Rabies control in South and Southeast Asia

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Abstract

We have the knowledge and tools to eliminate the threat of canine rabies but this disease, nevertheless, remains a public health threat in many parts of the world. Lack of motivation by governments, cultural issues and inadequate funding remain barriers. This is amazing since the number of human rabies deaths worldwide is greater than that from polio, meningococcal meningitis, Japanese encephalitis, yellow fever, SARS, bird flu and other scourges that attract more attention. Safe and effective vaccines are now widely available. Reduced dose effective and less expensive post-exposure vaccination regimens have helped eliminate nerve tissue vaccines in Thailand, Philippines and Sri Lanka. India and Pakistan, the major users of dangerous nerve tissue derived Semple type vaccine, are now considering following suite. Immediate wound care and prompt use of a potent vaccine will save a majority of infected persons. Rabies immunoglobulin, injected into and around bite wounds, provides added safety for the severely exposed. The high cost of rabies immunoglobulin and tissue culture vaccines are remaining barriers, but new manufacturers and the use of intradermal vaccination schedules can reduce costs. Ultimately, it is the need to control rabies in dogs that must occupy most of our attention. The tools are available, but attitudes must change before they can be applied. There have been many new developments since publication of the last WHO rabies expert committee report in 1992 [WHO Expert Committee on Rabies. Eighth Report. Tech Series 824. Geneva: World Health Organization; 1992 (new version in print)] and we will address those that have practical applicability.

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1. Introduction

Much of the Middle East, Pakistan, Afghanistan, India, Sri Lanka, Nepal, Bangladesh, Myanmar, Thailand, Laos, Cambodia, Vietnam, parts of Indonesia, Philippines and most former Soviet Republics remain canine rabies endemic. Wildlife rabies plays a very minor role in South and Southeast Asia but exists in some species including bats. The tools to control canine rabies are available but not applied. Advances have been made in recent decades but have focused mostly on post-exposure treatment and futile efforts to treat rabies in man. No new Asian country has rid itself of rabies during the past decades.

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2. Post-exposure prophylaxis (PEP)

KG Nicholsen [2], MJ Warrell and DA Warrell [3] and P Phanuphak [4] made important contributions to safe, effective and affordable post-exposure rabies prophylaxis (PEP). They developed two WHO approved reduced dose intradermal vaccination schedules [5,6]. These found a fertile ground in Asia where nurses already administer intradermal BCG to infants and could readily apply these skills to rabies PEP. We hope that wider application of the economical intradermal methods will hasten banishment of dangerous nerve tissue derived rabies vaccines.

Immunoglobulin, administered at the onset of post-exposure treatment and injected into potential inoculation sites, represents a safety net for the patient till vaccine-induced endogenous antibodies are formed. This was demonstrated in 1963 by Dean and Bear who infiltrated rabies antiserum into inoculation sites [7]. It neutralized rabies...
viruses, whereas antisera injected intramuscularly at other sites did not. These studies were reaffirmed in the 1990s, when several rabies vaccine treatment failures were attributed to the fact that immunoglobulin was injected intramuscularly without infiltrating bite wounds [8–10]. We used TC99m-isotope-labeled human rabies immunoglobulin (HRIG) with whole IgG to show that, when injected around simulated bite wounds, it diffuses readily into surrounding tissue. Moreover, 58% of it was retained there at 1 h and 24.5% could still be found around the injection site 24 h later [9]. There, it could neutralize virus before it entered nerve endings and ascend centrally as the "naked" form without the envelope protein that the immune system recognizes [11].

Human rabies immunoglobulin is a scarce commodity and virtually unaffordable in most of Asia. Purified equine immunoglobulin (ERIG) is a far cry from the original crude rabies antiserum developed in the 1950s, which caused adverse reactions that gave them a deserved bad reputation [12]. ERIGs are safe and sell at a fraction of the cost of HRIG [13–14]. It is a ritual to perform a skin test prior to administering ERIG. However, this test does not predict serum sickness, which can be anticipated approximately 1 week later in 1–2 percent of subjects [15]. There are no WHO directives on how the skin test is to be performed. We use a tuberculin syringe with 26 gauge needle. The ERIG is diluted 1:100 and 0.02 mL are injected intradermally raising a 3-mm wheel. A wheel, greater than 10 mm with or without flare, is then considered a positive test. The skin test may or may not predict very rare cases of anaphylaxis [15]. Our animal bite clinic experienced one case among over 100,000 recipients of purified ERIG manufactured by Pasteur, Aventis, Sclavo, the Swiss Serum and Vaccine Institute and the Thai Red Cross. Our one anaphylaxis patient had a negative skin test and recovered without complications. We have administered ERIG to severely rabies-exposed patients with a positive skin test under closed observation and did not encounter anaphylaxis in this group [15]. However, it must be emphasized that heterologous serum products (and most parenteral medications) should not be administered by staff or in locations that are unable to manage a rare case of anaphylaxis. The October 2004 WHO rabies expert committee conference reviewed recent unpublished research regarding efficacy of currently marketed ammonium sulfate and chromatography purified, peptic-digested and heat-treated equine rabies antibody preparations. It appears that excessive purification, which fractures the IgG molecule diminishes efficacy. This is thought to be due to a shorter half-life. The presence of whole IgG in the end product is important and we will have to accept a small number of serious, sickness reactions from the presence of whole IgG and other equine proteins in order to achieve efficacies identical to those of HRIG.

Animal bite patients often present with delay when wound infection is already well established. A prospective study comparing injecting animal bite wounds with ERIG to a group of contaminated lacerations infiltrated with an anesthetic prior to suture. Wound infection rates were the same in both groups [16]. This study showed that one could safely inject contaminated and infected wounds with immunoglobulin after good wound care and antibiotic cover.

Only four tissue and avian culture rabies vaccines have been recognized by WHO at this time. All of these have been extensively tested for safety and immunogenicity with results published in peer review journals. They are human diploid cell vaccine (HDCV; France, Canada and Germany); purified chick embryo vaccine (PCEC; Germany, India and Japan); purified vero cell vaccine (PVRV; France); purified duck embryo vaccine (PDEV; Switzerland). Hamster kidney cell-derived rabies vaccines of differing potencies; some lyophilised, others adjuvanted or liquid, are being manufactured in Russia and China. Potencies and shelf lives vary a lot and so do manufacturer’s recommended PET schedules. New manufacturers of inactivated tissue culture products are appearing in several Asian countries. We hope that some of these will soon be proven to be of high potency and efficacy.

WHO recognized two intramuscular full-dose and two economical intradermal-reduced dose post-exposure treatment regimens. The so-called “Essen” (gold standard) method consists of one full-dose injected into deltoid or lateral thigh muscles (never into fat) on days 0, 3, 7 and 28. An abbreviated intramuscular method, often called the “Zagreb” or 2–1–1 schedule, consists of two full-doses, injected into both deltoid and thigh muscles, followed by one injection on days 7 and 21. The Thai Red Cross intradermal method (TRC-ID) originally consisted of two intradermal injections of 0.1 mL on days 0, 3, 7 and one on days 28 and 90 [5,6]. TRC-ID has been simplified to two injections each on days 0, 3, 7 and 28. This omits the 90-day booster, which had a significant dropout rate (18–20%) without known treatment failures. This new version, which requires only four clinic visits, has now been approved by the WHO expert committee.

PVRV (Aventis, France) comes with 0.5 mL of diluent. PCEC (Chiron, India; Germany; Kaketsuken, Japan) comes with 1.0 mL of diluent [6]. This allows up to five, 0.1 mL intradermal doses using PVRV and up to ten doses of PCEC to be used with the TRC-ID regimen. The WHO expert committee has now approved use of 0.1 mL per dose for PCEC (Germany and India) at potencies of these vaccines have been high (usually greater than 6.0 IU/ampoule). The 8-site method consists of intradermal injections of 0.1 mL at 8 different body sites on day 0, and four injections on day 7, followed by one each on days 28 and 90. The Oxford method results in higher antibody titers by day 14 than TRC-ID or Essen schedules [3]. It had been implied that immunoglobulin may not be required if this method is used [17–19]. However, at least one death could be attributed to this apparently mistaken belief [20]. A prospective study documented that though the 8-site method resulted in higher circulating antibody titers by day 14, it did not cause a significantly earlier antibody response [21]. Human and equine immunoglobulins will thus remain essential biologicals for optimal rabies PEP.

We need less expensive vaccines, immunoglobulins and eventually monoclonal antibodies. The latter have been
shown to be more effective in neutralizing rabies virus than ERIG and HRIG [22]. Rabies antigen and antibody can also be made in genetically manipulated plants [23]. Unfortunately, most of this promising research is underfunded.

We know of no contraindications to post-exposure rabies treatment using inactivated tissue culture vaccines and immunoglobulins. Two studies have shown the safety of PEP in pregnancy [24]. In countries where nerve tissue derived rabies vaccines (NTV) are still being used, one will encounter patients with rabies exposures who have a history of prior PEP with NTV. We have been made aware of Semple and suckling mouse brain batches from Thailand, Pakistan and Africa that were found to contain poor or even no antigenicity [25]. This led us to study Thai patients who had received prior NTV vaccines and presented with new exposures. Some of these subjects, all normal hosts, had detectable neutralizing antibodies but some had none and did not develop an accelerated antibody response. There was no relationship with the time elapsed since the prior NTV vaccination. Such patients should, therefore, be managed as if they had never received rabies PEP [26]. An other recent study, followed by field application in rural Thailand, showed that one can store refrigerated reconstituted tissue culture vaccines for 1 week. The remainder of the ampoule may then be used to treat the same patient for the first three visits using the TRC-ID method [27–29]. This concept allows application of TRC-ID in clinics that see less than one PEP case daily. This procedure is not WHO approved and must only be utilized where good practices. It is still the “gold standard” for rabies immunology and will rise rapidly (within 5–9 days) following booster vaccination [P Khawplod and H Wilde, unpublished].

4. Antibody testing

Laboratory facilities for the determination of rabies antibodies are lacking in most endemic regions. The rapid fluorescent focus inhibition test (RFFIT) measures neutralizing antibodies in a cell culture system. It is technically demanding and only reproducible where it is carried out by dedicated staff. It is still the “gold standard” for rabies immunology and a WHO requirement for immunogenicity testing of new vaccines. It is required for certifying pet animals as immune and rabies free when transferred from endemic to rabies free countries. WHO considers an antibody titer of >0.5 IU/mL in serum or cerebrospinal fluid on day 14 after PEP as the minimum acceptable level [37]. Subjects should still have detectable titers after 1 year [38]. They identify virus epitopes and are not considered a neutralizing test. However, they can be quite reliable in experienced hands and are considered very sensitive at lower titers, near the important 0.5 IU/mL level [DJ Briggs, unpublished]. The mouse neutralization test is now rarely used for antibody determinations. Antibodies in serum or cerebrospinal fluid are best measured using RFFIT. Serum antibodies usually appear after 8 days of illness and are almost never present on admission of a human rabies case. Rabies antibodies are less frequently detected in cerebrospinal fluid but should be considered diagnostic if present even in a vaccinated patient. With increasing prevalence and testing for HIV infection worldwide, we have encountered false positive HIV tests in subjects that had recently received rabies vaccine [39].

3. Pre-exposure vaccination (PREP)

Pre-exposure vaccination (PREP) consists of one full-dose of tissue or avian culture vaccine given intramuscularly or 0.1 mL injected intradermally on days 0, 7, 21 or 28. It is recommended for individuals who are occupationally or recreationally exposed to rabies and for travelers to rabies endemic regions for extended stays or to remote areas where safe post-exposure treatment may not be available [1]. Occupationally exposed workers should have periodic antibody testing, the frequency of which should be determined on the basis of their last antibody titers. Travelers who had PREP must still receive boosters if exposed [1]. This is done by giving one intramuscular or intradermal injection on days 0 and 3. It can be accomplished in one clinic visit by giving four intradermal injections of 0.1 mL tissue culture vaccine at four different lymphatic drainage sites on the same day. This method provides a higher accelerated immune response and saves the second clinic visit [34]. It has now been approved by the WHO committee in October of 2004. Several studies have shown that the antibody response to WHO recognized rabies vaccines is long lasting [35–36]. Using sensitive techniques, neutralizing antibodies are detectable for as long as 15 years and will rise rapidly (within 5–9 days) following booster vaccination [P Khawplod and H Wilde, unpublished].

5. Diagnosing rabies

Diagnosing encephalitic (furious) human, canine and feline rabies is not difficult for an astute human or veterinary...
6. Treatment of human rabies

The Canadian government convened a workshop of rabies-experienced physicians to outline a humane treatment protocol when dealing with a human case [42]. We studied ineffective past treatment efforts including antiviral drugs, steroids, immunomodulators and even large amounts of intrathecal and intravenous immunoglobulin [43]. The group then reaffirmed that we have no promising current methods for treating rabies. A patient with rabies should therefore be provided the best comfort care possible. This consists of intravenous administration of morphine and a potent sedative. Intubation and ICU care should be avoided whenever possible as it only prolongs the suffering. As new knowledge appears and future animal experiments show promise, a suitable tertiary care center might initiate experimental treatments [42].

7. The canine rabies problem

Very little has been done in Asia to effectively control the disease in dogs. Periodic vaccination campaigns were not sustainable. This is at least partly due to the short life span of stray dogs and their rapid population turnover. It was found that one vaccine injection did not result in long lasting neutralizing antibodies and that 3–6% of rabid Thai dogs had a history of rabies vaccination [44–45]. These findings were later confirmed by others [46]. One cannot rely on one rabies vaccine injection to produce long lasting neutralizing antibodies in dogs. It is often the very young dog that represents the greatest risk and also the one that is least likely to have been vaccinated. They are more active and have closer contacts with humans, often children. We currently recommend that all newly acquired pet dogs (and cats) in canine rabies endemic regions receive two rabies vaccine injections 1–3 months apart and annual boosters after that. Primary vaccination should be started at 2 months and should be intramuscularly. Canine surgical sterilization was not sustainable and not effective in significantly reducing a large stray dog population. We, therefore, need to focus on innovative new methods for acceptable humane dog population management followed by mass vaccinations. This would require focused research, motivation of government officials, co-operation from the public as well as legislation that is enforced. Malaysia, bordering rabbits endemic Thailand, has eradicated canine rabies. It should be a model for other Asian countries. One whole continent (Australia) is listed as “rabies free” in spite of the fact that bat rabies has been shown to involve both fruit and insect-eating bats. Spill-over from a bat zoonosis to terrestrial mammals has been shown to occur in North America, and human rabies deaths due to bat rabies have been reported from Australia [47]. A region is either rabies free of not. Giving the local arboreal rabies virus a new name (as was done in Australia) does not change its genome or character.

8. The future

Current active research focuses mostly on better understanding of the pathophysiology of rabies, using the new tools of molecular biology. What are the cellular and molecular mechanisms that result in two different clinical manifestations of rabies seen in canines and humans? Molecular technology is also being applied to the study of geographic differences in rabies strains [48]. This work may cause better understanding of the dynamics of movement of this disease among canine populations and help design control measures. Ongoing studies of lyssaviruses of bats are making progress in the Philippines and Thailand. Published pre- and post-marketing studies of new locally manufactured tissue culture vaccines and immunoglobulins, using WHO acceptable study protocols, are urgently needed. Such vaccines are appearing in the market without independent documentation of safety, immunogenicity and efficacy.
9. WHO approved rabies vaccine schedules

9.1. Post-exposure regimens

(1) Intramuscular method (Essen schedule): One full-dose into muscle at deltoid or lateral thigh on days 0, 3, 7, 14, 28.

(2) Abbreviated intramuscular method (Zagreb schedule): Two full-doses into muscle at deltoid or lateral thigh on day 0 and one each on days 7 and 21. Three clinic visits.

(3) Thai Red Cross schedule: Two intradermal injections of 0.1 mL into both, arms or thighs on days 0, 3, 7 and 28. Four clinic visits.

(4) The 8-site intradermal method (Oxford schedule): Eight intradermal injections at different sites on day 0, four on day 7 and one each on days 28 and 90. Five clinic visits.

Methods 3 and 4 use considerably less vaccine per patient. Patients with severe exposures (WHO category III) must also be given human or equine rabies immunoglobulin on day 0. As much of it, and all if possible, is injected into and around the bite wounds. Brain tissue derived rabies vaccines (Simple and suckling mouse products) should no longer be used. They have dangerous adverse side effects and are of questionable immunogenicity.

9.2. Pre-exposure regimen

One intramuscular or intradermal (0.1 mL) injection on days 0, 7 and 14 or 28. Routine boosters are not recommended but two boosters on days 0 and 3 or 4 intradermal boosters at different lymphatic drainage sites at one sitting are required if an exposure has occurred.

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References


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