Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Siegel J., 2024. Risk Reduction Strategies for Rabies Exposures and Prophylaxis in Children. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5348

DOI: https://doi.org/10.18103/mra.v12i4.5348

ISSN: 2375-1924

RESEARCH ARTICLE

Risk Reduction Strategies for Rabies Exposures and Prophylaxis in Children

Jerry Siegel

jerry.siegel.rx@gmail.com

ABSTRACT

Annually, 59,000 people die of rabies, the world's oldest known infectious disease, globally. In the United States, canine rabies has been virtually eliminated but the risk of rabies due to wildlife, especially raccoons, skunks, and bats, has required post exposure prophylaxis (PEP) be administered to more than 60,000 patients annually[1]. In 2021, 5 people in the United States[2] died of rabies mostly due to misinformation or improper treatment. Rabies post exposure prophylaxis consists of three steps, wound washing, administration of human rabies immune globulin (HRIG) and a full course of vaccine[3]. In 2022, Whitehouse[4] published that there were 122 breakthrough rabies infections when PEP was given due to four factors: 1) deviations from core practice 2) delays in seeking health care 3) errors in administration of HRIG 4) comorbidities or immunosuppression. It is estimated that over 40% of PEP administration is given inappropriately.

The publication," Safety, and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure", Human Vaccines & Immunotherapeutics, 17:7, 2090–2096[5], was the first study that prospectively reviewed the use of human rabies immune globulin 150 IU/ml in 30 pediatric patients ages 0.5–14.9 years old.

Globally, 40% of people bitten by animals suspected of being infected with the rabies virus are children under the age of 15.[6]

This paper will look at risk reduction strategies that will include:

A. Proper Identification of major rabies vectors
B. Special risks associated with bat exposures in children
C. Administration of human rabies immune globulin with volume considerations in children
D. Special administration consideration for rabies vaccines
E. "Just -in- time "Education for health care providers

Illustrative cases will be used to demonstrate each of these strategies of risk as well as the strategies for risk reduction.

Background:

Every 9 minutes someone in the world dies of rabies[1]. Annually, 59,000 people die of rabies, the world's oldest known infectious disease, globally. Children under the age of 15 account for 40% of the exposures to rabies. In the United State of America (USA), canine rabies has been virtually eliminated but the risk of rabies due to wildlife, especially raccoons, skunks, and bats, has required post exposure prophylaxis (PEP) be administered to more than 60,000 patients annually. In 2021, 5 people in the USA died of rabies mostly due to misinformation or improper treatment. There is a continuous need for education of the general population as well as health-care workers to reduce the risk association with rabies post exposure. Why is this risk even higher in children?

Children are at a high risk of rabies[7] exposure as they are:

1. More likely to approach animals due to their inquisitive nature.
2. Smaller and closer to the ground, with an increased likelihood of severe bites
3. Less able to defend themselves during an animal attack.
4. Often bitten multiple times, in high-risk areas such as face, head, neck and hands

Introduction

According to the CDC-ACIP guidelines[8] Rabies PEP consists of 3 steps, wound washing, administration of human rabies immune globulin (HRIG) and a full course of vaccine. In 2022, Whitehouse[4] published that there were 122 breakthrough rabies infections when PEP was given due to four factors: 1) deviations from core practice 2) delays in seeking health care 3) errors in administration of HRIG 4) comorbidities or immunosuppression. It is estimated that over 40% of PEP administration is given inappropriately. Improper HRIG is defines as one of the following: not infiltrating wounds with HRIG or only giving HRIG IM (intramuscular) when wounds are present, failure to infiltrate all wounds with HRIG, failure to thoroughly infiltrate wounds with HRIG or failure to administer HRIG at all. Administration into the gluteus instead of the deltoid is ineffective and not giving the 5th dose of vaccine to immunosuppressed patients can result in rabies and death.

Objectives:

The objectives of this review were to assess the risk of each aspect of the administration of PEP and determine the potential risk and develop mitigation strategies to eliminate, decrease or raise awareness to these risks in prevention of rabies to vulnerable populations.

Develop a treatment Map and Decision Tree to determine if, when and what will be done in the event of rabies exposure. Within this decision tree, determine all risks that may occur if wrong decisions are made that do not follow proper protocols from core practice. These include failure to use PEP, delays in PEP, failure to use HRIG, failure to use HRIG properly, failure to vaccinate, failure to vaccinate properly.

A series of 4 case studies was used to focus on different aspects of PEP risk to highlight mitigation strategies. Additional risk points were identified by comparing the products themselves and highlighting the strengths and weaknesses of each product.

PROPER POST-EXPOSURE PROPYLAXIS FOR RABIES EXPOSURE:

WASH
- Wash wound with soap and water
- Use Virucidal if available

HRIG
- Dose 20 IU/kg HRIG (Adult or child actual body weight)
- Infiltrate wound as much as possible with remainder in deltoid or lateral thigh

VACCINE
- Inject vaccine in deltoid on Day 0;3;7;14
- Give 5th dose for immunocompromiised patients

Wildlife
- skunks, raccons, foxes
- bites, scratches licks to open wounds

Domestic Animals
- Dogs, Cats, Ferrets
- bites,scratches, licks to open wounds

Bats
- Known bites
- Wake up in room with bats, slleping child or intoxicated person

Wild Animal Available?
- If No start PEP
- If Yes test for rabies may stop vaccine if negative

Domestic Animal
- If acting abnormal or not avaialable start PEP
- If acting normal quarantine for 10 days and start PEP if acting abnormal or dies then test
- Even if animal has been vaccinated an observation peiriod is warranted after any bite

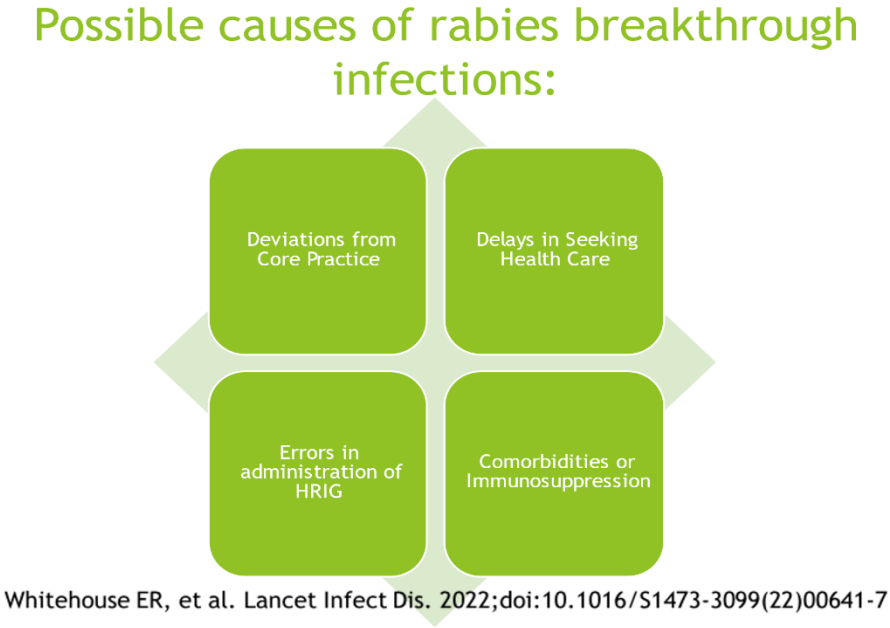
BATS
- Start PEP if bat not avaiable
- If bat available test and treat if positive
- Start PEP if in situations where a bat is found in the
- same room as a sleeping person, unattended child,
- intoxicated or mentally compromised person.

A study[4] was conducted perform a systematic review of post exposure infections after rabies exposure. According to the study, the researchers included 52 articles published between Jan. 1, 1980, and June 1, 2022, which included a total of 122 breakthrough infections.

Of the 122 breakthrough infections, 86 had available data showing a median time from exposure to symptom onset of 20 days (interquartile range = 16-24). Additionally, 115 had data on post-exposure prophylaxis (PEP) use that showed 89 (77%) had received PEP within 2 days of exposure. Of the 116 patients with data on wound severity available, severe wounds — defined as wounds involving multiple wound sites or bites to the head, face, or neck — were common, having been reported in 69% of participants with the available data.

The study also showed that "deviations from core practices" were reported in more than half of cases (56%), whereas other possible causes for breakthrough infections included errors in the administration of rabies immunoglobulin, such as delivery to the wrong site, the wound being sutured before immunoglobulin was administered or not all wounds being penetrated; errors in vaccine administration, such as not completing the vaccine series or receiving the wrong regimen; delays in seeking health care; and comorbidities or immunosuppression.

Whitehouse ER, et al. Lancet Infect Dis. 2022;doi:10.1016/S1473-3099(22)00641-7.



Whitehouse ER, et al. Lancet Infect Dis. 2022;doi:10.1016/S1473-3099(22)00641-7

A. PROPER IDENTIFICATION OF RABIES VECTORS

Case 1: The Feral Cat

14-year-old female reports to a local emergency room in the San Diego, California area after being attacked by a feral cat. The cat had attacked her pet dog and she pulled it away from the dog and so the cat bit and scratched her on the arms and legs in multiple locations. After the attack the cat ran away. She said she lives very close to the Mexican border and stray cats are very common in this area.

She was treated in the emergency room with a tetanus "shot" and her wounds were cleaned up with soap and water. None required stitching. They said they felt there was no need for treatment for rabies since cats do not carry rabies.

RISK:

Cats can occasionally be the victims of rabies, but they are not the cause. There has not been a single confirmed human case of rabies transmitted from a cat in over 40 years in the United States.

Are feral cats from Mexico prone to have rabies? Mexico is still reporting cases of rabies in wildlife. The most recent reported cases were of two cats in Yucatan in 2021 that were infected with a wildlife variant, possibly from coatis – a native mammal.

First case in Mexico of rabies transmitted to humans by a domestic cat. After the cases of rabies that occurred in the state of Oaxaca, now a woman who was bitten by her cat, which was not vaccinated, the first case in all of Mexico of human rabies transmitted by a domestic cat was confirmed.[9]

On November 13, a 29-year-old woman was bitten by a domestic cat she owned that had not been vaccinated against rabies, which exhibited aggressive behavior and died three days later.[9]

RISK MITIGATION:

1. Historical low risk of feral cat rabies in the USA
2. Cat may have been from Mexican origin with possible higher incidence of rabies.
3. Cat was not exhibiting normal behavior as it attacked domestic dogs and human.
4. ED personnel felt that victim behavior pulling the cat away from the dog was responsible for the cat's aggressive behavior and therefore the attack was not unprovoked.
5. The lack of the cat's availability makes the cat's rabies diagnosis unknown.

Based on this assessment would you have administered PEP?

Is there a time limit upon which PEP can be administered?

Even though it is ideal to start PEP as soon as possible after rabies exposure there is no time limit regarding the administration of PEP after exposure.

What is the incubation period for rabies in humans?

The incubation period in humans is typically between 20 and 90 days, although incubation periods as short as 4 days and longer than 6 years have been documented. This variation is probably related to the site of inoculation, the severity of the wound, and the amount of virus introduced.[10]

B. SPECIAL CONSIDERATION WITH BAT EXPOSURES

Case 2: The Bat in the Bedroom

A man in northern Canada wakes up to the sound of his 8 year old daughter screaming and a bat flying around in her bedroom. He chases the bat and kills it with his tennis racket. He places the bat in a garbage bag and placed it out for the trash pick-up. His wife woke up to all this commotion and asked what was going

on and asked if her daughter was bitten. He said he did not think so and asked her the same question. She also replied that she did not think she had been bitten. The next day they called for advice and were told to retrieve the bat from the garbage, but it was already gone so they were advised to go to the local emergency department for evaluation.

RISK:

What is the incidence of Bat rabies in North America?[11]

In 2020, nearly 6% of approximately 24,000 bats tested for rabies were confirmed as positive. Jan 6, 2022

People cannot get rabies just by being near a bat.[12]

What animal causes the most rabies in the US?

Contact with infected bats is the leading cause of human rabies deaths in this country; at least 7 out of 10 Americans who die from rabies in the US were infected by bats.

Most people who have been bitten by a bat report a stinging or needle prick sensation. However, bat bites may not be noticed, especially if someone is asleep, and bat bites may leave little or no evidence of a wound or puncture.

Bat Bite on Finger

If the bat could have been retrieved it could have been tested and if it were negative no PEP would have been necessary assuming only one bat was in the bedroom. If positive, then PEP was warranted even without any visible bite wounds.

Without the bat availability both the man who fought the bat and his daughter who woke up with the bat in her bedroom should start PEP within 24 hours of the incident. Even though only 6% of bats test positive to rabies 70% of the deaths due to rabies are from bats. Mostly this is due to either failure to implement PEP, refusal to start PEP or lack of awareness or the risks related to bat rabies.

Special Considerations when administering PEP for bat bites.

1. When there is no visible bat bite the HRIG dose is 20 IU/kg and the entire dose is given IM in the Deltoid in divided doses but in anatomical sites distant from the rabies vaccine.
2. Do not mix the rabies vaccine and HRIG in the same syringe as it will be neutralized.
3. If there is a visible bite mark as demonstrated in the photo above, then all steps including wound washing and infiltration with HRIG should be included.
4. Caution should be exercised in sites such as fingers, toes, lips, and nose to prevent compartment syndrome. *

*Compartment Syndrome: An intense condition of painful swelling and pressure within a musculoskeletal compartment that may inhibit adequate blood supply to an area, associated with excessive infiltration of HRIG into a wound[1]

In a prospective study involving 100 high-risk injections (fingers and toes), **no case of**

compartment syndrome was found. The study authors never encountered any cases of compartment syndrome in the past 2 decades.[2]

: 1. Bookstaver PB, Akpunonu P, Nguyen HB, Swan JT, Howington GT. Administration of rabies immunoglobulin: Improving evidence-based guidance for wound infiltration. *Pharmacotherapy*. 2021 Aug;41(8):644-648. doi: 10.1002/phar.2604. Epub 2021 Jul 5.

2. Shantavasinkul P, Wilde H. Postexposure prophylaxis for rabies in resource-limited/ poor countries. *Adv Virus Res*. 2011; 79:291-307. doi:10.1016/B978-0-12-387040-7.00013-5

RISK MITIGATION[12]

1. Education is imperative on rabies risk in bats.

a. Rabies in bats cannot be detected by looking at them.
b. Rabid bats are more likely to fly in the daytime.
c. Rabid bats may struggle to get off the ground.
d. The rabies virus is active for 24 hours after a bat is dead.
e. Never handle a bat
f. Bats can bat through cotton.
g. Bats do not fly into your hair and get stuck (old wives' tale)
h. Only handle bats with leather gloves
i. You may not feel or see a bat bite.
j. Waking up in a bedroom with a bat may warrant PEP.
k. You cannot get rabies from a bat just flying nearby.
l. You cannot get rabies from bat guano.

15,000 year old Bat Gauno in the Caverns near San Antonio, Texas.

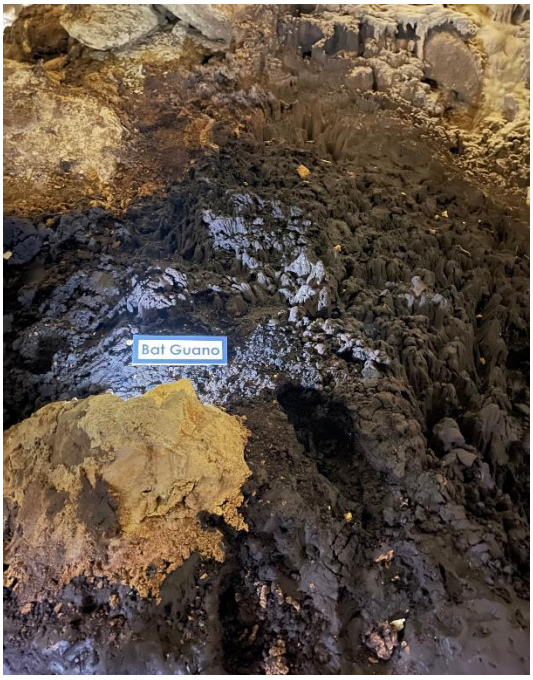


Photo credit J.Siegel

2. Administration of HRIG infiltration is necessary when bat bite is visible.

3. Administer carefully in small areas like fingers, toes, lips, and nose though compartment syndrome is unlikely.

C. Administration of human rabies immune globulin with volume considerations in children

Case Study 3: Skunk is too Cute!

RISK: INFILTRATE ALL WOUNDS

A 6-year-old girl sees a skunk in the backyard during the day while she is playing. She thinks the skunk is so cute and wants to pet it.

The skunk runs towards her initially then sprays her and stops momentarily and then attacks her biting her multiple times on the arms neck and face.

She weighs 66 pounds or 30 kg. The HRIG dose is calculated to be 20 IU/kg X 30kg = 600 IU.

For the 300 IU/ml product that equals 2 ml

For the 150 IU/ml product that equals 4 ml.

There are a total of 10 bites and numerous other scratches.

It is estimated that at least 4 ml will be necessary to infiltrate all wounds. The concentrated product will need to be diluted with D5W (Dextrose 5% in water) 1:1 to a final concentration of 150 IU/ml.

RISK MITIGATION:

1. 40% of the victims of rabies attacks are children under the age of fifteen.
2. Children are more vulnerable for high-risk injury because of their short stature and more likely to get bit above the neck.
3. Children are curious and may think all wild animals are safe.
4. Strategy is to educate children and parents about the risks of rabies and the mammals.

The author developed a board game "RABIDOPOLY'© to provide education to both children and adults about rabies prevention and PEP use in a fun and memorable way. By playing this board game the players learn which mammals are high risk for rabies and which mammals are not vulnerable to the rabies virus. It teaches about the need to vaccinate domestic animals and what to do in case you are bitten or scratched by a potentially rabid animal. The player collects game pieces such as soap, HRIG (rabies immune globulin) and rabies vaccine vials. The goal of the game is to collect 1 soap, I HRIG and 4 vaccines for full protection and WIN the game. 3-D settings enhance the visualization of where skunks/raccoons and foxes are most likely to be encountered. A series of game cards tell the player what actions to take after they land on starred sections of the board tracing the outline of a bat.

The author's granddaughter improved her knowledge of rabies prevention from 20% to 80% after one session of playing the game.

The plan is to expand the use and testing of this game to larger cohorts of children and adults with different levels of education and testing.

RABIDOPOLY BOARD GAME

Current HRIG products in the USA

Imogam Rabies-HT is no longer being distributed (12/31/22)

KEDRAB FDA approval **August 2017**	HyperRAB FDA approval **February 2018**
Kedrion Biopharma Inc.	Grifols Therapeutics LLC
Strength 150 IU ml	Strength 300 IU ml
Dose 20 IU/kg: (30 kg = 600 IU = 4 ml)	Dose 20 IU/kg: (30kg = 600 IU = 2 ml)
Vial sizes 2 ml ;10 ml	Vial sizes 1 ml ; 3 ml ; 5 ml
Diluent NS (> 1:1 if required)	Diluent D5W* (only 1:1)
RT stability 1 month	RT stability 6 month
Replacement program YES	Replacement program NO
Patient assistance YES	Patient assistance YES
Pediatric Safety Data YES	Pediatric Safety Data NO
	• Corn allergy precaution

KEDRAB [package insert]. Fort Lee, NJ: Kedrion Biopharma Inc.; 2017(rev2021)
HyperRAB [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; 2018(rev2021)

See Full Prescribing Information for each product

RISK: HRIG PRODUCT SELECTION [13,14,15,16]

CONCENTRATION

Choosing the proper HRIG is not without risk. HyperRab[16] replaced HyperRab S/D[14] in 2018 as a concentrated product at 300 IU/ ml instead of 150 IU/ml as the standard concentration. At the time there were two other products Kedrab[13] and Imogam[15] at the standard concentration. There was concern that there would be confusion

and medication errors with two different concentrations on the market.[17]

RISK MITIGATION

1. After concerns were reported to ISMP (Institution for Safe Medication Management) they published a warning regarding this potential risk.
2. Imogam Rabies-HT is no longer being distributed or produced.
3. HyperRab S/D is no longer being produced.
4. Kedrab is still being produced but is only 150 IU/ml, so the risk of error remains.

VIAL SIZE

HyperRab comes in 3 vial sizes 1,3 and 5 ml but their physical appearance looks the same. The risk is that the vials could be mixed up and the wrong dose given due to a look-alike error. The Kedrab comes in two vial sizes 2 ml and 10ml that are physically distinct, diminishing the risk of this type of error.

RISK MITIGATION

1. After concerns were reported to ISMP (Institution for Safe Medication Management) they published a warning regarding this potential risk.[19]
2. The HyperRab vials are now color-coded, and bar coded with vertical bar codes.
3. The Kedrab vials are also now color-coded with vertical bar codes instead of horizontal bar codes that were harder to read.

RISK: DILUTION

If the patient has multiple bites, especially children, HRIG volume is important, and dilution of the concentrated product may be necessary. Only D5W can be used at a ratio of 1:1 to a concentration of 150 IU/ml. D5W may not be readily available and is not available in prepackaged vials. In addition, dextrose should not be used in patients with corn allergies.

RISK MITIGATION:

1. **Assess the anticipated volume of HRIG required prior to the start of administration.**
2. For children when multiple bites are present the use of a 150 IU/ml product may be warranted.
3. If the concentrated product is used assure that it is properly diluted with D5W at 1:1.
4. If greater than 1:1 dilution is necessary Kedrab may be diluted > 1;1 with normal saline.
5. **Doses of HRIG > 20 IU/kg are not warranted as this may negatively impact the vaccine response.**

RISK: PRODUCT REPLACEMENT

HRIG Products are generally stored refrigerated but should be allowed to warm to room temperature prior to administration. Once it reaches room temperature it cannot be placed back in the refrigerator for original dating. To prevent this pharmacist usually keep the products in the refrigerator until just before use. Administration of cold HRIG increases pain upon infiltration or IM injection.

RISK MITIGATION:

1. To encourage warming of the HRIG in advance without wasting the product, Kedrion introduced a product

replacement program to assure that the product would be replaced in the event of temperature excursion and loss due to expiration. The current Room temperature stability for Kedrab is 30 days.

2. The current room temperature stability for HyperRab is 6 months but there is no product replacement program to date.

RISK: PEDIATRIC SAFETY DATA

Until recently there had not been any studies specifically designed to look at the pediatric population for safety and efficacy data with the use of HRIG for rabies prevention with PEP.

RISK MITIGATION:

Safety and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure Nicholas Hobart-Porter,[a] Michal Stein,[b] Naveh Toh,[b] Novinyo Amega,[c] Huy-Binh Nguyen,[c,*] and James Linakis[d,*]

Hum Vaccin Immunother. 2021; 17(7): 2090–2096.

This was a study of 30 patients in the age range of 6 months to 15 years old. These results demonstrate that HRIG 150 IU/ml is well tolerated and effective in pediatric patients as a component of PEP. To the authors' knowledge, this study is the first to establish pediatric safety and efficacy of HRIG in the US.

A follow up paper, **Commentary on the implications of safety and efficacy studies in pediatric patients with administration of human rabies immune globulin (HRIG)?**[19] Jerry Siegel[1], Karl Kappeler[1] Hum Vaccin Immunother . 2022 Nov 30;18(5):2054262. Discussed the implications of this safety data and the risk associated with using products in pediatric populations without safety data.

A new observational study is now recruiting patients to look at 50 patients from 2/23 till 6/24 to determine what adverse events may occur in patients up to age 17. This study is looking only at safety and not efficacy as far as the administration of HRIG except for ultimate outcome for patient infection. **Survey of Human Rabies Immune Globulin Safety in Children** conducted by the Houston Methodist Hospital and sponsored by Grifols.

D. Special administration consideration for rabies vaccines

RISK: WHY IS THERE A DELAY IN SEEKING RABIES TREATMENT

The original vaccines were doses of 5- 10 ml given in the stomach over 14-21 days.[20] While this is true in some third world countries the modern vaccines are given as 1 ml IM administration in the deltoid muscle over 4 days with 2 weeks. (a 5th dose is given for patients that are immunocompromised) *

Today there still is a common misperception that rabies treatment is still this very painful multiple injection stomach injection therapy thus causing hesitancy seeking treatment.

RISK MITIGATION

EDUCATE PATIENTS AND HEALTH CARE PRACTITIONERS ABOUT THE DIFFERENCE IN VACCINES AND PROPER ADMINISTRATION[21]

1. HDCV vaccine (Imovax, Sanofi Pasteur)[22] is produced in human diploid cell

culture. PCECV vaccine (RabAvert, Bavarian Nordic)[23] is produced in chick embryo cell culture.

2. Both vaccines considered safe, effective and interchangeable. Therefore, if the patient received one brand on day 0 and it is not available on day 3 the other brand is acceptable.
3. Never give the vaccine in the gluteus maximus. If it is administered in this site, it does not count and must be repeated in a proper site. (Deltoid or lateral thigh)
4. What happens if the patient misses their scheduled vaccine dose? Just give the vaccine and pick up the schedule you do not need to start over.
5. A pregnant woman should receive rabies vaccine if indicated. No fetal abnormalities have been reported with the rabies vaccine.

- For the first time a PEP failure was reported. The prophylaxis failure was imputed to lack of response to rabies vaccine due to the presence of an unsuspected monoclonal gammopathy, with no evidence of vaccine-induced immune response in the patient, that is, unsuspected immunocompromise. A Sufficiency of Caution.
    - Catherine M Brown, Alfred DeMaria, Jr Author Notes
    - Clinical Infectious Diseases, ciad169, https://doi.org/10.1093/cid/ciad169
    - Published: 28 March 2023

RISK MITIGATION:

Since the post pandemic era the number of primary immunodeficiency disorders has risen to > 480 with our better understanding of genetic defects and enzyme deficiencies. Even though the PEP guidelines (ACIP) reduced the number of vaccine doses from 5 to 4 except for immune compromised patients this case illustrates that the real possibility of unsuspected immunocompromised patients is quite possible. In the case of rabies, especially if the mammal is confirmed to be positive, the additional 5th dose or testing for the presence of a neutralizing antibody or RVU titer might be warranted. [25,26]

RISK: IMPROPER NEEDLE FOR INJECTION

Intramuscular injections should be given with the proper needle length and gauge based on patient weight and age. For Rabies vaccines the injection should always be in the Deltoid muscle or lateral thigh for children but never in the gluteus maximus due to poor absorption.

Imovax is provided as a lyophilized vial with a prefilled syringe and a needle for reconstitution. This 18-gauge needle is intended for reconstitution only and the provider must use their own proper needle size and gauge for administration.

Rabivert is provided as a lyophilized vial with a prefilled syringe of diluent and two needles. One for reconstitution and a one-inch needle for administration. (This is not a safety needle)

After surveying two major medical centers it was discovered that some nurses use the Imovax needle for both reconstitution and administration. Some nurses use the Rabivert needle provided for all patients without the

use of a safety needle. Some nurses discard the needle provided and use a proper sized safety needle dependent upon the size of the patient. Use of Safety needles is a Joint Commission Imperative to prevent needle sticks.

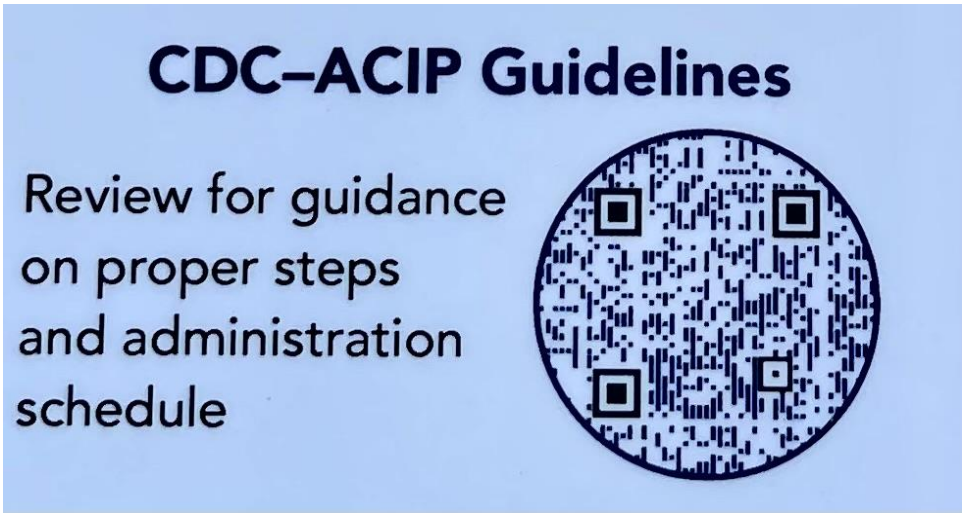
RISK MITIGATION:

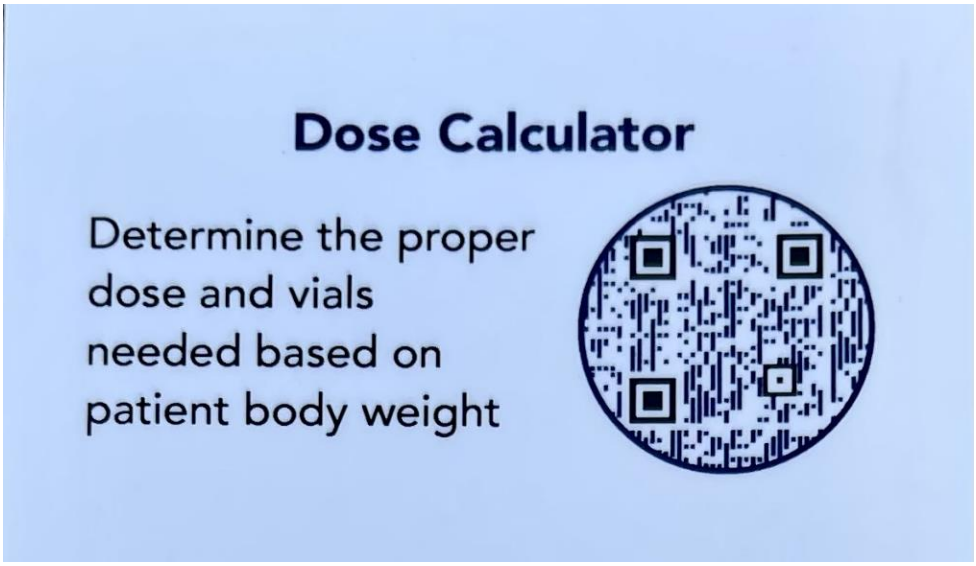
1. Education needs to be provided to health care providers regarding proper sites for injection of rabies vaccines.
2. Education needs to be provided to health care providers regarding proper use of safety needles and size and gauge of needles for patients based on size of patient.
3. Recommendation was made to Bavarian-Nordic to remove the one size fits all non-safety needle from their current vaccine packaging.

E. "Just -in- time "Education for health care providers

The author has presented to over ten emergency nursing association (ENA) meetings over the past two years and received feedback that the most important issue related to treatment for rabies patients is education at the time of treatment. Since rabies treatment is not something that is done frequently in the United States being up to date on protocols is not easy to maintain and familiarity with guidelines, dosing and calculations can be challenging. In order to facilitate this request as a consultant to one of the product providers an educational brochure was developed to link QR codes with QR (quick reference) photo links that can directly take the provider with the use of a smart phone to the CDC-ACIP guidelines, a dosage calculator and a video that will show the proper administration technique for human rabies immune globulin. The nurses refer to this as "just in time" education as they can refresh their memory of the essentials of proper post-exposure prophylaxis (PEP). Remember rabies treatment is only 100% effective if administered properly.[27]

Use "just in time "education tools such as QR codes to directly link dose calculators and administration videos to the HCP so that they can reduce the chance of dosage error and administration error when giving HRIG.





Discussion

This paper has illustrated the numerous risk points for errors that can and do occur when the opportunity for post exposure prophylaxis (PEP) presents. Lack of knowledge of rabies generally is prevalent in both adult and pediatric populations and likewise amongst healthcare providers. Approximately 4.7 million people in the US report to the Emergency departments or other health care facilities with "dog" bites alone but because of the vaccine program in the USA it is rare that the victims of these bites will require PEP. If the patient was bitten by a dog outside the USA, then PEP may in fact be warranted and all unvaccinated and stray dog bites may warrant treatment. Cats have not been associated with rabies in the USA for over 40 years but still should be vaccinated as domestic animals to prevent them from becoming a reservoir. All ferrets should be vaccinated as domestic pets and some states, such as California have banned ferrets as domestic pets. The predominate risk in the USA is exposure to wildlife especially raccoons, bats, skunks and foxes. Some specific areas like Puerto Rico are mongoose specific and Alaska is specific to the Arctic Fox. Only Hawaii is free from the risk of rabies from wildlife.

One of the most common errors in PEP is failure to infiltrate the wounds and therefore not neutralizing the virus at the bite site. Proper infiltration would include giving as much of the HRIG as possible with the remaining portion given IM in a site opposite the vaccine. When there is a known bite site, simply giving the HRIG IM with no infiltration allows for transit of the virus through the neuromuscular junction prior to the vaccine titer rising and holding the virus in check.

Vaccine errors can originate by using the wrong needle or site of injection.

1. Use a safety needle of the proper length and gauge for the patients' anatomy and age.
2. Inject the vaccine in the Deltoid muscle or lateral thigh but never in the Gluteus Maximus
3. Give the vaccine on Day 0, 3, 7 14 and (28 if immunocompromised)
4. Do not give vaccine mixed with HRIG or same site as HRIG.

Even though the frequency of rabies in the USA has diminished greatly since vaccination of canines and other domestic pets has become routine practice, the risk of rabies remains relatively constant due to the reservoir of rabies in bats and skunks throughout the country. The death rate related to rabies infection remains nearly 100% but it is nearly 100% preventable[26] with proper administration of prophylaxis post exposure to high-risk mammals. The latter is dependent on proper education and training.

RESULTS TO DATE

To date, presentations and publications were generated to increase rabies awareness. Manufacturers have changed vial bar coding and label coloring while QR codes are utilized for PI, dose calculators and administration videos to improve safety. A children's board game "Rabidopoly" has been developed to improve education for children. Even though rabies is 100% preventable[26] if PEP is given properly there are significant opportunities for improvement for awareness and risk reduction with additional education tools. Rabies remains nearly 100% fatal.

Conflict of Interest Statement:

None

Funding Statement:

None

Acknowledgement Statement:

Kedrion Biopharma and Bavarian Nordic

References:

1. CDC. Every 9 minutes, someone in the world dies of rabies [press release]. September 28, 2015. www.cdc.gov/media/releases/2015/p0928-rabies.html. Accessed April 22, 2019.

2. https://www.everydayhealth.com/rabies/people-died-of-rabies-in-the-us-the-most-in-a-decade/

3. Centers for Disease Control and Prevention. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2010;59(2):1-9.

4. Human rabies despite post-exposure prophylaxis: a systematic review of fatal breakthrough infections after zoonotic exposures Erin R Whitehouse, PhD et al Published: December 16, 2022 DOI:https://doi.org/10.1016/S1473-3099(22)00641-7

5. Safety, and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure", Human Vaccines & Immunotherapeutics, 17:7, 2090–2096

6. https://www.who.int/news-room/fact-sheets/detail/rabies#:~:text=It%20causes%20tens%20of%20thousands,and%20prevention%20of%20dog%20bites

7. https://www.stanfordchildrens.org/en/topic/default?id=rabies-in-children-90-P02537

8. https://www.cdc.gov/mmwr/volumes/71/wr/mm7118a2.htm#:~:text=Report%20(MMWR) -,Use%20of%20a%20Modified%20Preexposure%20Prophylaxis%20Vaccination%20Schedule%20to%20Prevent%20Human%20Rabies%3A%20Recommendations%20of%20the%20Advisory%20Committee%20on%20Immunization%20Practices%20%E2%80%94%20United%20States%2C%202022,-Weekly%20/%20May%20

9. https://mexicodailypost.com/2023/01/02/first-case-in-mexico-of-rabies-transmitted-to-humans-by-a-domestic-cat/#:~:text=First%20case%20in%20Mexico%20of%20rabies%20transmitted%20to%20humans%20by%20a%20domestic%20cat,-January%202%2C%202023&text=After%20the%20cases%20of%20rabies,a%20domestic%20cat%20was%20confirmed.

10. http://publichealth.lacounty.gov/vet/rabiesmanual/clinical.htm#:~:text=The%20incubation%20period%20in%20humans,the%20amount%20of%20virus%20introduced.

11. https://www.usnews.com/news/health-news/articles/2022-01-06/beware-of-bats-after-3-recent-rabies-deaths-cdc-says#:~:text=The%20Top%2010%20Causes%20of%20Death%20in%20the%20U.S.&text=Despite%20deaths%20from%20rabies%20being,rabies%20were%20confirmed%20as%20positive.

12. https://www.cdc.gov/rabies/animals/bats/index.html

13. KEDRAB [package insert]. Fort Lee, NJ: Kedrion Biopharma Inc.; 2017.

14. HyperRAB S/D [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; 2012

15. IMOGAM [package insert]. Swiftwater, PA: Sanofi Pasteur; 2014.

16. HyperRAB [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; 2018.

17. ISMP. *ISMP Medication Safety Alert. Acute Care edition*. June 28, 2018;23(13):2.

18. ISMP. Rabies immune globulin vial sizes look similar. https://www.ismp.org/resources/rabies-immune-globulin-vial-sizes-look-similar. Accessed August 12, 2019.

19. Jerry Siegel[1], Karl Kappeler[1] Hum Vaccin Immunother. 2022 Nov 30;18(5):2054262.

20. Rohde RE. Common Myths and Legends of Rabies. Rabies. 2020:69–78. doi: 10.1016/B978-0-323-63979-8.00005-2. Epub 2019 Apr 19. PMCID: PMC7152084.

21. Siegel J. Rabies Immune Globulin: Ensuring Administration Safety. Pharmacy Practice News Special Edition. 2019: 47-52.

22. https://www.fda.gov/media/75709/download Imovax, Sanofi Pasteur

23. https://www.fda.gov/media/83874/download?attachment RabAvert, Bavarian Nordic

24. Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2010;59(RR02):1-9.

25. Scott TP, Nel LH. Subversion of the immune response by rabies virus. *Viruses*. 2016;8(8): e231.

26. Abela-Ridder B. Rabies: 100 per cent fatal 100 per cent preventable. *Vet Rec*. 2015;177 (6):148-149.

Additional References

1. Fooks AR, Banyard AC, Horton DL, et al. Current status of rabies and prospects for elimination. *Lancet*. 2014;384(9951):1389-1399.

2. Lackay SN, Kuang Y, Fu ZF. Rabies in small animals. *Vet Clin North Am Small Anim Pract.* 2008;38(4):851-861.

3. Rupprecht C,Kuzmin I, Meslin F. *F1000Research*. 2017;6:184. doi: 10.12688/f1000research.10416.1

4. CDC. What are the signs and symptoms of rabies? www.cdc.gov/rabies/symptoms/index.html. Accessed August 12, 2019.

5. Hampson K, Coudeville L, Lembo T, et al. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis.* 2015;9(4):e0003709.

6. Pieracci EG, Pearson CM, Wallace RM, et al. Vital signs. Trends in human rabies deaths and exposures—United States, 1938-2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(23): 524-528.

7. CDC. Rabies. Human rabies. https://www.cdc.gov/rabies/location/usa/surveillance/human_rabies.html. Accessed August 12, 2019.

8. CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2008;57(RR-3):1-28.

9. Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine. 2007;25(44):7605-7609.

10. Kastango ES, Bradshaw BD. USP Chapter 797: establishing a practice standard for compounding sterile preparations in pharmacy. Am J Health Syst Pharm. 2004;61(18):1928-1938.

11. World Health Organization. WHO/EMC/ZOO/96.6. WHO recommendations on rabies post-exposure treatment and the correct technique of intradermal immunization against rabies. www.who.int/rabies/en/WHO_

recommendation_post_exp_treatment.pdf.
Accessed August 27, 2019.

12. Wilde H, Sirikawin S, Sabcharoen A, et al. Failure of postexposure treatment of rabies in children. Clin Infect Dis. 1996;22(2):228-232.

13. Centers for Disease Control and Prevention. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2008;57(RR-3):1-28.

14. Wilde H, Sirikawin S, Sabcharoen A. et al. Failure of postexposure treatment of rabies in children. *Clin Infect Dis*. 1996;22(2):228-232.

15. Centers for Disease Control and Prevention. Animals and Rabies. Published January 6, 2022. Accessed January 13, 2023. https://www.cdc.gov/rabies/animals/index.html

16. Moran GJ, Talan DA, Mower W, et al. Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. Emergency ID Net Study Group. JAMA. 2000;284(8):1001-7.
doi: 10.1001/jama.284.8.1001.