability by poor patients. This preliminary study needs to be done on larger scale in other centers with long term follow up to substantiate the results of our study.

**68 Both L et al. Passive immunity in the prevention of rabies. Lancet Infect Dis. 2012; 12(5), pp.397-407.**

Prevention of clinical disease in those exposed to viral infection is an important goal of human medicine. Using rabies virus infection as an example, we discuss the advances in passive immunoprophylaxis, most notably the shift from the recommended polyclonal human or equine immunoglobulins to monoclonal antibody therapies. The first rabies-specific monoclonal antibodies are undergoing clinical trials, so passive immunisation might finally become an accessible, affordable, and routinely used part of global health practices for rabies. Coupled with an adequate supply of modern tissue-culture vaccines, replacing the less efficient and unsafe nerve-tissue-derived rabies vaccines, the burden of this disease could be substantially reduced.

**69 WHO. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection. – 2nd ed.2007. Available at [http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/QualityAssurancePharmVol2.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/QualityAssurancePharmVol2.pdf), accessed March 2018.**

No abstract available.

**70 Warrell M. Current rabies vaccines and prophylaxis schedules: Preventing rabies before and after exposure. Travel Med Infect Dis. 2012; 10: 1-15.**

Travellers are probably the largest group in the general population to receive rabies pre-exposure prophylaxis. The dangerous consequences of the unavailability of rabies immune globulin in many countries could be ameliorated if pre-exposure rabies vaccination were practised more widely, especially in children, living in dog rabies enzootic countries. The WHO has recommended several different regimens for post-exposure prophylaxis, while individual countries decide on protocols for local use. Intramuscular regimens are expensive and waste vaccine. Although failure to receive vaccine is usually due to the cost, the economical potential of intradermal vaccination has still not been realised 19 years after its introduction. The currently recommended 2-site intradermal post-exposure regimen is not economical for use in rural areas where 80% of Indian rabies deaths occur. Most countries using it demand higher potency vaccine, indicating that they do not have complete confidence in the method. This intradermal regimen has only been used where immunoglobulin is likely to be available for severely bitten patients. Increased intradermal doses are sometimes used for selected patients. Provision of economical rabies prophylaxis can be improved. Decisions to change recommendations should take account of the immunological, financial, practical and logistical aspects of dog bite treatment in remote areas.

**71 WHO Rabies Modelling Consortium: Modelling the potential impact of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries. Submitted.**



**BACKGROUND:** Tens of thousands of people die from rabies each year. Deaths can be prevented through post-exposure prophylaxis (PEP) to bite victims, and disease eliminated through dog vaccination. Current PEP use saves many lives, but access remains limited in many rabies endemic countries due to high costs and/or poor supply.

**METHODS:** We developed epidemiological and economic models to investigate the impact of an investment in rabies PEP by Gavi, the Vaccine Alliance. We modelled rabies PEP according to the status quo, and with improved access using WHO-recommended intradermal vaccination, with and without rabies immunoglobulin (RIG) and with and without dog vaccination.

**FINDINGS:** During 2020-2035 we predict >1 million rabies deaths will occur in 67 rabies-endemic countries under the status quo. Current PEP levels prevent ~56,000 deaths annually. Expanded access to, and free provision of PEP, with concomitant improvements in health-seeking and compliance, would prevent an additional 494,000 deaths between 2020-2035. Use of rabies vaccine alone would be extremely cost-effective at \$517 / death and \$27 / DALY averted. Incremental analysis suggests that increasing RIG provision would not be cost-effective. Switching to efficient intradermal PEP regimens means vaccine requirements will decline from 57 to 55 million vials. Scaling-up dog vaccination programmes could eliminate human rabies deaths over this time horizon; improved PEP access remains cost-effective in this scenario, especially in combination with Integrated Bite Case Management.

**INTERPRETATION:** Investing in rabies PEP would substantially reduce disease burden and is likely to be an extremely cost-effective intervention.

**72 Ponsich A et al. A prospective study on the incidence of dog bites and management in a rural Cambodian, rabies-endemic setting. *Acta Trop.* 2016; 160: 62-7.**

Rabies circulates intensely in Cambodia, mainly affecting rural populations. We conducted a prospective study to estimate the baseline incidence of potentially infective dog bites in rural villages of Siem Reap province, Cambodia. The study was conducted in a convenience sample of 844 families totaling 1779 persons in four villages. The study collected data in a total of 802.3 person-years. Trained village health workers (VHW) exhaustively documented consecutive dog bites at the end of each month. Between May 15th and November 15th, 2011, a total of 40 attacks (43 bites; 1.07 bites per attack) were notified by 39 persons (50% female; one suffered two distinct incidents) to VHW. The all-age attack rate for bites over this 6-month period was 2.3% (CI95%: 1.7-3.1%), with a global incidence rate estimated at 4.84 bites/100 person-years (CI95%: 3.5-6.6). The mean age in bite victims was 20.8±18.9years (median 12.5; interquartile range 6-36; range 1-63). The dog was identified in 39 (97.5%) of cases, being the household dog in 9 (22.5%) of cases. Bites were classified as severe (WHO Category III-broken skin with bleeding) in 33 (82.5%) of cases with a severe dog bites incidence estimated at 4/100 person-years (CI95%: 2.8-5.6). The bites involved the hand or face in 1 (2.5%) case each (both Category III). In 20 incidents (50%), only rice was applied to the wounds. There were no suspected or confirmed human rabies deaths during the study period but one dog died after biting (2 others were lost to follow-up and 14 were put down by their owner). Our study documented an extremely high incidence of dog bites in of rural Cambodian adults and children. Adapted control policies for canine vaccination are urgently needed.

73 WHO. Evidence to recommendation Table 1: Time- and dose-sparing PEP regimens . Available at [http://www.who.int/immunization/policy/position\\_papers/rabies\\_time\\_dose\\_pep\\_regimens.pdf](http://www.who.int/immunization/policy/position_papers/rabies_time_dose_pep_regimens.pdf), accessed April 2018.

74 WHO. Evidence to Recommendation Table 2: Simplified administration of RIG as a part of PEP. Available at [http://www.who.int/immunization/policy/position\\_papers/rabies\\_simple\\_admin\\_rig\\_pep.pdf](http://www.who.int/immunization/policy/position_papers/rabies_simple_admin_rig_pep.pdf), accessed April 2018.

75 WHO. Evidence to recommendation Table 3: Prioritization of RIG. Available at [http://www.who.int/immunization/policy/position\\_papers/rabies\\_prioritization\\_rig.pdf](http://www.who.int/immunization/policy/position_papers/rabies_prioritization_rig.pdf), accessed April 2018.

76 WHO. Evidence to recommendation Table 4: Time and dose sparing PrEP. Available [http://www.who.int/immunization/policy/position\\_papers/rabies\\_time\\_dose\\_sparing\\_prep.pdf](http://www.who.int/immunization/policy/position_papers/rabies_time_dose_sparing_prep.pdf), accessed April 2018.