

Cat-borne rabies as the new epidemiology of rabies disease in the Andes Mountains

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SUMMARY

Rabies virus (RABV) is the etiologic agent of rabies, a fatal brain disease in mammals. Rabies circulation has historically involved the dog as the main source of human rabies worldwide. Nevertheless, in Colombia, cats have become a relevant species in the epidemiology of rabies. We aimed to characterize rabies cases in humans in Colombia in the last three decades in the context of the epidemiology of the aggressor animal. We conducted a retrospective longitudinal epidemiological study of human rabies caused by cats' aggression, collecting primary and secondary information. Variables considered included the demography of the patient, symptoms, information about the aggressor animal as the source of infection, and the viral variant identified. We found that the distribution of rabies incidence over the years has been constant in Colombia. Nevertheless, between 2003 and 2012 a peak of cases occurred in rural Colombia where cats were the most frequent aggressor animal reported. Most cats

involved in aggression were unvaccinated against rabies. Cat's clinical signs at the time of the report of the human cases included hypersalivation and changes in behavior. Human patients were mostly children and female and the exposure primarily corresponded to bite and puncture lacerations in hands. The RABV lineage detected in most cases corresponded to variant 3, linked to the common vampire bat (*Desmodus rotundus*). The geographical presentation of cat-borne RABV in humans occurred along the Andes mountains, epidemiologically known as the rabies red Andean corridor. By finding cats as the primary source of rabies spillover transmission in Colombia, this report highlights the importance of revising national rabies control and prevention protocol in countries in the Andes region. In conclusion, our results demonstrate that rabies vaccination for outdoor cats needs to be prioritized to reduce the number of rabies-related human deaths.

KEYWORDS

Bat, rabies, cat, Colombia, epidemiology, RABV.

47 **IMPACTS**

- 48 • A total of 14 cat-borne rabies cases in humans reveal an epidemiological switch from
49 dog-borne to primarily cat-borne rabies in Colombia.
- 50 • Children (9-13 years old) living in the highlands of Colombia were the most affected.
- 51 • Cat-borne rabies incidence had a tendency to increase in recent years.
- 52 • National rabies control strategies in the Andes region should emphasize cat vaccination
53 and humane population control, and strengthen epidemiological surveillance systems.

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INTRODUCTION

Rabies virus (RABV) is the etiologic agent of rabies, a zoonotic disease reported in all continents but Antarctica. Rabies is considered a neglected tropical disease, mainly affecting low-income populations in hard-to-reach rural areas (WHO, 2022). Rabies incubation period is variable (30-90 days) and may depend on the site of exposure (distance to the brain), but 7 days or even up to 6 years have been reported (Hemachudha et al., 2022) and even as long as 25 years (Shankar et al., 2012). The onset of the disease is similar to any febrile illness, including symptoms such as weakness or general discomfort, fever, headache, and stinging or itching feeling at the bite site. The symptomatology progresses to brain dysfunction, anxiety, confusion, agitation, delusions, abnormal behavior (e.g., hallucinations, hydrophobia, insomnia, aggression, and self-mutilation), dysfunction of the cranial nerves, ataxia, weakness, paralysis, convulsions, difficulty breathing, difficulty swallowing, excessive salivation, and finally the death of the patient (CDC, 2019).

RABV belongs to the genus *Lyssavirus* composed of 16 viral species, and 10 of species have been isolated from bats (Banyard et al., 2014). The virus presents sylvatic and urban cycles of transmission and maintenance. The urban cycle involves the dog as the main host and transmissor of RABV, while the sylvatic cycle includes a variety of wildlife species, ranging from carnivores to bat, transmitting RABV to other species including humans (Cisterna et al., 2005). The idea of an aerial sylvatic cycle has been recently proposed to differentiate transmission among bat species from other non-volant wildlife species (San Miguel de Vera, 2016).

Dogs have been historically considered as the main source of human rabies worldwide. Nevertheless, cats are also a relevant species in rabies epidemiology (Tierradentro-García et al., 2022). The predatory and nocturnal behavior of cats facilitates their direct contact with bats, and their role as pets facilitates zoonotic transmission (Grisi-Filho et al., 2008) (Figure 1).



FIGURE 1. The domestic-wildlife interface of rabies transmission involving cats and bats. Rabid bats could change their behavior to approach other animals and be fearless. The cat hunts a rabid bat maybe with more success than hunting a healthy bat. The rabid bat bites the cat and RABV enters the cat's body through the wound by infiltration of the infected bat's saliva. RABV replicates in the peripheral muscles of the cat, near the wound, and migrates to the central nervous system. RABV is then distributed to other organs and finally reaches the cat's salivary glands. The rabid cat now shows behavioral changes and predisposed to attack humans and infect other animals. Direct infection from the bat to the human can also occur.

MATERIALS AND METHODS

TABLE 1. A summary of fatal cases of human rabies due to different animal sources in Colombia (1990-2021)

| Year | Number of cases/province (municipality) | Sex (age in years) | Aggressor animal | Viral variant (host) |
|-------------|--|---|-------------------------|-----------------------------|
| 1990 | 1/ Caldas (Aguadas) | Female (9) | Cat | N/A |
| 1999 | 1/Putumayo (Orito) | Female (6) | Dog | V1 (dog) |
| | 2/Magdalena (Pedraza-Ciénaga) | Male (5, 9) | | |
| 2000 | 1/Putumayo (Orito) | Female (24) | Dog | V1 (dog) |
| 2003 | 1/Cundinamarca (Quipile) | Male (13) | Cat | V8 (skunk) |
| 2004 | 14/Chocó (Pizarro) | Female (3, 7, 8*, 9), Male (4, 5, 6**, 7, 8*, 12) | Bat | V3 (vampire bat) |
| 2005 | 3/Chocó (Bajo Baudó) | Female (13), Male (12, 14) | Bat | V3 (vampire bat) |
| 2006 | 2/Magdalena (Santa Marta) | Male (14, 29) | Dog | V1 (dog) |
| 2007 | 2/Magdalena (Santa Marta) | Male (3, 20) | Dog | V1 (dog) |
| | 1/Casanare (San Luis de Palenque) | Female (N/A) | Bat | V3 (vampire bat) |
| 2008 | 2/Cauca (Santander de Quilichao) | Female (12), Male (10) | Cat | V3 (vampire bat) |
| | 1/Santander (Floridablanca) | Male (15) | Bat | |

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|------|--------------------------------------|--------------|-----|--------------------------------------|
| | 1/Bolívar (San Jacinto del Cauca) | Female (9) | Cat | |
| 2009 | 1/Boyacá (Moniquirá) | Female (76) | Cat | V4 (insectivorous bat) |
| | 1/Santander (Barrancabermeja) | Female (N/A) | Bat | V3 (vampire bat) |
| 2010 | 1/Santander (Enciso) | Female (13) | Cat | V3 (vampire bat) |
| | 1/Santander (Piedecuesta) | Female (46) | Bat | |
| | 1/Tolima (San Luis) | Male (11) | Cat | |
| 2012 | 1/Valle del Cauca (Roldanillo) | Female (19) | Cat | V4 (insectivorous bat) |
| 2015 | 1/Cundinamarca (Mesitas del colegio) | Male (9) | Cat | V3 (vampire bat) |
| 2016 | 1/Cundinamarca (Girardot) | N/A | Cat | Atypical variable, AV1 (vampire bat) |
| 2017 | 1/Cundinamarca (Tena) | N/A | Cat | Atypical variable, AV1 (vampire bat) |
| 2020 | 1/Huila (Neiva) | Female (26) | Cat | V3 (vampire bat) |
| 2021 | 1/Huila (La Argentina) | Male (29) | Cat | V3 (vampire bat) |

Source: <https://sirvera.panaftosa.org.br/>

*Two cases each; ** Three cases each; N/A: Not Available.

First, data on rabies cases in humans were collected from the Regional Information System for the Epidemiological Surveillance of Rabies (SIRVERA) during the 1990-2021 period CITE. SIRVERA is a data repository of the epidemiology of rabies in the Americas and is

updated monthly by health authorities in countries across the Americas CITE. We recovered SIRVERA data using the following inclusion criteria, country=Colombia, types of cases=human, date of notification=1990-2021, and target species=human.

A more detailed retrospective longitudinal epidemiological assessment of the cases was carried out, collecting information from primary (i.e., Ministry of Health of Colombia) and secondary sources (i.e., scientific publications and news describing the cases). Variables considered for the data collection included year of the report, epidemiological week, municipality, province, type of settlement (i.e., rural, urban). In addition, information on the cat (i.e. sex, age in months, vaccination status, behavior, and clinical signs at the time of the report) and the human patient (i.e. sex, age in years, occupation, clinical signs). For the human clinical signs we also accounted for the date of animal aggression, onset of signs, request for medical care, and of death, the time elapsed between the aggression and the onset of clinical signs, and the time elapsed between the aggression and the death in days. When available, we also collected the type and site of exposure, description of the aggression, clinical features of the case, diagnostic tests results, and the RABV variant identified.

RESULTS

Forty-three human rabies cases have been reported in Colombia, from 1990 to 2021, with a greatest presentation of bat-borne RABV transmitted by cats in the last decade (n=14) (Table 1). Rabies cases in which the dog was considered an aggressor were eight for the last decade. Human rabies cases involving cats were constant between 2003 and 2012 and occurred across Andean provinces (Figure 2). Rural area was a great contributor to the number of cases (6/14). All aggressor cats were reported as unvaccinated for rabies, and cat vaccination status was not known by the owners or people related to the patient for most cases. Cat's clinical signs described at the time of the report of the identification of the human case were predominantly related to hypersalivation and irritability. Human patients were mainly females (7/12) and the type and site of exposure corresponded to bite (4/14) and puncture laceration in hands (7/14). Variant 3, linked to vampire bats, was the most frequent RABV lineage identified (7/13). Although data was not available for all cases, detailed information

of the known rabid human patient linked to a cat as the aggressor animal are summarized geographically (Figure 2) and temporally (see below).

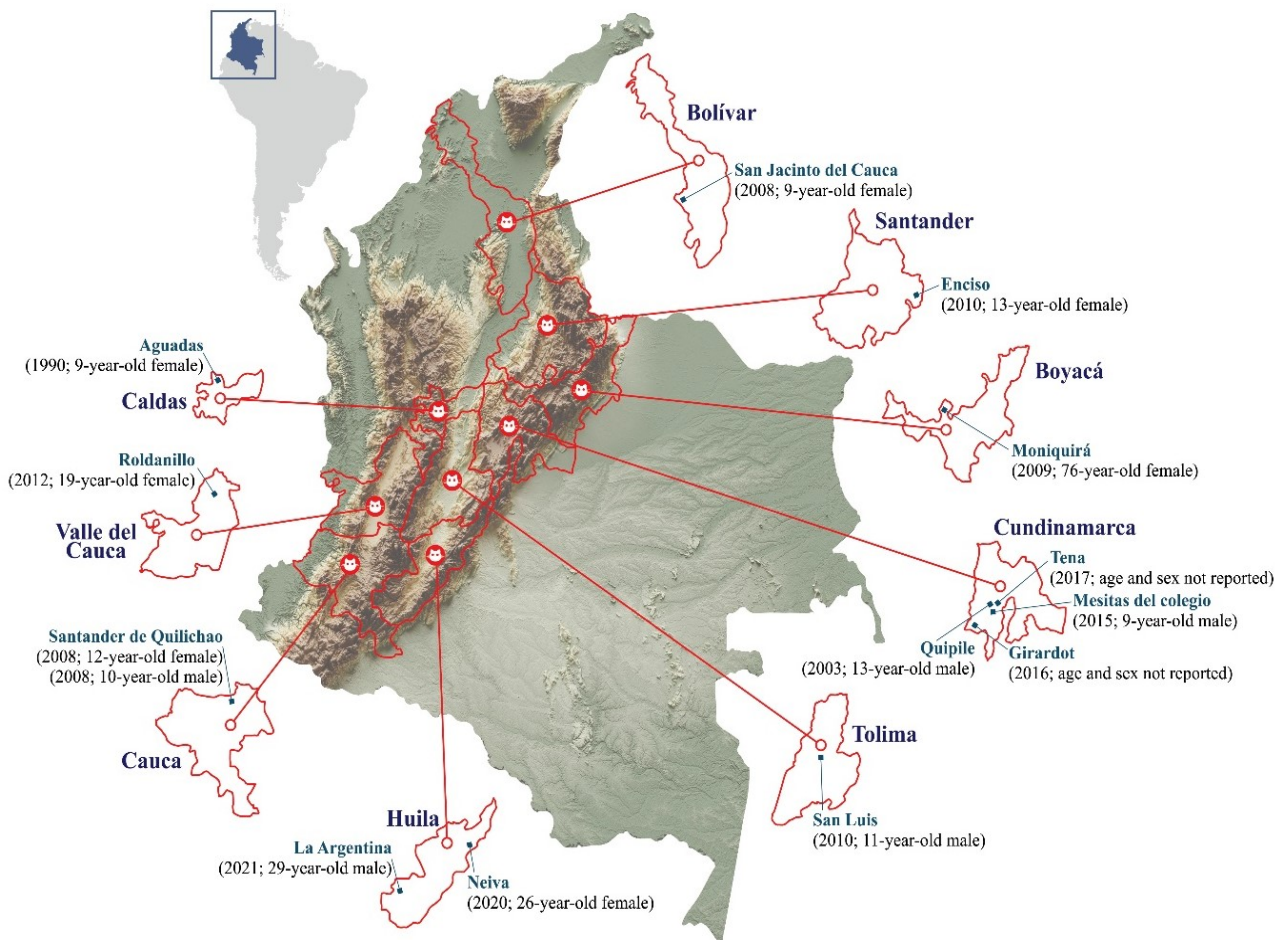


FIGURE 2. Geographical distribution of the 14 fatal human cases with laboratory-confirmed rabies transmitted by cats in Colombia (1990-2021). Map denotes elevational gradients across the Colombian territory with areas of low (dark green) and high (brown) elevations. Specific localities where cases occurred (blue squares) were grouped at the municipality level (red polygon). The year of the report and demographic information of the case was recorded (parenthesis).

1990s decade (1990-1999): One case. In 1990, a 9-year-old female from the rural municipality of Aguadas, province of Caldas, was bitten in the left thumb by an unvaccinated cat when she was trying to separate it from attacking a chicken. The cat died three days after the aggression. Seven days after the attack, the patient showed clinical signs and died seven

days later. The patient was taken to medical services but the history of aggression by the cat was not mentioned. The patient's physician diagnosed a viral infection and gave palliative treatment for it. Three days later, the patient was taken back to the hospital due to both neck and left arm paralysis. The cat aggression was mentioned in the second visit to the hospital and rabies-related interventions were carried out (e.g., post-exposure vaccination). The confirmation of rabies was given after the death of the patient. The viral variant was not identified or reported. The patient died 14 days after the aggression occurred (Observatorio de Salud de Caldas, 2020).

2000s decade (2000-2009): Five cases. In 2003 (epidemiological week 44), a 13-year-old male patient from the municipality of Quipile, province of Cundinamarca, was diagnosed with rabies V8, a rabies lineage linked to skunks (MinSalud, 2016). Three additional cases were reported in 2008, when the same cat attacked a 10-year-old male patient and a 12-year-old female patient. Thirty-five days later, the male patient showed clinical signs, including odynophagia, neck pain, and fever. Physical examination revealed acute tonsillitis, dicloxacillin and acetaminophen were prescribed. Two days after the first examination, the patient returned with pruritic wheals on the body, being handled as a case of urticaria, and was sent home with azithromycin. Three days after the second exam, the patient presented mild trismus with loss of muscle tone in the left upper limb, odynophagia, neck pain, fever, cervical lymphadenopathy, and suppurative hypertrophic tonsils. Subsequently, difficulty speaking, anesthesia in the left upper limb without muscle tone, cyanosis, convulsions, and respiratory distress were observed. The patient died 49 days after the aggression.

The female patient showed clinical signs 30 days after the attack and consulted a health center due to a 5-days history of right upper limb pain and fever. The patient was sent home with a prescription for analgesics. The next day, the patient returned to the clinic due to persistent symptoms of headache, emesis, pain, and decreased strength in the upper limbs, being diagnosed with scarlet fever, treatment with cephalexin and acetaminophen was initiated. The patient was readmitted due to right upper limb pain and fever, osteomyalgia, headache, pain with decreased strength in the upper limbs, emesis, generalized muscle weakness, drooling, cyanosis, respiratory distress, tonic-clonic seizures in the inferior limbs,

cardiorespiratory arrest, and finally, brain death. The patient died 41 days after the aggression. In both cases, the rabies variant was V3, linked to vampire bats (INS, 2008; Páez et al., 2009).

The third case in 2008 occurred in July when a 9-year-old female from the rural area of the municipality of San Jacinto del Cauca, province of Bolívar, was attacked by a cat at the hands. After the attack, the cat was killed and buried in the same rural area. The girl consulted the health services and specific treatment for rabies was initiated. The patient, however, did not return to continue the immunization protocol. The patient then returned to the health services with neurological symptoms, including an inability to walk, numbness of arms and feet, irritability, and excessive salivation. The viral variant recovered from the patient was V3 (Periódico El País, 2008; Periódico El Tiempo, 2008; Revista Portafolio, 2008; MinSalud, 2012).

In 2009 (epidemiological week 21), a 76-year-old female from the rural area of the municipality of Moniquirá, province of Boyacá, was bitten by her own cat on the left hand. The cat was 24 months old and unvaccinated, and was absent from home for three days before the attack. The cat was reported to have behavioral changes, excessive salivation, and loss of appetite, staying away from people. The patient was assaulted while trying to feed the cat that refused to eat. The cat disappeared from the home two days after the attack. On the same day of the attack, a 5-year-old dog in the same locality and with no previous rabies vaccination, died after losing his appetite for a few days. Thirty-two days after the attack by the cat, the patient showed clinical signs. The patient died 16 days later after the start of the signs. The report mentioned that immediately after the attack, the patient applied lime and salt to the wound. Two weeks later, the patient consulted the medical service due to symptoms of diarrhea, emesis, and headache but did not comment on the bite. One month later, the patient presented tingling in her left arm and initiated with headache that intensified until taken to a physician, referring to blood pressure problems. Relatives told the physician about the cat's bite. The physician did not link the cat's aggression with the symptoms. The patient began to lose mobility in the left arm and the pain spread to the entire arm, back, and head. Three days later, the patient presented emesis and severe general pain, and the health

condition worsened. The patient could not keep her head steady, showed aggressiveness, drooled, lost their memory at times, vomited, screamed, and talked to herself. The patient died 48 days after the aggression and the confirmation of rabies was given after the death by direct immunofluorescence. The rabies variant recovered was V4, linked to insectivorous bats (INS, 2009; Periódico El Tiempo, 2009).

2010s decade (2010-2021): Eight cases. Two cases were reported in 2010. The first case occurred in August when a 13-year-old female patient from the municipality of Enciso, province of Santander, was attacked by a cat. The patient died in August (Santander Hoy, 2010; Vanguardia, 2010). The second case occurred in December when an 11-year-old male from a rural area of the municipality of San Luis, province of Tolima, was attacked by a cat. The viral variant was V3 in both cases (Radio Santa Fe, 2010). In 2012 (epidemiological week 21), a 19-year-old female from the municipality of Roldanillo, province of Valle del Cauca, was attacked by a cat and after four months showed clinical signs and died 131 days after the original report of the aggression. The viral variant was V4 (MinSalud, 2012; INS, 2012).

In 2015, a 9-year-old female patient in a rural area of the municipality of Mesitas del Colegio, province of Cundinamarca, was scratched by a cat and received clinical attention but died 11 days later, the viral variant was V3 (Periódico El Tiempo, 2015; MinSalud, 2017; El Paciente Colombiano, 2019; Cediél, 2020). In 2016, a case of human rabies linked to a cat attack in Girardot, province of Cundinamarca, was reported. The viral variant was an atypical variant related to vampire bats (AV1) (INS, 2019). In 2017 (epidemiological week 3), a case of human rabies linked to a cat attack in the municipality of Tena, province of Cundinamarca, was reported. The viral variant was AV1 (INS, 2019; Cediél, 2020; Observatorio de Salud de Caldas, 2020).

In 2020 (epidemiological week 5), a case of human rabies linked to a cat attack in the municipality of Neiva, province of Huila, was reported in a 26-year-old female. The patient was attacked by their own cat. The cat was absent from home for one day before the incident and presented irritability and hypersalivation. Twenty-three days after the attack, the patient

showed clinical signs, dying 30 days after the aggression. The viral variant was V3 and the confirmation of rabies was given after the death of the patient by direct immunofluorescence, biological test, immunohistochemistry, biological test, and immunohistochemistry (Cediel, 2020; Revista Semana, 2020).

In 2021, a 29-year-old male patient from the rural area of the municipality of La Argentina, province of Huila, was bitten by their own unvaccinated two-months-old female kitten. The patient showed clinical signs 22 days after the attack and consulted a health center due to right arm pain and headache. A few days later the patient presented odontalgia, and paresis and paresthesia on the right upper limb, right hemicrania paresis, hallucinations, psychomotor agitation, difficult swallowing, nystagmus, and right-hand decreased strength, as well as aggressive behavior. The patient was then referred to the ICU with hyporeactive isochores, persistent nystagmus, and a super refractory status. Two days later, bilateral paresis, absence of corneal reflex, areflexia of the upper limbs, bilateral neutral plantar response, no meningeal or cranial activity signs, and endocranial hypertension were observed until his death 41 days after the aggression. The confirmation of rabies was given after the death of the patient by direct immunofluorescence. Although, a PCR-negative result was reported, immunohistochemistry revealed RABV variant V3 (ICA, 2021).

DISCUSSION

Rabies virus spillover transmission from animals to humans has historically focused on dogs as the main aggressor and source of the infection in Colombia. Between 2004 and 2022, animal rabies in Colombia draw attention to a significant concentration of the urban lineage (V1) in the province of Magdalena. During that period there were 27 outbreaks of dog rabies variant V1 in various municipalities. Meanwhile, wildlife RABV lineages exhibited 1357 outbreaks in livestock along the Atlantic coast in the provinces of Santander, Norte de Santander, Arauca, Orinoquia, and Amazonia, including their mountains. In addition, 13 outbreaks of bat RABV lineages were recorded in cats, dogs, and bats in the provinces of Antioquia, Cundinamarca, Huila, Tolima, Valle, Casanare, Magdalena, Meta, and Sucre. Forty cases of human rabies were reported between 2000 and 2022 in the country, with the

latest cases recorded in Neiva and La Argentina, province of Huila, in 2020 and 2021, respectively.

Since 2015, rabies in humans have been clustered in central Colombia, involving the wild lineage of RABV as the pathogen and cats as sources of infection for four rabies cases in humans in the province of Cundinamarca and two in the province of Huila (INS,2022). As such, data presented here support a new epidemiology of rabies where cats are the main transmitter of RABV to humans. This new epidemiology of rabies is not particular to Colombia. There was a marked increase of 17.6% in positive cases of rabies in cats in 2020 in the United States, reaching a total of 288 cases compared to the 245 reported in 2019. This increase in rabid cats was reflected in a significantly higher percentage of rabies incidence in cats (1.7%) compared to the average incidence of the previous five years (1.2%; 95%CI: 1.1-1.2). Notably, nearly 70% of rabid cats were concentrated in six specific states, main in Pennsylvania (19.8%), followed by Maryland, New York, Virginia, Texas, and New Jersey. In the United States, RABV was characterized in only 32.3% of the cases, from which 68 cats were infected with RABV from the Eastern raccoon and 25 with RABV from the Central skunk (Ma et al., 2022). Thus, cat vaccination should be considered the first front of rabies prevention considering the broad RABV circulation in wildlife.

Regarding the risk derived from animal aggressions to humans, a retrospective analysis in Ukraine showed a higher report of dog bites with low human rabies prevalence (0.86%), while cat bites resulted in a higher rabies prevalence (3.7%) (Makovska et al., 2018). In Colombia in 2020, 108,633 animal aggressions to humans with potential RABV exposure were reported in 2020, 23% more compared to 2019 (Observatorio de Salud de Caldas, 2020). Rabies control strategies in Colombia are based on animal attacks or exposure to animal species of risk. Since 2008, this responsive approach has been included within the public health surveillance system (SIVIGILA) (INS, 2018).

In the Americas, there has been a successful reduction in the incidence of human rabies transmitted by dogs. Nevertheless, in the last decade there has been an increase in human rabies involving RABV of wildlife origin. The common vampire bat (*Desmodus rotundus*)

is emerging as the primary source of RABV to other species (Velasco-Villa et al., 2017). The epidemiological trend of RABV in Colombia, however, includes cats as a source of infection to human rabies, but not vampire bats. Since bats are common prey of domestic and feral cats (Welch and Leppanen, 2017), bat RABV lineages now lead the epidemiology of rabies in Colombia over dog RABV lineages (Table 1).

The role of cats in human societies has evolved over history, from being a symbol of sacred origin in ancient Egypt to becoming a preferred pet for families worldwide (Serpell, 2014). Cats can be classified based on their socio-environmental situation where feral cats denote cats that have returned to the wild or developed without human contact, stray cats refer to lost or abandoned cats that maintain a tolerance to humans, domestic cats as those living with their owners indoors, and semidomestic cats as animals under human care but allowed to roam freely outdoors (Turner, 2017). These changing dynamics have led to an increase in the cat population in urban and rural areas, raising the likelihood of encounters with wild species and the risk of various diseases. Nevertheless, the main factor driving cats situation is their owners' who often abandon their pets, contributing to the growth of stray cats and increasing their exposure to diseases (Makovska et al., 2018).

In Latin America, vampire bats and frugivorous bats (e.g., *Artibeus* spp.) have been identified as RABV reservoirs (Castelo-Branco et al., 2023). Vampire bats feed on the blood of livestock, wildlife, and humans, and are typically found in rural habitats. Insectivorous and frugivorous bats, however, have been identified as potential sources of RABV in urban areas (Nunes et al., 2017). In urban areas, stray and feral cats, generally lacking rabies vaccination and basic veterinary care, could be particularly exposed to bat-borne rabies. This situation underscores the importance of addressing the lack of preventive veterinary medicine for urban cats as a means to reduce the risk of bat-borne rabies to humans.

The geographical presentation of rabies cases in humans in Colombia has a well-defined distribution restricted to an Andean corridor (Figure 2). The Andean rabies corridor can be linked to the presence and abundance of bat reservoirs (perhaps presenting a similar dynamic to that mentioned in Brazil), sustaining the sylvatic cycle of RABV in these areas or a high

density of outdoor cats with access to infected bats. Alternatively, this geographic pattern could highlight a biased epidemiology influenced by higher detectability of cases in sites of the higher human densities as occurs in the highlands of Colombia.

In conclusion, the epidemiological patterns reported here should be used to update our understanding of the epidemiology of rabies. Human population dynamics have changed in recent decades in the Colombian highlands, likely influencing the population of cats in urban and rural areas, and disturbing the ecology of local bat colonies. Higher human density can lead to higher densities of unvaccinated cats with access to outdoors in areas with the presence of bats, with cats narrowing the human-wildlife interface.

Epidemiological information of cats involved in human rabies cases was found to be generally lacking and scattered, limiting effective and timely patient management after exposure. As such, it is essential to promote improved disease management protocols aiming to enhance early detection of cat attacks and strengthen epidemiological surveillance of cat-borne rabies. In addition, laboratory characterization of RABV lineages linked to outbreaks should be decentralized and mandatory at the government level to elucidate the sources of infections. Most rabies cases occurred in children (9-13 years old) living in the highlands, which emphasizes the need to revise mass vaccination programs in areas of risk. We argue that establishing pet vaccination in the Andes should be mandatory and prioritizing cats, especially outdoor cats. Our findings suggest that cats under three months of age should be considered in vaccination programs. Mass cat vaccination could lead to reduce the risk of rabies infection in cats and the consequent spillover transmission to humans.

CONFLICT OF INTEREST

he authors declare that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from references cited and also from the corresponding author upon request.

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