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Redefining ED Utilization: A Rabies Post-Exposure Prophylaxis Perspective

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Redefining ED Utilization: A Rabies Post-Exposure Prophylaxis Perspective

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Abstract

Rabies, though rare in the United States, remains a lethal viral disease with significant public health implications. Post-exposure prophylaxis (PEP) through timely administration of rabies vaccines and rabies immune globulin (RIG) is critical for preventing the progression of the virus following potential exposure. However, the current system of healthcare delivery in the United States has witnessed an alarming trend: the unnecessary utilization of emergency department (ED) visits for rabies PEP, including follow-up vaccinations. This paper aims to examine and address this issue through a review of the factors contributing to the inappropriate use of ED services for rabies treatment.

Through a review of existing literature, this paper highlights the complexities surrounding rabies PEP, including accessibility to vaccination clinics, patient education, and healthcare policy implications. The misuse of ED resources for rabies PEP not only strains healthcare infrastructure but also leads to inefficiencies in patient care and increased healthcare costs. By understanding the underlying issues, healthcare providers and policymakers can implement targeted interventions to redirect patients to more appropriate and cost-effective care settings. By redefining the standard of rabies PEP delivery, healthcare systems can optimize resource allocation, improve patient outcomes, and mitigate the burden on EDs in the Commonwealth.

This review highlights the substantial potential for cost reduction associated with optimizing rabies PEP. A modest decrease of 27% in emergency department visits would effectively address the cost burden of medication provision at secondary rabies care centers. Reducing the current number of return visits to the ED for the follow-up vaccination series by 50% could result in the state healthcare system saving over $1 million. The ancillary benefits, such as reduced ED wait times leading to reduced mortality rates, hold promise for additional cost-saving advantages for the Commonwealth.

This paper reiterates the importance of continued reevaluation of healthcare utilization patterns and advocates for a paradigm shift towards more efficient and patient-centered care delivery models. By addressing the root causes of unnecessary ED visits for rabies treatment, stakeholders can work towards enhancing the accessibility, affordability, and effectiveness of rabies PEP while ensuring the prudent use of healthcare resources.

Acronyms & Abbreviations

ACIP - Advisory Committee on Immunizations Practices
CDC – Centers for Disease Control
CNS – Central nervous system
COVID-19 – Coronavirus Disease 2019
dFA - Direct fluorescent antibody
ELISA - Enzyme-linked immunosorbent assay
ESI – Emergency Severity Index
HHS – U.S. Department of Health and Human Services
RIG – Rabies Immune Globulin
PEP – Post-exposure Prophylaxis
RFFIT - Rapid Fluorescent Focus Inhibition Test
RREID - Rapid rabies enzyme immunodiagnostic
U.S. – United States
USDA – United States Department of Agriculture
WHO – World Health Organization

Introduction

Overview of Rabies Virus

Rabies, a single-stranded RNA zoonotic viral disease from the genus Lyssavirus of the family Rhabdoviridae, poses a grave threat to human health, transmitted primarily through the bite or scratch of a rabid animal. [1-3] Its impact on the nervous system is fatal if left untreated.

Rabies manifests in two main forms: furious rabies, which accounts for approximately 80% of cases, and paralytic rabies. Patients experience acute encephalitis accompanied by various neurological symptoms. During the prodromal period, both furious and paralytic rabies initially present with flu-like symptoms such as fever, itching, tingling sensations, among others. [2,3]

Furious rabies is characterized by hyperactivity, confusion, agitation, hyperaggressive behavior, hallucinations, and other manifestations. On the other hand, paralytic rabies presents with symptoms such as drowsiness, difficulty swallowing, fear of water, slurred speech, and other neurological signs. Once the virus enters the body, it progresses from muscle tissue to acetylcholine receptors and travels through the central nervous system (CNS) via axonal transport along motor nerve axons. Once in the CNS, the virus spreads to various organs including the kidneys, salivary glands, heart, gastrointestinal tract, and throughout the body.

Transmission of the disease predominantly occurs through contact with the saliva of infected wildlife such as bats, dogs, skunks, and raccoons, among others. The significant global impact of rabies is evident in the substantial toll it takes, resulting in over 59,000 deaths annually and causing a loss of 3.7 million disability-adjusted life years. [2,4] Despite advances in medical science, once symptoms manifest, the disease is fatal. Despite the high virulence of the rabies virus, the disease is 100% vaccine-preventable.

The United States (U.S.) witnesses a significant incidence of animal bites, with an estimated 4 million occurrences annually, resulting in over 55,000 individuals receiving PEP each year. [2] Based on current estimates, there is a discernible trend when examining historical data. For instance, estimates from 1981 indicated approximately 16,000 annual PEP cases, which surged to around 39,000 by 1996. [5,6] States like Kentucky have seen a surge in animal rabies cases, registering a notable 63.6% increase from 2017 to 2018, with skunks emerging as the state's primary carrier. The financial burden of rabies treatment is substantial, ranging from $1,000 to $6,000 per course, exclusive of hospital charges. The cost-effectiveness of treatment, reflected in the average cost per life saved, spans a wide spectrum from $10,000 to $100 million, contingent upon factors such as regional rabies probability and other variables.[2]

Despite the World Health Organization (WHO) designating several countries, including the United States, as dog rabies-free, the nation struggles with diverse viral variants and animal reservoirs.[7] This demands ongoing investment in monitoring and prevention efforts. Public

health expenditures soar to half a billion dollars annually, sustaining surveillance programs that rigorously test 30 suspected rabid animals per 100,000 citizens each year. [2]

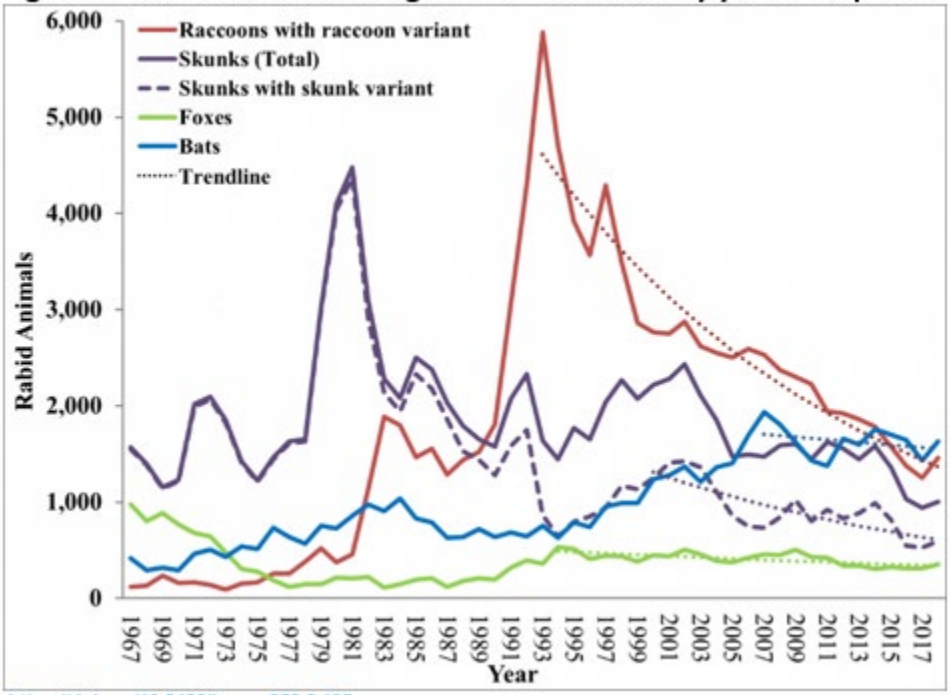
History of Rabies

The earliest documented case of Rabies traces back over 4000 years to Babylon. However, it wasn't until the 19th century that the etiology of this fatal disease was pinpointed to be viral in nature. In 1885, Louis Pasteur marked a significant milestone by administering the first rabies vaccination to a human who had suffered a bite from a rabid dog. [1,2,7]

In the United States, surveillance and prevention efforts against rabies have been ongoing for decades. In 1944, both human and animal rabies were classified as nationally notifiable diseases, catalyzing a collaborative effort between federal and state authorities to collect surveillance data. This robust surveillance system encompasses more than 125 laboratories that conduct the fluorescent antibody test, enabling passive monitoring of rabies trends across the nation. [2]

Wildlife constitutes the majority of rabies cases in the US, accounting for 92.7% of reported cases in 2018, with bats comprising a significant portion at 33%. **Figure 1** illustrates the incidence of rabies among wildlife species in the United States from 1967 to 2018. [1,2] It's also worth reinforcing that cross-species transmission of the rabies virus is possible.

Figure 1. Cases of rabies among wildlife in the U.S. by year and species



https://doi.org/10.2460/javma.256.2.195

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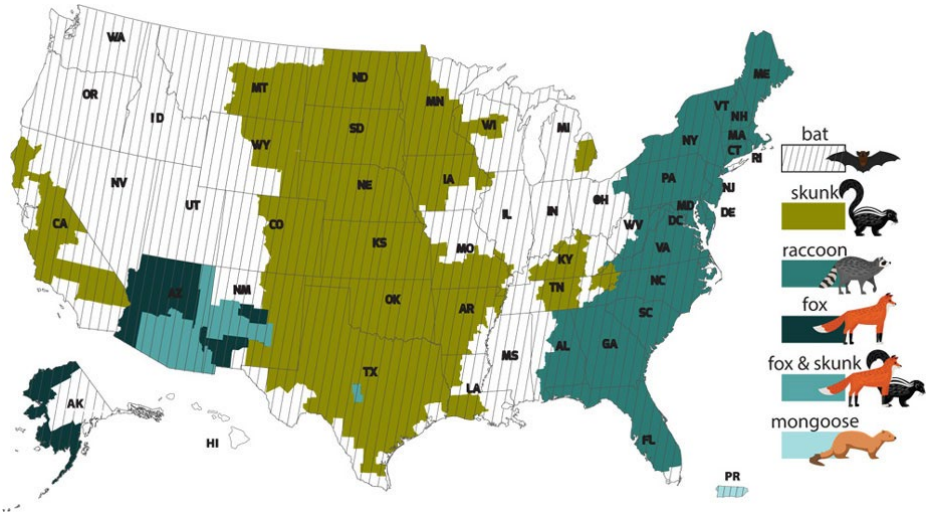
Despite the common association of rabies with dogs, preventive measures and widespread vaccination have drastically reduced the incidence of rabies in domestic canines. Notably, recent data illustrate a steady rise in rabies cases among bats. Between 2013-2017 review by the CDC found that bats with rabies were found in every state except for Hawaii. **Figure 2** illustrates the regions of the U.S. with the most dominant wildlife species with the disease. In the CDC's 2018 report, it was noted that cats are more likely to test positive for rabies (1.1%) compared to dogs (0.3%). [2]

Figure 2. Distribution of common rabies wildlife within the U.S.



https://www.cdc.gov/rabies/location/usa/surveillance/wild_animals.html

Diagnosis:

According to the CDC and WHO no single test can definitively diagnose a human with rabies infection before the onset of clinical disease. Diagnosis is primarily via clinical presentation and history of exposure. The WHO defines a clinical case of rabies as:

> "A subject presenting with an acute neurological syndrome (encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic signs (paralytic rabies) progressing towards coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the first sign."[7]

Cases are classified as suspected, probable, or confirmed. A suspected case is consistent with the clinical case definition. A probable case includes clinical symptoms and a reliable history of contact with a rabid animal. Confirmed requires laboratory confirmation of a suspected or probable case. **Table 1** contains the risk categories, and PEP recommendations, as defined by the WHO.

Direct fluorescent antibody test (dFA) is the most widely used test for postmortem, after-death, rabies diagnosis and is the gold standard for diagnosis. This test involves collecting fresh brain smears during autopsy or brain biopsy, utilizing immunofluorescence to detect the rabies virus nucleoprotein antigen. Despite its 99% sensitivity, its post-mortem nature renders it ineffective for early detection and treatment. [7,8]

The Rapid Fluorescent Focus Inhibition Test (RFFIT) remains the gold standard for determining rabies antibodies, requiring specialized equipment and trained personnel. However, it has been supplanted by the Enzyme-linked immunosorbent assay (ELISA), which solely assesses antigen-binding and does not identify neutralizing antibodies. Although a cost-effective alternative called the Rapid Rabies Enzyme Immunodiagnostic (RREID) exists for surveys, the WHO does not advocate its substitution for the dFA test in diagnosis. [7,8]

Table 1. WHO Risk Categories of Exposure

Exposure Category	Description	PEP Recommendations
Category I	Touching or feeding animals, licks on intact skin, contact of intact skin with secretions or excretions of rabid animal or person	No PEP required
Category II	Nibbling of uncovered skin, minor scratches, or abrasions without bleeding	Vaccination as soon as possible *Severely Immunocompromised patients should receive vaccine and immunoglobulin
Category III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure to bats	Vaccination and immunoglobulin should be administered at distant sites as soon as possible. Immunoglobulin can be administered

Prevalence:

Beyond posing a threat to human health, rabies in wildlife can also have significant repercussions on economic and ecological systems. The rising prevalence of bat rabies, for instance, has resulted in heightened livestock mortality rates, directly affecting commercial farmers in regions like Mexico and South America.[7] The United States has implemented proactive measures to mitigate the risk to both human and livestock populations through robust surveillance and testing protocols. The CDC regularly releases annual reports on notifiable infectious diseases and conditions compiled from the National Notifiable Diseases Surveillance Systems. Below, **Table 2** illustrates the trajectory of confirmed rabies cases in both animals and humans in the U.S. spanning from 2016 to 2020. Prior to the COVID-19 pandemic, the trend indicated a national uptick in confirmed cases. During 2018 in the U.S. 23 human patients had antemortem samples taken and of those 3 (13%) were confirmed positive for rabies. [2]

Table 2. Human & Animal Rabies Cases by Year

	2020*	2019*	2018	2017	2016
US	4457	4645	4984 (+ 3 human)	4423 (+2 human)	4609
Kentucky	17	13	18	11	21

* Incomplete data from multiple jurisdictions due to the COVID-19 pandemic.

Prevention:

In the United States, the primary responsibility for prevention and control efforts lies with local and state departments. These efforts are concentrated on promoting the vaccination of domesticated animals, averting secondary exposure from wildlife, offering laboratory testing for suspected cases, providing animal control services, and ensuring access to rabies PEP for confirmed or suspected human encounters. Federal agencies like the CDC and USDA collaborate to support large-scale control and prevention measures.

Additionally, the Advisory Committee on Immunization Practices (ACIP) in the U.S. furnishes guidance on recommendations aimed at preventing human rabies cases. The most recent update from ACIP on rabies guidance introduced several modifications to pre-exposure prophylaxis (PrEP). [9] A summary of these updates can be found in the Supplemental Information and is beyond the scope of this paper.

Treatment:

In cases where patients exhibit detectable exposure from a bite or non-bite incident, the WHO and ACIP advise immediate washing of the wounds for at least 15 minutes. [2,7] Additionally, disinfection using a detergent with viricidal activity such as ethanol or iodine is recommended.

For individuals who are not vaccinated and may have been exposed through a bite or non-bite incident, both RIG and vaccine administration are recommended unless direct fluorescent antibody testing on the animal responsible for the exposure confirms it is not rabid. RIG is administered to provide rapid rabies-neutralizing antibody coverage until the vaccine establishes active immunity, protecting the patient from further spread. It is typically injected intramuscularly near the site of exposure. The rabies vaccine schedule recommends that patients obtain the additional vaccinations on days 3, 7, and 14 following the initial administration. **Table 3** & **Table 4** review the recommended treatment for non-immunized and immunized individuals. Both the human diploid cell rabies vaccine (HDCV) and purified chick embryo cell (PCEC) vaccines are recommended by the CDC. [2,7,9]

Table 3. PEP for Non-immunized Individuals

Treatment	Regimen
Wound cleansing	All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
RIG	If possible, the full dose should be infiltrated around any wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.
Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area), one each on days 0 , 3, 7, and 14.

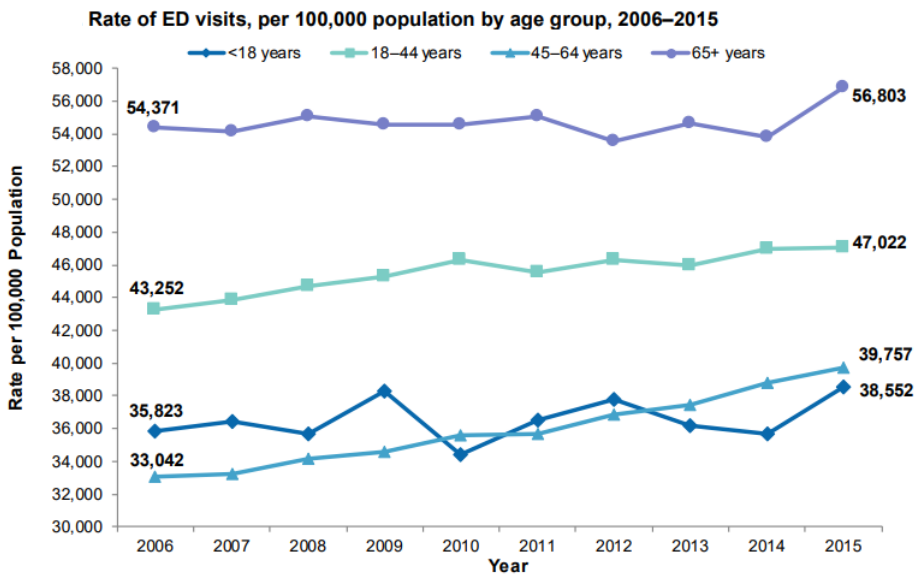
Table 4. PEP for Previously Immunized Individuals

Treatment	Regimen
Wound cleansing	All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
RIG	RIG should not be administered.
Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area), one each on days 0 and 3.

Overview of Non-urgent Visits to the Emergency Department

Over the past few decades, the number of ED visits have increased dramatically. An increased number of non-urgent patients presenting to the ED has resulted in negative effects through increased wait times and decreased quality of care. This trend is evident across all age groups, as depicted in **Figure 1**, which showcases the escalating rate of ED visits per 100,000 population from 2005 to 2015. [10,11]

Figure 1



Abbreviation: ED, emergency department

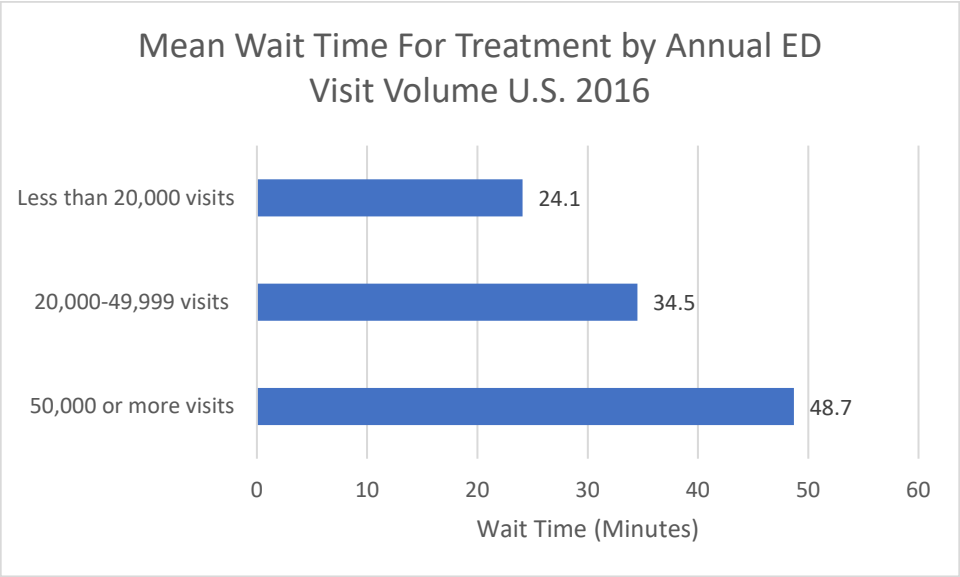
Source: Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets. Healthcare Cost and Utilization Project (HCUP), Nationwide Emergency Department Sample (NEDS), 2006–2015

The issue of non-urgent visits to the ED, a concern that is not new and has persisted since the inception of emergency departments, is multilayered and complex, with numerous contributing factors. It is essential to note that this trend cannot be attributed to any single cause, making it challenging to implement a one-size-fits-all solution to fix it. As depicted in **Figure 2**, overcrowding within EDs has a direct impact on the average wait times for patients seeking care. This increase in delay to care is associated with adverse outcomes, which is just one of the many reasons why it is imperative to consider an overhaul of the current healthcare system model.

Furthermore, disparities in healthcare delivery have been observed, particularly when it comes to homeless patients who experience even longer wait times for similar care, especially when their conditions are severe. This exacerbation of delays for vulnerable populations highlights the potential for ED overcrowding to worsen health inequalities, necessitating the implementation of policies aimed at reducing this burden. According to the 2022 Annual Homelessness Assessment Report to Congress, an estimated 33,129 veterans were experiencing homelessness over the prior year. [12] The same report details that a large portion of this population has a disability or chronic illness with a high likelihood of ED visits.

Based on data sourced from the Department of Health & Human Services (HHS), spanning the period 2019-2021, it was observed that EDs in Kentucky were operating at or above 85% maximum capacity for an average of 25 days per month. This underscores the imperative to curtail non-urgent visits to the ED. Concurrently, the average daily volume of ED visits across the 92 hospital-owned EDs within the state during this timeframe stood at 5,767 from 2019-2021. [13]

Figure 2



MCHS, National Hospital Ambulatory Medical Care Survey, 2016

Background of U.S. Emergency Medicine:

Emergency departments are essential components of our healthcare infrastructure, serving as vital hubs for managing acute injuries and illnesses. These departments are staffed with healthcare professionals who possess specialized skills in rapidly assessing and prioritizing patient care. They serve as the primary entry point for individuals requiring extended hospitalization, playing a pivotal role in the continuum of care. In the United States, there are more than 6,200 hospitals equipped with emergency departments, collectively providing crucial care to around 330 million citizens, according to data from the American Hospital Association. [14]

While Hippocrates, the ancient Greek physician, holds the title of the "Father of Medicine," Dr. James Styner is credited with pioneering the field of Emergency Medicine, earning him the moniker of the "Father of Emergency Medicine" in the mid-20th century. Despite the essential nature of today's emergency medical services, the organized system for emergency care didn't fully materialize until the late 20th century. This field's primary objective is to diagnose and promptly treat acute, life-threatening conditions, which encompass various medical conditions, traumas, injuries, and more. [14, 15]

Since the 1970s, emergency departments have taken on an increasingly critical role within our healthcare system. However, this growth in ED utilization has been accompanied by a troubling surge in non-urgent care being sought within these departments. The steady rise in such visits over the last two decades has far outstripped population growth, thereby necessitating a thorough examination and reform of the existing healthcare system. The influx of non-urgent

cases in the ED contributes significantly to the problem of ED overcrowding. This, in turn, leads to protracted wait times and delayed care for patients with critical conditions. Beyond the immediate consequences of delayed care, this influx places an elevated level of stress on the department's staff. They are compelled to manage a larger patient load throughout the day, increasing the potential for medical errors and contributing to staff burnout, which stems from diminished job satisfaction.

Rabies & ED

Consequences of Avoidable Rabies ED Visits

While recognized as a medical urgency by the CDC, in the majority of cases fall short of constituting a medical emergency. However, suspected exposure warrants a comprehensive treatment regimen, which typically involves administering RIG along with a vaccine regimen. This regimen typically spans across days 0, 3, 7, 14, and 28, with additional considerations for immunocompromised individuals. [1-3,4,6]

The consequences of avoidable rabies ED visits extend beyond the immediate healthcare setting and carry significant economic burdens. Despite the lack of necessity for emergency care, a substantial number of individuals, estimated by the CDC to range from 30,000 to 60,000 annually, present to the ED for PEP. A 1994 study conducted in Kentucky proposed that a significant proportion of cases receiving PEP may be unnecessary. [17]

The direct costs associated with these unnecessary ED visits are considerable, as estimated by the CDC to range between $1023 and $3378, with additional indirect costs ranging from $161 to $2161. A study involving 105 patients who received an infectious disease referral for follow-up vaccinations demonstrated the potential for substantial cost avoidance, estimating a range of $107,415 to $354,690 based on average institutional charges. [11]

Furthermore, among patients with avoidable ED visits for rabies PEP, research indicates a high likelihood of return visits for follow-up vaccines, with some studies reporting a large number of patients returning to the ED. This cycle of unnecessary visits not only strains healthcare resources but also perpetuates a costly and inefficient pattern of care delivery.

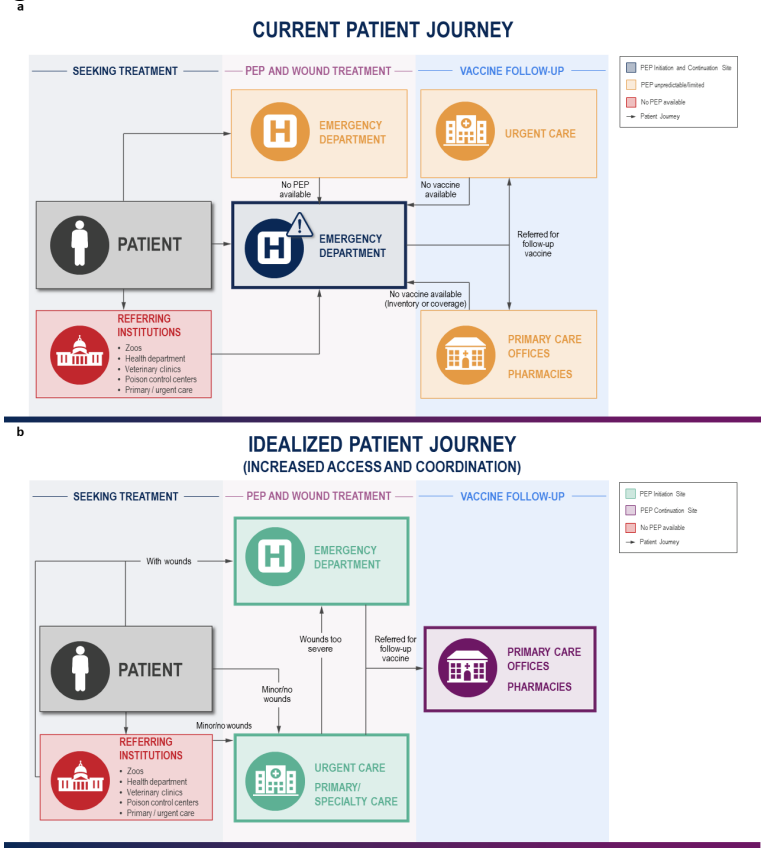
Patient Access

The influx of suspected rabies exposures seeking rabies PEP in EDs is often categorized as nonurgent upon triage. This trend has prompted many EDs across the country to stock rabies PEP, particularly for wound care cases. However, the high cost and relatively low demand for rabies vaccine and RIG pose challenges for facilities outside the ED, which may not stock these products.

Outpatient resources encounter hurdles due to inadequate coverage for the rabies vaccine. According to the Centers for Medicare & Medicaid Services (CMS), the average price for the rabies vaccine under Medicare Part B in 2024 stands at $324.74, with patients typically responsible for a 20% co-insurance, amounting to $65 per vaccine or $260 for the entire treatment course, excluding any hospital or clinic visit fees. [16]

Furthermore, the lack of incentive for clinics and pharmacies to carry the rabies vaccine contributes to coordination challenges in patient care, often resulting in patients returning to the ED. **Figure 3** provides a visual representation of the current complex system and ideal follow-up pathways for these patients. Presently, many patients unnecessarily visit the ED for both initial consultations and follow-up vaccinations, highlighting systemic inefficiencies. It's crucial to highlight that not all adjustments outlined in the Inflation Reduction Act regarding Medicare have been fully implemented. Assessing the repercussions of these alterations on drug price negotiations and their financial implications for medical practices and patients remains imperative.

Figure 3.



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Patient Journey & Potential Solutions:

The majority of suspected rabies exposures present to the ED for rabies PEP. However, most of these are triaged as Emergency Severity Index (ESI) level 4 (less urgent) or 5 (nonurgent). Due to this, most EDs have RIG and the rabies vaccines stocked. However, outside of EDs the options for treatment is limited due to a lack of insurance reimbursement, lack of patient presentation, and referral processes. [18]

The current model results in patients frequently returning to the ED for follow-up vaccinations. This results in increasing wait times for all patients which has the potential to negatively impact patient outcomes. Additionally, this path results in a higher burden for the healthcare system including burnout for healthcare staff. [18] The ideal treatment scenario, **Figure 4**, would be patients with minor or no wounds presenting to a local public health department, urgent care, or primary care clinic. In coordination with dispatch and emergency services patients could be informed on the most appropriate triage location for their medical care. Patients who present to the ED with absent or minor wounds should then be referred per protocol to local alternatives to reduce ED congestion. After the initial presentation, patients would ideally follow up at a clinic, pharmacy, or local health department for the vaccine series.

Statewide policy reforms hold the potential to alleviate ED congestion and enhance patient outcomes. One approach could involve mandating that at least one urgent care center per county and all public health departments with a provider within the state maintain a stock of RIG. According to the manufacturer of the RIG product HyperRAB®, when stored properly, has a shelf life of three years. [19] By enforcing the stocking of this medication, the need for patient transfers between facilities with stocked medication would be minimized. Additionally, requiring major population center health departments to maintain a minimum stock of the medication could further reduce unnecessary presentations. To address concerns regarding medication waste and its impact on smaller facilities' financial resources, manufacturers and distributors could offer credit for returned medication related to rabies PEP within six months of expiration.

Expansion of the involvement of emergency services could assist in alleviating the burden of EDs. Emergency dispatch personnel can undergo education on treatment locations within their respective regions to better triage calls regarding suspected rabies cases to the most appropriate resources. Emergency Medical Technicians (EMTs) could under protocols triage and divert patients requesting ambulance services to the most suitable treatment facilities based on the patient's status. A nationwide study estimated that from 1997 to 2007 there was an increase in unnecessary EMS transports by 31%. [20] With over 250 million responses to 911 calls each year engaging EMS in the triage and proper facility for treatment can maximize the impact of a program to optimize care.

Though evidence regarding the implementation of strategies aimed at reducing suspected rabies exposures in EDs is scarce, the potential cost reductions by diverting patients to more suitable centers could effectively alleviate ED congestion while also serving as an avenue for public education. Existing studies on other disease management strategies suggest that recurrence rates can be reduced through effective case management. [21,22] Therefore,

policymakers, in collaboration with public health officials and ED administrators, could establish a case manager-to-patient ratio aimed at coordinating follow-up care for various disease states including rabies PEP. Case managers could facilitate the coordination of follow-up vaccination appointments, location arrangements, and insurance coverage for patients. Providing advanced notice of vaccination requirements to primary care offices could enable patients to receive vaccinations from their primary care providers, thus optimizing access to care.

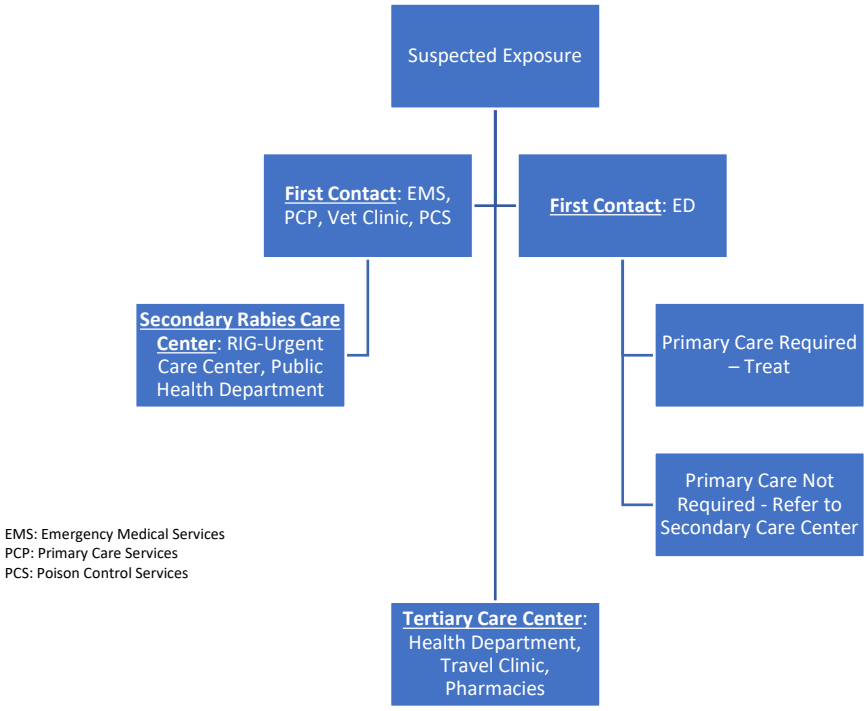
In implementing a statewide rabies PEP program aimed at alleviating ED overcrowding, various stakeholders play integral roles in its success. Firstly, public health departments at both the state and local levels are pivotal in establishing guidelines and protocols for the administration of RIG and rabies vaccine. These departments collaborate with healthcare providers, including physicians, nurses, and pharmacists, to ensure proper training and adherence to protocols. Additionally, animal control agencies and veterinary services are essential stakeholders in preventing rabies exposure through education, vaccination programs for domestic animals, and handling of potentially rabid animals. Furthermore, EMS personnel are crucial in the timely transportation of patients potentially exposed to rabies to appropriate healthcare facilities. State policymakers and legislators also have a role in providing funding and legislative support for the program's sustainability and effectiveness. Lastly, community engagement and public education campaigns are vital to raising awareness about rabies prevention measures and the availability of PEP services, ultimately reducing unnecessary ED visits related to rabies exposure concerns. Collaboration among these stakeholders ensures a comprehensive and coordinated approach to reducing ED overcrowding while effectively managing rabies exposures statewide.

Patients who present to the ED can be triaged and referred under a mock protocol such as the example below:

1) Initial Assessment:
    a. Patients with suspected nonurgent rabies exposure will undergo prompt triage based on established criteria by a BSN.
        i. Nursing staff must complete training for rabies exposure triage and undergo an annual review.
2) Evaluation and Education:
    a. ED staff will conduct a thorough evaluation and provide education on rabies exposure and the importance of timely treatment to patients.
3) Referral to Urgent Care or Public Health Department:
    a. Nonurgent cases will be referred directly to an urgent care center or public health department for further management of HRIG and vaccine administration.
4) Documentation and Follow-Up:
    a. Referral details will be documented in the patient's record, and follow-up arrangements will be made by the case manager.
        i. Case manager will ensure patients location preference for vaccination follow-up can obtain vaccine and location is covered under insurance.
5) Communication with Receiving Facility:
    a. The ED will communicate referral information to the receiving facility to ensure seamless care transition.

6) Monitoring and Surveillance:
    a. Public health authorities will continue monitor and conduct surveillance of all suspected rabies exposures, facilitating community-wide management. Annual assessment of the cost savings of ED visits will be provided by the public health department for review and analysis of the state-wide program.

Figure 4 Idealized Patient Journey For Suspected Rabies Exposure



Kentucky has taken steps to decrease fatalities and increasing monitoring of rabies in the state. Under Kentucky Revised Statute (KRS) 258.065 all incidents involving person(s) bitten by animals must be reported to the Health Department within twelve (12) hours after the physician's first attendance. The state requires that the animals that caused the injury be quarantined for 10 days for observation. If the animal is suspected to have been infected by rabies and the animals become sick during the quarantine they are euthanized and tested in the State Rabies Lab. [23] In pursuit of effective control measures while ensuring affordability, the health department is empowered to sponsor annual countywide rabies vaccination clinics, wherein a maximum out-of-pocket cost of ten dollars per animal is mandated. Leveraging these vaccination clinics, augmented educational efforts targeting the public regarding appropriate avenues for rabies exposure treatment could effectively mitigate unnecessary Emergency Department visits.

Analysis of Kentucky Data

The Kentucky Office of Data Analytics (ODA) provided an aggregate pull of data spanning from 2019 to 2022. This section examines the incidence of patients seeking care for suspected exposure to rabies, as indicated by the ICD-10 codes Z20.3, Z29.14, and Z23. These codes correspond to suspected exposure to rabies, encounters for prophylactic rabies immune globulin, and encounters for immunization, respectively. For outpatient care, CPT codes 90375, 90377, and 90376 are also pertinent to capture relevant encounters.

Table 5 presents the outpatient data for Suspected Exposure to Rabies in Kentucky from 2019 to 2022. This dataset encompasses all encounters related to suspected rabies, including both initial visits and subsequent follow-up vaccinations. ED encounters for suspected exposure denote patients who either present initially or return for vaccination. It's important to note that each patient who receives RIG will require follow-up visits, which may contribute to the overall increase in total encounters.

Table 5. Kentucky Suspected Exposure to Rabies Statistics 2019-2022 Outpatient Data

Year	All Encounters For Suspected Exposure To Rabies	ED Encounters For Suspected Exposure To Rabies	Encounters With RIG
2019	1079	805	539
2020	1001	706	353
2021	1191	870	373
2022	1927	1490	642

It is worth reiterating that the majority of patient presentations are ESI level 4 or 5 as mentioned previously and are less urgent. Although data varies, some estimates are as high as 3 out of every 4 presentations for suspected exposure could be cared for at a lower acuity setting. In Kentucky, 74.5% of all ED encounters for suspected rabies exposure are patients who are initially seen or return to the ED. The demographics data pertaining to outpatient encounters for suspected exposure to Rabies in Kentucky are delineated in **Table 6**, presented below.

Table 6. Kentucky Suspected Exposure to Rabies
Demographics 2019-2022 Outpatient Data

Variable	Percentage
Race	
▪ White	▪ 91.2%
▪ African American	▪ 5.3%
▪ Other	▪ 2%
Age	
▪ 0-19	▪ 10.2%
▪ 20-39	▪ 44.8%
▪ 40-59	▪ 26.3%
▪ 60+	▪ 18.7%

Program Benefits

The cost of RIG varies by brand and wholesaler. Public data from the Texas Department of State Health Services has a price cost of around $700 for HyperRab and $350 for the vaccine Rabavert. [24] By increasing the availability for patients to obtain treatment at alternate locations we can estimate that each patient cold result in

Data from UnitedHealthcare Network Providers found that the average increase in cost in going to an ED over an urgent care is an increase of $2,400. [25] The average wait time for patients in the ED was 2 hours compared to an average of 30 minutes or less for an urgent care. If the number of patients who need rabies PEP continues to increase, the cost can be offset and reduced through implementation of this while improving the health of those within Kentucky. With Kentucky EDs at ≥85% capacity for 25days/month this significantly increases the burden of the negative effects of ED overcrowding on the general public. Studies have show linear relationship between overcrowsing an mortality.

The wholesale cost to supply 2 RIG doses and 4 vaccine doses at urgent care and local public health department for Kentucky we estimate to be $672,000. With the data from **Table 5**, we can estimate that only half of patients who present for a suspected exposure receive RIG.

With the average number of ED encounters from 2019-2022 in Kentucky totaling 968 and an expected reduction of the average cost at visiting an urgent care center ($2,400) only 269 patients (27.7%) of patients would need to go to a secondary care center to pay for the cost of the state providing the medication doses at secondary care centers in the county.

The average number of encounters for RIG from 2019-2022 of 477 would result in an estimated 1431 follow-up visits to complete the vaccination series. An example cost difference from a physician noted that the cost billed to insurance and the patient for the rabies vaccine from the local emergency room compared to a clinic was $1,509. [26] If only half of the patients could

have initial care established with a health department, urgenct care center the cost reduction could lead to an overall savings to the healthcare system of over $1 million.

The savings to the healthcare system above does not take into account the reduced burnout in emergency medical personel, and the benefit of reduced ED wait times.

Discussion

The connection between zoonotic diseases such as COVID-19 and rabies poses significant challenges for public health systems worldwide, with implications extending beyond immediate medical concerns to societal infrastructure. Rabies, remains a persistent threat in many regions, necessitating proactive vaccination campaigns. However, while vaccination is crucial for preventing rabies transmission, its administration can inadvertently contribute to overcrowding in EDs.

The administration of rabies vaccinations often involves multiple doses over a prescribed period, typically following exposure to potentially infected animals. This regimen, coupled with the necessity for timely administration to prevent the onset of symptoms, can strain healthcare resources, leading to increased ED visits. Patients seeking PEP for rabies may present to EDs due to limited access to alternative healthcare settings or the urgency of their condition, exacerbating existing pressures on emergency services. Moreover, the need for specialized expertise in assessing and administering rabies vaccinations further compounds the burden on ED staff, potentially impacting the quality of care delivered to other patients.

Addressing the challenges posed by the rabies vaccination process requires a multifaceted approach that encompasses both preventative measures and healthcare system optimization. Efforts to streamline the delivery of rabies vaccinations through primary care providers or specialized clinics could alleviate the strain on EDs while ensuring timely access to PEP for those in need. By addressing the root causes of ED overcrowding associated with rabies vaccination, policymakers and healthcare stakeholders can work towards building more resilient and efficient systems capable of managing the ongoing threat of zoonotic diseases in the future.

To our Knowledge, there is currently no comprehensive statewide program aimed at mitigating emergency department overcrowding through the optimization of rabies exposure practices at the state level. It's worth mentioning that the North Carolina Department of Health and Human Services has established guidelines for a standing order protocol enabling public health nursing staff to administer approved rabies immune globulin. Similarly, in Ontario, Ottawa Public Health offers rabies immune globulin to requesting healthcare providers for patients potentially exposed to rabies.

Limitations

Due to the Coronavirus Disease 2019 (COVID-19) data collection from 2019-2021 for certain jurisdictions have been deemed incomplete by CDC surveillance programs. The pandemic has disrupted various aspects of public health systems worldwide, including data collection and surveillance programs. Due to the strain on resources, prioritization of COVID-19-related data collection, and changes in healthcare-seeking behaviors, data collection for diseases such as rabies may have been compromised. The incomplete data for certain jurisdictions during the period of 2019-2021, as noted by the CDC surveillance programs, introduces a significant limitation to the review of recent trends. Without comprehensive and accurate data, it becomes challenging to draw definitive conclusions or assess trends accurately.

The IRA represents a significant policy change that could potentially affect patient affordability and access to healthcare services, including the rabies vaccine. However, despite its potential implications, the specific impact of the IRA on Medicare beneficiaries' ability to access rabies PEP is not known. This lack of empirical evidence regarding the IRA's influence on patient behavior, healthcare utilization, and out-of-pocket expenses introduces a notable limitation to the future trends of vaccine access. Therefore, future research endeavors should aim to investigate the IRA's effects on healthcare access, affordability, and patient outcomes, particularly concerning preventive measures like rabies PEP. Addressing this limitation is essential for informing evidence-based policy decisions and ensuring equitable healthcare access for all individuals, including Medicare beneficiaries.

Data provided by the Kentucky ODA had some limitations with reporting. Per 900 KAR 7:040, aggregate counts of 5 or less must be suppressed to avoid patient identification with small counts. HB 444 updated KRS 216.2927 to allow ODA to collect the necessary identifying information to assign a unique patient ID to each discharge starting with data collection in 2019. For this reason, counting individuals can only be accomplished from this data after 2019. Encounters reported for RIG were categorized into two groups: All Encounters and ED Encounters, revealing notable disparities in the reported figures. It is worth noting that, to the best of our knowledge, RIG is exclusively accessible at major hospitals, primarily due to the medication's associated costs, and is not readily available at smaller facilities such as urgent care centers.

References

1. Ma, Xiaoyue, et al. "Public Veterinary Medicine: Public Health: Rabies surveillance in the United States during 2018". *Journal of the American Veterinary Medical Association* 256.2 (2020): 195-208. < https://doi.org/10.2460/javma.256.2.195>. Web. 22 Feb. 2024.
2. Rabies Postexposure prophylaxis (PEP) | Medical care | Rabies | CDC. Rabies Postexposure prophylaxis (PEP) | Medical care | Rabies | CDC. https://www.cdc.gov/rabies/medical_care/index.html
3. Singh R, Singh KP, Cherian S, et al. Rabies - epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review. *Vet Q*. 2017;37(1):212-251. doi:10.1080/01652176.2017.1343516
4. Shafaati M, Akbarpour S, Priyanka, Saied AA, Choudhary OP. Tackling rabies by one health approach: Pitfalls on the road to global eradication. *New Microbes New Infect*. 2023;52:101098. Published 2023 Feb 4. doi:10.1016/j.nmni.2023.101098
5. Robbins, Sarah Jane, "Rabies in Kentucky from 1989-2020: A case for surveillance" (2021). *Theses and Dissertations--Public Health (M.P.H. & Dr.P.H.)*. 316. https://uknowledge.uky.edu/cph_etds/316
6. Krebs JW, Long-Marin SC, Childs JE. Causes, costs, and estimates of rabies postexposure prophylaxis treatments in the United States. J Public Health Management Practice. 1998 Sep; 4(5): 56-62.
7. World Health Organization: WHO. Rabies. Published September 23, 2019. https://www.who.int/health-topics/rabies#tab=tab_1
8. Mani, Reeta Subramaniam, and Shampur Narayan Madhusudana. “Laboratory diagnosis of human rabies: recent advances.” *TheScientificWorldJournal* vol. 2013 569712. 14 Nov. 2013, doi:10.1155/2013/569712
9. Rao, Agam K et al. “Use of a Modified Preexposure Prophylaxis Vaccination Schedule to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022.” *MMWR. Morbidity and mortality weekly report* vol. 71,18 619-627. 6 May. 2022, doi:10.15585/mmwr.mm7118a2
10. Iso T, Yuan F, Rizk E, Tran AT, Saldana RB, Boyareddigari PR, Nguyen NA, Espino D, Benoit JS, Swan JT. Avoidable emergency department visits for rabies vaccination. Am J Emerg Med. 2022 Apr;54:242-248. doi: 10.1016/j.ajem.2022.02.007. Epub 2022 Feb 7. PMID: 35183888.
11. Frederickson, Jessica J et al. “Characterization of Emergency Department Rabies Post-Exposure Prophylaxis Procedures with an Infectious Diseases Clinic Referral Process.” *Hospital pharmacy* vol. 57,1 (2022): 38-44. doi:10.1177/0018578720973889
12. *Homelessness Resources*. HUD.gov / U.S. Department of Housing and Urban Development (HUD). (2020, July 8). https://www.hud.gov/homelessness_resources
13. https://hcup-us.ahrq.gov/reports/trendtables/summarytrendtables.jsp#export
14. Fast facts on U.S. hospitals, 2024 | AHA. American Hospital Association. Published April 17, 2024. https://www.aha.org/statistics/fast-facts-us-hospitals

15. Suter, Robert E. “Emergency medicine in the United States: a systemic review.” *World journal of emergency medicine* vol. 3,1 (2012): 5-10. doi:10.5847/wjem.j.issn.1920-8642.2012.01.001
16. Vaccine pricing | CMS. https://www.cms.gov/medicare/payment/all-fee-service-providers/medicare-part-b-drug-average-sales-price/vaccine-pricing
17. Auslander M, Kaelin C. Rabies postexposure prophylaxis survey- Kentucky, 1994. Emerging Infectious Diseases. 1997; 3(2): 199
18. Howington GT, Nguyen HB, Bookstaver PB, Akpunonu P, Swan JT. Rabies postexposure prophylaxis in the United States: Opportunities to improve access, coordination, and delivery. *PLoS Negl Trop Dis*. 2021;15(7):e0009461. Published 2021 Jul 15. doi:10.1371/journal.pntd.0009461
19. Rabies Resources for health care Professionals | HyperRAB®. HyperRAB. https://www.hyperrab.com/en/hcp/resources#:~:text=What%20is%20the%20shelf%20life,of%20unused%20and%20expired%20inventory.
20. Langabeer JR 2nd, Gonzalez M, Alqusairi D, et al. Telehealth-Enabled Emergency Medical Services Program Reduces Ambulance Transport to Urban Emergency Departments. *West J Emerg Med*. 2016;17(6):713-720. doi:10.5811/westjem.2016.8.30660
21. Joo JY, Liu MF. Case management effectiveness in reducing hospital use: a systematic review. Int Nurs Rev. 2017 Jun;64(2):296-308. doi: 10.1111/inr.12335. Epub 2016 Nov 11. PMID: 27861853.
22. McCants KM, Reid KB, Williams I, Miller DE, Rubin R, Dutton S. The Impact of Case Management on Reducing Readmission for Patients Diagnosed With Heart Failure and Diabetes. Prof Case Manag. 2019 Jul/Aug;24(4):177-193. doi: 10.1097/NCM.0000000000000359. PMID: 31145236.
23. https://apps.legislature.ky.gov/law/kar/titles/902/002/070/
24. https://www.dshs.texas.gov/sites/default/files/immunize/Anti-Rabies_Biological_Cost_Fees_Website_Rev_11-2023.xlsx
25. What are my care options and their costs? UnitedHealthcare. https://www.uhc.com/member-resources/where-to-go-for-medical-care/care-options-and-costs
26. Rabies Immunization Charges | Edward R. Rensimer, MD | Rabies Doc Houston. Edward R. Rensimer, MD | Rabies Doc Houston. https://www.rabiesdoc.com/rabies-immunization-charges

Supplemental Information

I. Pre-exposure prophylaxis (PrEP)

Updates to the ACIP recommendations to prevent human rabies, 2022

- A 2-dose PrEP schedule has replaced the 3-dose PrEP schedule to protect for up to 3 years. Options for maintaining protection beyond 3 years are also described.
- Risk categories have been redefined into 5 risk groups.
- The minimum acceptable laboratory value (antibody titer) used to determine whether rabies vaccine booster doses are needed was revised and standardized.
- Many people for whom serial titers were recommended every 2 years now require only a one-time titer (and booster if below a certain level) OR a one-time booster.
- Clinical guidance for administering PrEP to people with weakened immune systems has been outlined and includes recommendations to confirm that the vaccine was effective.

Source: https://www.cdc.gov/rabies/prevention/pre-exposure_vaccinations.html#:~:text=These%20people%20should%20receive%20rabies,contact%20with%20the%20rabies%20virus.&text=A%202%2Ddose%20PrEP%20schedule,3%20years%20are%20also%20described

II. Risk Categories & PrEP Recommendations

Risk categories and PrEP recommendations

Risk category	Who this typically* affects	Recommendations
Risk category 1 *Highest risk*	People who work with live or concentrated rabies virus in laboratories	2 doses, days 0 and 7 Check titer every 6 months
Risk category 2	People who frequently do at least one of the following: handle bats, have contact with bats, enter high-density bat environments like caves, or perform animal necropsies	2 doses, days 0 and 7 Check titer every 2 years
Risk category 3	People who interact with, or are at higher risk to interact, with mammals other than bats that could be rabid, for a period longer than three years after they receive PrEP This group includes: • Most veterinarians, veterinary technicians, animal control officers, wildlife biologists, rehabilitators, trappers, and spelunkers (cave explorers) • Certain travelers to regions outside of the United States where rabies in dogs is commonly found	2 doses, days 0 and 7, plus: Either a one-time titer check after 1 year and up to 3 years following the first 2-dose vaccination **OR** 1-dose booster between 3 weeks and 3 years following the first vaccine in the 2-dose vaccination
Risk category 4	Same population as risk category 3, but at a higher risk for ≤ three years after they receive PrEP	2 doses, days 0 and 7
Risk category 5 *Lowest risk*	General U.S. population	None

Source: https://www.cdc.gov/rabies/prevention/pre-exposure_vaccinations.html#:~:text=These%20people%20should%20receive%20rabies,contact%20with%20the%20rabies%20virus.&text=A%202%2Ddose%20PrEP%20schedule,3%20years%20are%20also%20described

III. ICD-10 & CPT Codes

ICD-10 or CPT Code	Interpretation
Z29.14	**Encounter for prophylactic rabies immune globin**
Z20.3	**Contact with and (suspected) exposure to rabies**
Z23	**Encounter for Immunization**
90375	**Rabies Immune Globulin (RIG), Human, for Intramuscular and/or Subcutaneous Use**
90376	**Rabies Immune Globulin (RIG), Heat-treated (RIG-HT), Human, for Intramuscular and/or Subcutaneous Use**
90377	**Rabies immune globulin, heat- and solvent/detergent-treated (right s/d), human, for intramuscular and/or subcutaneous use**