Epidemiology of Rabies and Current US Vaccine Guidelines

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ABSTRACT

Rabies is an acute encephalitis that is caused by rabies virus (RABV) infection, which belongs to the Rhabdoviridae family of viruses. It causes about 59,000 human deaths per year (although this number may be under-reported) and is generally fatal, once signs and symptoms begin to appear. Rabies is still very prevalent and under-reported, particularly in low to middle-income countries such as Asia and Africa, where there is lack of access to healthcare and domestic dogs are not widely vaccinated. Although not commonplace in the USA, rabies is mostly transmitted by wild animals such as bats, raccoons, skunks and foxes. Domesticated cats and dogs are also at risk of acquiring rabies, if they have not been vaccinated. Larger carnivores, such as coyotes, bobcats, mountain lions, wolves, bears, woodchucks, and beavers, should also be considered rabid (unless proven otherwise) if they are involved in an unprovoked attack on a person. The rabies vaccine can prevent 99% of deaths if administered promptly after exposure. There are two main vaccination strategies for rabies prevention: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). This article reviews background and epidemiology of rabies and current guidelines for rabies PrEP and PEP regimens for the United States.

KEYWORDS: rabies, animal bites, dogs, rabies vaccine, rabies immunoglobulin

BACKGROUND

Rabies is an acute progressive encephalitis caused by the rabies virus (RABV), a single stranded RNA virus that's part of the family Rhabdoviridae, genus Lyssavirus. The virus is most commonly transmitted through the saliva of a rabid animal. It can also be transmitted through exposure to urine, sweat, and nervous tissues. RABV is not considered to be a bloodborne pathogen. When a human/animal is bitten by a rabid animal, the virus travels from the bite wound into the peripheral nervous system and then makes its way to the brain where the virus replicates and then disseminates back into various tissues, including the salivary glands, where the transmission cycle repeats itself. Human-to-human transmission has never been confirmed except in extremely rare case reports of transmission from infected tissue/organ transplantation.[1] The incubation period on average lasts 1–3 months, but has been documented to range from weeks up to more than a year. Clinical rabies rarely occurs after one year from exposure.[2] Signs and symptoms include pain/paresthesias at the wound site, fever, paralysis, delirium, convulsions, and hydrophobia. Death is almost always imminent within 7–10 days once the infection clinically manifests itself. The rabies vaccine and rabies immunoglobulin (RIG) are very effective in preventing rabies if administered during the incubation period. Rabies vaccines activate the immune system to produce rabies virus neutralizing antibodies (VNAs). Detectable antibodies take about 7–10 days to develop and generally last for several years.

Louis Pasteur and Emile Roux developed and tested the first live attenuated injectable rabies vaccine in 1885. It was made from rabbit nerve tissue. Since 1984, the WHO has recommended discontinuation of production and use of nerve tissue vaccines and replacing them with modern, concentrated, purified cell culture and embryonated egg-based rabies vaccines (CCEEVs). Nerve tissue vaccines can cause severe adverse events and are not as effective. However, they are still being used in some developing countries. Since the 1960s, CCEEVs have been widely distributed and used in the U.S.2 There are two types of CCEEVs licensed for use in the U.S: human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV). Both are formulated for intramuscular (IM) administration and can be used for pre- or post-exposure prophylaxis.[3] Intradermal injections are sometimes used off license in the USA, but are not approved by the FDA.

There are two human RIG, HyperRabTM S/D and Imogam® Rabies-HT, licensed for use in the U.S. for PEP. They are IgG preparations made from human donor plasma and formulated for IM administration only.[3] RIG provides passive immunity that is intended to protect the victim until active immunity produced by the administered vaccine kicks in.

EPIDEMIOLOGY

Rabies causes about 59,000 deaths globally per year and associated loss of 3.7 million disease associated life years (DALYs). The majority of deaths occur in Asia and Africa.[2]

Children under 15 years account for approximately 40% of deaths.[5] Children are more susceptible because of their curious nature and their shorter stature, making them more likely to sustain a wound in a higher-risk anatomical location such as the head.[1] Transmission by unvaccinated domestic dogs is responsible for the majority of human rabies cases globally. Mass vaccination of domestic dogs has been an effective strategy at decreasing the prevalence of rabies in many countries in Africa, Asia, Europe and the Americas. Dog-mediated rabies has been eliminated from the U.S. (i.e. no cases of dog-mediated rabies in the last 2 years).[2] Rabies in the U.S. is rare and is now primarily transmitted through wild animal vectors such as bats, foxes, raccoons, and skunks. Since 1980, there has been an average of 2 deaths per year in the U.S. Between 2000 and 2007, 20 of 25 cases of human rabies reported in the United States were acquired domestically. Among those 20 cases, 17 were associated with bat rabies virus variants.[4] The rate of rabies exposures is about 16 to 200 per 100,000 travelers.[1] Approximately 16,000 to 39,000 patients are exposed to rabies and receive PEP annually in the U.S. Since routine use of cell culture vaccines and HRIG, no PEP failures have been reported in the United States.

PREEXPOSURE PROPHYLAXIS (PREP)

PrEP should be offered to high-risk populations, such as travelers who will spend a long time in a rabies endemic country, veterinarians and their staff, animal handlers, rabies researchers, certain laboratory workers, and those with frequent exposures to rabid animals (i.e. cavers, animal control officers).

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends a series of three 1-mL IM injections in the deltoid. Immunizations should be administered on days 0, 7, 21 or 28. If exposed to rabies, PrEP does not eliminate the need to seek out PEP; however, it reduces the number of vaccine injections post-exposure and eliminates the need for RIG. A few studies have demonstrated that a two-dose regimen given over the course of a week is just as effective as three doses, and more cost-effective.

Rabies occurs most often in resource limited settings. A clinical trial of 500 healthy volunteers showed that an intradermal 2-dose regimen given on days 0 and 7 did not elicit less of an immune response compared with a 3-dose regimen given over the course of a month.[6] The WHO recommends a 2-dose vaccination regimen in resource limited settings given on days 0 and 7 given either IM or ID.

SEROLOGIC TESTING

Rabies virus researchers or those who work in vaccine production are at highest risk for rabies and should get virus neutralizing antibody titer testing every 6 months. Those in the frequent exposure risk category (i.e. cavers, veterinarians, wildlife workers in areas where rabies is enzootic) require antibody titer testing every 2 years. If titers fall under the acceptable level of complete neutralization at a serum dilution of 1:5, a single IM booster vaccine should be administered. Routine antibody testing for travelers in the infrequent risk exposure category is not recommended.

POSTEXPOSURE PROPHYLAXIS (PEP)

All persons exposed to rabies should start by thoroughly washing and cleaning out the wound with soap and water or a virucidal agent. This should be followed immediately by passive rabies immunization with RIG in unvaccinated patients and vaccination with a cell culture rabies vaccine. HRIG is made from the plasma of hyperimmunized healthy volunteers and is not easily accessible in some resource poor settings. Equine rabies immunoglobulin may also be used as an alternative if HRIG is not available.

After a Rabies Workgroup met in 2008 to review current literature and expert opinion, the ACIP published revised guidelines in favor of reducing PEP vaccination from 5 doses to 4 doses.[5] Unvaccinated individuals should receive four 1-mL dose vaccines and RIG promptly after being exposed to the rabies virus. For adults and older children, the only acceptable area to administer the vaccine is in the deltoid area. In younger children, the outer thigh can be used as well. Vaccine should never be administered in the gluteal area because efficacy is decreased.

The first dose of the vaccine should be administered as soon as possible after the exposure on what is considered day 0. It can also be started weeks to months after exposure within the incubation period if signs and symptoms of rabies have not yet appeared. The next 3 doses should then be administered on days 3, 7, and 14 after the first vaccination. Serum antibody titer testing is not recommended for healthy patients as the vaccine has been shown to consistently produce adequate VNAs.

For immunosuppressed persons, rabies PEP should be administered by using the 5-dose vaccine regimen (ie, 1 dose of vaccine on days 0, 3, 7, 14, and 28). Immunosuppressed patients should undergo rabies serum antibody testing 1 to 2 weeks after the fifth dose of vaccine. The WHO specified minimum serum antibody concentration of 0.5 IU/mL is widely used as a measure of adequate seroconversion after vaccination.[2]

RIG should only be administered once on day 0 to exposed humans who have never previously received a complete vaccination regimen (pre- or post-exposure). If RIG administration is delayed, it can be administered at any time up to day 7.2 HRIG is intended to provide passive rabies VNAs while the active antibody production is occurring. After day 7, we presume that antibodies have already been produced from vaccine administration. The recommended dose for patients of all ages is 20 IU/kg of body weight. RIG should be

infiltrated around the wound(s) as much as possible and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. RIG should be administered in a different syringe than the vaccine. No more than the recommended dose should be given because it may suppress active immunity production.[3]

Persons who have previously received complete vaccination regimens (pre-exposure or postexposure) with a rabies vaccine and have a documented rabies virus neutralizing antibody titer should receive only 2 vaccine injections 3 days apart (i.e. days 0 and 3). RIG should not be administered.

If an individual has a repeat exposure within 3 months, RIG and vaccine are not indicated. However, if the repeat exposure occurs >3 months, then the protocol for postexposure prophylaxis in a person who has been previously vaccinated should be followed (i.e. IM injection of vaccine on days 0 and 3).[2]

Minor deviations from the schedule by a few days are inconsequential. The schedule should be resumed with the same intervals between doses. For more substantial deviations from the schedule, antibody titers should be checked 1–2 weeks after the final dose of the vaccine is administered, as effects have not been properly studied.

Post exposure prophylaxis can be discontinued if the appropriate diagnostic laboratory testing (i.e., the direct fluorescent antibody test) concludes that the animal in question was not rabid.

ADVERSE EFFECTS AND SPECIAL CONSIDERATIONS

Serious hypersensitivity, neurological, and fatal adverse events following immunization are extremely rare. Considering the risk of death from rabies, there are no contraindications to rabies vaccination. Local symptoms of erythema, pain and swelling at the site of injection commonly occur. Mild systemic symptoms such as transient fever, headache, dizziness, nausea, and abdominal pain can present in about 5–15% of people after receiving the vaccine.[2] Prophylaxis should not be discontinued or interrupted because of minor or local adverse events.

Rabies vaccines and RIG should be administered normally to infants and children. Limited data suggests that rabies vaccines are safe in pregnancy and is not associated with abortion, premature births, or fetal abnormalities.[7]

Some studies suggest that antimalarial prophylaxis with chloroquine may blunt the immune response to rabies vaccine. According to the WHO, the effect of antimalarial agents on antibody production is unlikely to be clinically significant. They previously recommended IM over ID administration in persons taking antimalarial prophylaxis but removed this statement from their 2018 position paper.[2]

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