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Human Rabies Epidemiology and Diagnosis

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1. Introduction

Rabies is a fatal viral infection that is most commonly spread to humans through the bite of an infected animal. The disease is an acute progressive encephalitis caused by highly neurotropic zoonotic viruses belonging to the *Lyssavirus* genus in the *Rhabdoviridae* family (Kuzmin, 2009). Of the twelve species of lyssaviruses, rabies virus (RABV) is the most important with respect to its impact on public health. RABV is distributed globally and found on all continents except Australia and Antarctica. In the United States, multiple RABV variants circulate in wild mammalian reservoir populations including raccoons, skunks, foxes, and bats. Rabies has the highest case fatality rate of any infectious disease and kills an estimated 55,000 people annually, primarily in developing countries within Africa and Asia (Knobel, 2005). However, rabies is a preventable disease. Postexposure prophylaxis (PEP) consisting of rabies immune globulin and rabies vaccine is successful in preventing the disease when administered promptly after an exposure to the virus has occurred. Additionally, vaccination of domestic animals against rabies and stray animal control programs greatly reduce the risk of RABV transmission to humans. Implementation of these measures in developed countries such as the United States has led to drastic declines in the incidence of human rabies. Despite this success, rabies remains a significant public health issue. Each year approximately 7,000 rabid animals are reported in the United States (Blanton, 2010). Up to 35,000 people annually are estimated to receive PEP due to exposures to suspect rabid animals (Christian, 2009). Given the high cost of rabies PEP, this represents a substantial economic burden as well. A clear understanding of the epidemiology of human rabies in the United States can help to manage these human exposures using the best available evidence. In this way, the risk of infection can be assessed more precisely and ensure rabies PEP is administered more judiciously. The identification of epidemiologic patterns can also be used to focus educational messages for human rabies prevention and thereby increase public awareness of rabies and the importance of seeking medical care after a potential exposure occurs. Furthermore, providing accurate descriptions of the clinical presentation of human rabies is essential in recognizing and diagnosing the disease in a timely fashion. Delayed or missed diagnoses place others at risk of exposure if appropriate infection control precautions are not instituted, exposures are not treated appropriately, or organs or tissues from an infected individual are used for transplantation (Houff, 1979; Javadi, 1996; Hellenbrand, 2005; Kusne, 2005; Srinivasan, 2005). An early diagnosis also

provides the patient with the opportunity for treatment and possible survival. Insights gained from each attempt at treatment further our understanding of the disease and add to the body of knowledge that can be applied to future cases. When rabies is ruled out, efforts can be focused on identifying more treatable causes of encephalitis. With these goals in mind, this review will describe the epidemiology of human rabies, examine the signs and symptoms of disease, and review the laboratory diagnostic testing and results for all reported human rabies cases in the United States between 1960 and 2010.

2. Methods

2.1 Case definition and data sources

This review includes all cases of human rabies reported to the Centers for Disease Control and Prevention (CDC) that occurred within the United States and its territories between the years 1960–2010. These cases include both indigenous cases occurring in United States nationals as well as imported cases in foreign nationals diagnosed and treated within the United States and it territories. All cases were confirmed using standard diagnostic laboratory tests performed by CDC or by a state laboratory and were reported by health authorities as part of ongoing national surveillance. The clinical and laboratory findings were taken from CDC's Morbidity and Mortality Reports, published journal articles, and unpublished CDC notes. In addition, this review contains clinical data from patients with suspected rabies submitted to the CDC for laboratory diagnostic testing between the years 2007–2010 for whom rabies was subsequently ruled out (non-rabies cases).

2.2 Variable definitions

Onset of illness was defined as either the first day of reported symptoms attributable to rabies or, when this date was unknown, the date when medical care was first sought prior to the confirmation of rabies. Signs and symptoms attributable to rabies included aerophobia, hydrophobia, paresthesia or localized pain, priapism or spontaneous ejaculation, dysphagia, localized weakness, fever, muscle spasm, hypersalivation, anxiety, hallucinations, autonomic instability, agitation or combativeness, nausea or vomiting, ataxia, anorexia, insomnia, seizures, confusion or delirium, malaise or fatigue, and headache. When a bite from a known species, laboratory RABV exposure, or transplantation of infected organs or tissue was reported the species of biting animal or type of exposure and the location of the exposure incident are indicated in the exposure history. Probable exposures where no known bite occurred but physical contact with an animal or close proximity to an animal was reported are also indicated. All other exposures were defined as "unknown." The RABV variant determined by antigenic or molecular typing also provides evidence of the likely source of infection and is particularly useful when no exposure history is known. The type of case was defined as indigenous if the bite incident occurred in the United States or its territories or if the RABV variant identified matched an indigenous source. Imported cases were defined by an exposure occurring outside of the United States or its territories or by identification of a RABV variant not found within the United States. The diagnosis of rabies was considered antemortem when samples were obtained specifically for rabies diagnostic testing before death or when the signs, symptoms, and clinical history were deemed sufficient by the clinicians involved to establish the diagnosis.

2.3 Statistical analysis

Data analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Data were summarized using descriptive statistics and comparisons between human rabies cases and cases of encephalopathy with negative rabies diagnostic testing were made using Chi-square or Fisher's exact test. Some variables were dichotomized before statistical comparisons for determination of odds ratios (OR) and 95% confidence intervals (CI). Associations were considered statistically significant at p-values less than 0.05.

2.4 Diagnostic laboratory testing
2.4.1 Detection of antigen

RABV antigens were detected using the direct fluorescent antibody (DFA) test of skin biopsy specimens, touch impressions of corneal epithelial cells, or fresh brain tissue as described (CDC, 2006). Skin biopsy specimens were taken from the nuchal area of the neck where viral antigens can be present in hair follicles containing cutaneous nerves, as described previously (Noah, 1998).

2.4.2 Serology

RABV antibody testing for cases reported before 1973 utilized the mouse neutralization test (Jackson, 2003). After 1973, serology was determined using the rapid fluorescent focus inhibition test (RFFIT) or the indirect fluorescence assay (IFA), as described previously (Noah, 1998). The RFFIT measures RABV neutralizing antibodies while the IFA detects serum reactive with RABV antigen in infected cell cultures. Antibodies in serum were considered diagnostic if there was no history of rabies immunization prior to sample collection. Antibodies in cerebrospinal fluid (CSF) were considered diagnostic regardless of rabies immunization history.

2.4.3 Virus isolation

RABV was isolated through intracerebral inoculation of suckling mice or by addition of suspensions of brain or saliva specimens to cultured mouse neuroblastoma cells, as described previously (Noah, 1998).

2.4.4 RNA detection

Viral nucleic acids were obtained using standard extraction procedures and reagents. Samples used for nucleic acid extraction included saliva, fresh brain, paraffin-embedded brain, and nuchal skin. Reverse transcription polymerase chain reaction (RT-PCR) was performed using primers targeting the sequence of the nucleoprotein gene. Standard dideoxynucleotide sequencing methods were utilized to determine the nucleotide sequences of all PCR products obtained, as described previously (Noah, 1998).

2.4.5 Identification of rabies virus variants

RABV variants were identified through antigenic and/or molecular typing. Antigenic typing uses a reference panel of monoclonal antibodies directed against the nucleoprotein to determine the variant of RABV isolates. Molecular typing methods identify the RABV variant by comparing the nucleotide sequence obtained by RT-PCR with a database of sequences from known reservoirs within the United States as well as foreign countries throughout the world.

Patient	Date of Death	Date of Onset	Age (yrs)	Sex	State/ Territory of Death	Exposure History	Variant*	Type	Diagnosis	PEP (n)	Ref.
1	5/21/1960	5/19/1960	9	Male	Georgia	Dog-Georgia	--	Indigenous	Postmortem	--	1
2	8/6/1960	8/1/1960	19	Female	Ohio	Cat-Guatemala	--	Imported	Postmortem	--	2
3	1/6/1961	12/30/1960	53	Female	Kentucky	Fox-Kentucky	--	Indigenous	Postmortem	--	3
4	1/20/1961	1/7/1961	76	Male	California	Dog-California	--	Indigenous	Postmortem	--	4
5	6/26/1961	6/22/1961	74	Male	Kentucky	Fox-Kentucky	--	Indigenous	Postmortem	--	5
6	7/25/1962	7/16/1962	3	Male	Texas	Dog†-Texas	--	Indigenous	Postmortem	--	6
7	10/8/1962	10/1/1962	11	Male	Idaho	Bat†-Idaho	--	Indigenous	Postmortem	--	7
8	9/4/1963	8/29/1963	52	Female	Alabama	Dog†-Alabama	--	Indigenous	Postmortem	--	8
9	9/1/1964	8/24/1964	10	Male	Minnesota	Skunk-Minnesota	--	Indigenous	Postmortem	--	9
10	5/21/1965	5/14/1965	60	Male	West Virginia	Dog-West Virginia	--	Indigenous	Postmortem	--	10
11	9/5/1966	8/27/1966	10	Male	South Dakota	Skunk-South Dakota	--	Indigenous	Postmortem	--	11
12	7/25/1967	7/16/1967	58	Female	New York	Dog-Guinea	--	Imported	Postmortem	--	12
13	7/31/1967	7/21/1967	8	Male	Oregon	Dog-Egypt	--	Imported	Antemortem‡	--	13
14	10/10/1968	8/7/1968	14	Male	Kansas	Dog-Kansas	--	Indigenous	Antemortem	--	14
15	8/29/1969	4/18/1969	2	Male	California	Bobcat-California	--	Indigenous	Antemortem	--	15
16	7/31/1970	7/20/1970	11	Male	Arizona	Skunk-Arizona	--	Indigenous	Postmortem	--	16
17	8/2/1970	7/25/1970	4	Male	South Dakota	Skunk-South Dakota	--	Indigenous	Antemortem‡	--	16
18	Survived	10/30/1970	6	Male	Ohio	Bat-Ohio	--	Indigenous	Antemortem	--	17
19	4/23/1971	3/27/1971	6	Male	California	Dog-Mexico	--	Imported	Antemortem	--	18
20	11/25/1971	11/17/1971	64	Male	New Jersey	Bat-New Jersey	--	Indigenous	Postmortem	--	19
21	2/22/1972	2/9/1972	70	Male	California	Dog-Philippines	--	Imported	Postmortem	8	20
22	3/9/1972	3/1/1972	56	Male	Texas	Lab aerosol-Texas	--	Indigenous	Postmortem	18	21
23	9/22/1973	9/7/1973	26	Male	Kentucky	Bat-Kentucky	--	Indigenous	Antemortem	--	22
24	1/15/1975	1/1/1975	60	Male	Minnesota	Cat-Minnesota	Skunk§	Indigenous	Postmortem	--	23
25	8/2/1975	7/27/1975	51	Male	Puerto Rico	Dog-Puerto Rico	--	Indigenous	Postmortem	--	24
26	8/30/1975	8/11/1975	16	Female	California	Dog-Mexico	--	Imported	Antemortem	--	25
27	6/27/1976	6/4/1976	55	Female	Maryland	Bat-Maryland	Bat§	Indigenous	Antemortem	--	26
28	9/3/1976	8/30/1976	17	Male	Texas	Dog-Mexico	--	Imported	Postmortem	19	27
29	Survived	4/14/1977	32	Male	New York	Lab-NY	--	Indigenous	Antemortem	--	28
30	7/22/1978	7/1/1978	39	Male	Oregon	Unknown	Bat§	Indigenous	Postmortem	--	29

Patient	Date of Death	Date of Onset	Age (yrs)	Sex	State/ Territory of Death	Exposure History	Variant*	Type	Diagnosis	PEP (n)	Ref.
31	9/17/1978	9/1/1978	37	Female	Idaho	Transplant-ID	Bat§	Indigenous	Postmortem	--	29
32	6/17/1978	6/13/1978	25	Male	Texas	Unknown	--	Imported	Postmortem	14	30
33	1/4/1979	12/1/1978	50	Male	Pennsylvania	Unknown	--	Indigenous	Postmortem	180	31
34	7/15/1979	6/5/1979	8	Male	Texas	Dog†-Mexico	--	Imported	Antemortem	31	32
35	7/3/1979	6/24/1979	7	Female	Texas	Dog-Texas	Dog§	Indigenous	Antemortem	--	33
36	8/5/1979	7/18/1979	37	Male	California	Dog-Mexico	--	Imported	Postmortem	37	34
37	10/4/1979	9/15/1979	24	Male	Oklahoma	Unknown	Bat§	Indigenous	Antemortem	52	35
38	11/30/1979	11/20/1979	45	Male	Kentucky	Unknown	Bat§	Indigenous	Antemortem	--	36
39	7/4/1981	6/21/1981	27	Male	Oklahoma	Unknown	Skunk§	Indigenous	Postmortem	102	37
40	9/11/1981	8/19/1981	40	Male	Arizona	Dog-Mexico	Dog	Imported	Antemortem	41	38
41	1/28/1983	1/1/1983	30	Male	Massachusetts	Dog-Nigeria	Dog	Imported	Antemortem	28	39
42	3/9/1983	2/5/1983	5	Female	Michigan	Bat†-Michigan	No Isolate	Indigenous	Antemortem	54	40
43	8/8/1984	7/11/1984	12	Female	Texas	Unknown	Dog	Imported	Antemortem	142	41,42
44	9/29/1984	9/14/1984	12	Male	Pennsylvania	Unknown	Bat§	Indigenous	Antemortem	46	43
45	10/1/1984	9/3/1984	72	Female	California	Dog-Guatemala	Dog	Imported	Postmortem	179	44
46	5/20/1985	5/2/1985	19	Male	Texas	Unknown	Dog	Imported	Postmortem	85	45
47	12/15/1987	11/26/1987	13	Male	California	Unknown	Dog	Imported	Postmortem	87	42,46 47
48	2/3/1989	1/17/1989	18	Male	Oregon	Unknown	Dog	Imported	Postmortem	9	42,48
49	6/5/1990	5/30/1990	22	Male	Texas	Bat-Texas	Tb	Indigenous	Antemortem	67	49
50	8/20/1991	8/7/1991	55	Female	Texas	Unknown	Dog	Indigenous	Antemortem	43	50
51	8/25/1991	8/17/1991	29	Male	Arkansas	Bat†-Arkansas	Ln/Ps	Indigenous	Postmortem	99	50
52	10/8/1991	10/2/1991	27	Female	Georgia	Unknown	Ln/Ps	Indigenous	Postmortem	--	50
53	5/8/1992	4/21/1992	11	Male	California	Dog-India	Dog	Imported	Antemortem	17	51
54	7/11/1993	7/5/1993	11	Female	New York	Unknown	Ln/Ps	Indigenous	Postmortem	55	52
55	11/9/1993	11/3/1993	82	Male	Texas	Unknown	Ln/Ps	Indigenous	Antemortem	73	53
56	11/21/1993	11/7/1993	69	Male	California	Dog-Mexico	Dog	Imported	Antemortem	34	53
57	1/18/1994	1/1/1994	44	Male	California	Unknown	Ln/Ps	Indigenous	Postmortem	26	54
58	6/21/1994	6/3/1994	40	Male	Florida	Unknown	Dog	Imported	Postmortem	16	55
59	10/11/1994	9/29/1994	24	Female	Alabama	Bat†-Alabama	Tb	Indigenous	Postmortem	99	56
60	10/15/1994	10/3/1994	41	Male	West Virginia	Bat†-West Virginia	Ln/Ps	Indigenous	Antemortem	48	57
61	11/23/1994	11/8/1994	42	Female	Tennessee	Unknown	Ln/Ps	Indigenous	Antemortem	47	56

Patient	Date of Death	Date of Onset	Age (yrs)	Sex	State/ Territory of Death	Exposure History	Variant*	Type	Diagnosis	PEP (n)	Ref.
62	11/27/1994	11/13/1994	14	Male	Texas	Dog†-Texas	Dog	Indigenous	Antemortem	54	56
63	3/15/1995	3/6/1995	4	Female	Washington	Bat†-Washington	Msp	Indigenous	Antemortem	72	58
64	9/21/1995	9/8/1995	27	Male	California	Bat†-California	Tb	Indigenous	Antemortem	12	59
65	10/3/1995	9/18/1995	13	Female	Connecticut	Bat†-Connecticut	Ln/Ps	Indigenous	Antemortem	83	60
66	11/9/1995	10/26/1995	74	Male	California	Bat†-California	Ln/Ps	Indigenous	Postmortem	76	59
67	2/8/1996	12/29/1995	26	Male	Florida	Dog†-Mexico	Dog	Imported	Antemortem	4	61
68	8/20/1996	8/10/1996	32	Female	New Hampshire	Dog-Nepal	Dog	Imported	Antemortem	7	62,63
69	10/15/1996	9/28/1996	42	Female	Kentucky	Unknown	Ln/Ps	Indigenous	Antemortem	87	64
70	12/19/1996	12/4/1996	49	Male	Montana	Unknown	Ln/Ps	Indigenous	Antemortem	26	64
71	1/5/1997	12/20/1996	65	Male	Montana	Bat†-Montana	Ln/Ps	Indigenous	Postmortem	60	65
72	1/18/1997	12/30/1996	64	Male	Washington	Unknown	Ef	Indigenous	Postmortem	55	65
73	10/17/1997	10/3/1997	71	Male	Texas	Bat†-Texas	Ln/Ps	Indigenous	Postmortem	46	66
74	10/23/1998	10/12/1998	32	Male	New Jersey	Bat†-New Jersey	Ln/Ps	Indigenous	Antemortem	50	66
75	12/31/1998	12/14/1998	29	Male	Virginia	Unknown	Ln/Ps	Indigenous	Antemortem	48	67
76	9/20/2000	9/13/2000	49	Male	California	Bat†-California	Tb	Indigenous	Antemortem	37	68
77	10/9/2000	9/26/2000	54	Male	New York	Dog-Ghana	Dog, African	Imported	Antemortem	24	68,69
78	10/10/2000	10/3/2000	26	Male	Georgia	Bat†-Georgia	Tb	Indigenous	Postmortem	71	68
79	10/25/2000	10/8/2000	47	Male	Minnesota	Bat-Minnesota	Ln/Ps	Indigenous	Antemortem	20	68
80	11/1/2000	10/12/2000	69	Male	Wisconsin	Bat†-Wisconsin	Ln/Ps	Indigenous	Postmortem	27	68
81	2/4/2001	1/19/2001	72	Male	California	Unknown	Dog, Philippines	Imported	Postmortem	11	70
82	3/31/2002	3/18/2002	28	Male	California	Bat†-California	Tb	Indigenous	Antemortem	46	71
83	8/31/2002	8/21/2002	13	Male	Tennessee	Bat†-Tennessee	Ln/Ps	Indigenous	Antemortem	23	72
84	9/28/2002	9/16/2002	20	Male	Iowa	Unknown	Ln/Ps	Indigenous	Antemortem	124	73
85	3/10/2003	2/17/2003	25	Male	Virginia	Unknown	Raccoon	Indigenous	Postmortem	8	74
86	6/5/2003	5/28/2003	65	Male	Puerto Rico	Dog-Puerto Rico	Mongoose/ Dog	Indigenous	Postmortem	--	75
87	9/14/2003	8/23/2003	66	Male	California	Bat-California	Ln/Ps	Indigenous	Antemortem	6	76
88	2/15/2004	2/9/2004	41	Male	Florida	Dog-Haiti	Dog, Haiti	Imported	Postmortem	24	77
89	5/4/2004	4/27/2004	20	Male	Arkansas	Bat-Arkansas	Tb	Indigenous	Postmortem	--	78,79

Patient	Date of Death	Date of Onset	Age (yrs)	Sex	State / Territory of Death	Exposure History	Variant*	Type	Diagnosis	PEP (n)	Ref.
90	5/31/2004	5/25/2004	53	Male	Texas	Transplant-Texas	Tb	Indigenous	Postmortem	--	78,79
91	6/9/2004	5/29/2004	50	Female	Texas	Transplant-Texas	Tb	Indigenous	Postmortem	--	78,79
92	6/10/2004	6/2/2004	55	Female	Texas	Tissue Graft-Texas	Tb	Indigenous	Postmortem	--	79
93	6/21/2004	5/31/2004	18	Male	Texas	Transplant-Texas	Tb	Indigenous	Postmortem	--	78,79
94	Survived	10/13/2004	15	Female	Wisconsin	Bat-Wisconsin	No Isolate	Indigenous	Antemortem	37	80,81
95	10/26/2004	10/19/2004	22	Male	California	Unknown	Dog, El Salvador	Imported	Postmortem	39	82
96	9/27/2005	9/11/2005	10	Male	Mississippi	Bat†-Mississippi	No Isolate	Indigenous	Postmortem	32	83
97	5/12/2006	5/4/2006	16	Male	Texas	Bat†-Texas	Tb	Indigenous	Antemortem	53	84,85
98	11/2/2006	9/30/2006	10	Female	Indiana	Bat-Indiana	Ln/Ps	Indigenous	Antemortem	66	86
99	12/13/2006	11/15/2006	11	Male	California	Dog-Philippines	Dog, Philippines	Imported	Antemortem	24	86
100	10/20/2007	9/19/2007	46	Male	Minnesota	Bat-Minnesota	No Isolate	Indigenous	Antemortem	54	87
101	3/18/2008	3/17/2008	16	Male	California	Dog/Fox-Mexico	Tbr Related	Imported	Postmortem	20	88
102	11/30/2008	11/19/2008	55	Male	Missouri	Bat†-Missouri	Ln/Ps	Indigenous	Antemortem	5	89
103	Survived	2/25/2009	17	Female	Texas	Bat†-Texas	No Isolate	Indigenous	Antemortem	1	90
104	10/20/2009	10/5/2009	43	Male	Indiana	Unknown	Ln/Ps	Indigenous	Postmortem	20	91
105	11/11/2009	10/20/2009	55	Male	Michigan	Bat†-Michigan	Ln/Ps	Indigenous	Postmortem	17	92
106	11/20/2009	10/23/2009	42	Male	Virginia	Dog-India	Dog, India	Imported	Antemortem	32	93
107	8/21/2010	7/30/2010	19	Male	Louisiana	Bat-Mexico	Ds	Imported	Antemortem	95	94
108	1/8/2011	12/23/2010	70	Male	Wisconsin	Unknown	Ln/Ps	Indigenous	Antemortem	7	95

* Ln/Ps = *Lasionycteris noctivagans* or *Perimyotis subflavus*, the silver-haired bat or the tricolored bat; Msp = *Myotis*, species unknown; Tb = *Tadarida brasiliensis*, the Brazilian (Mexican) free-tailed bat; Ef = *Eptesicus fuscus*, the big brown bat; Ds = *Desmodus rotundus*, the common vampire bat; -- = Not performed or unknown,
† Probable location or source of exposure, ‡ Diagnosis based on signs, symptoms, and clinical history, § RABV variant determined from archived pathological tissue

Table 1. Human Rabies in the United States, 1960–2010

3. Results

A total of 108 cases of human rabies were reported in the United States from 1960 through 2010 (Table 1). One hundred and four cases (96%) died and 4 (4%) survived. Fifty-three cases were diagnosed antemortem while 55 cases were diagnosed postmortem. Fifty-one of the cases diagnosed antemortem had positive laboratory diagnostic test results with the remaining 2 cases diagnosed based on the signs, symptoms, and clinical history alone

3.1 Demographic Information

The median age of patients was 29 years and ranged from 2 to 82 years. Forty cases (37%) were less than 20 years of age and 20 (19%) were 60 years or older. Eighty-three cases (77%) were male and 25 (33%) were female. Cases were reported from 35 states and territories (Figure 1); California and Texas were the only states with more than 5 cases and reported 20 cases (19%) and 19 cases (18%) respectively. Of the states not represented in this series, all had reported a case of human rabies within the last century with the exception of Hawaii, North Dakota, Wyoming and Vermont. Illness onset occurred in all months but was most likely to occur during the fall (August, September, and October) when compared to other seasons (P-value = 0.001). Similarly, definite exposures occurring within the United States were more frequent in fall and summer months though this observation was not statistically significant (P-value = 0.27).
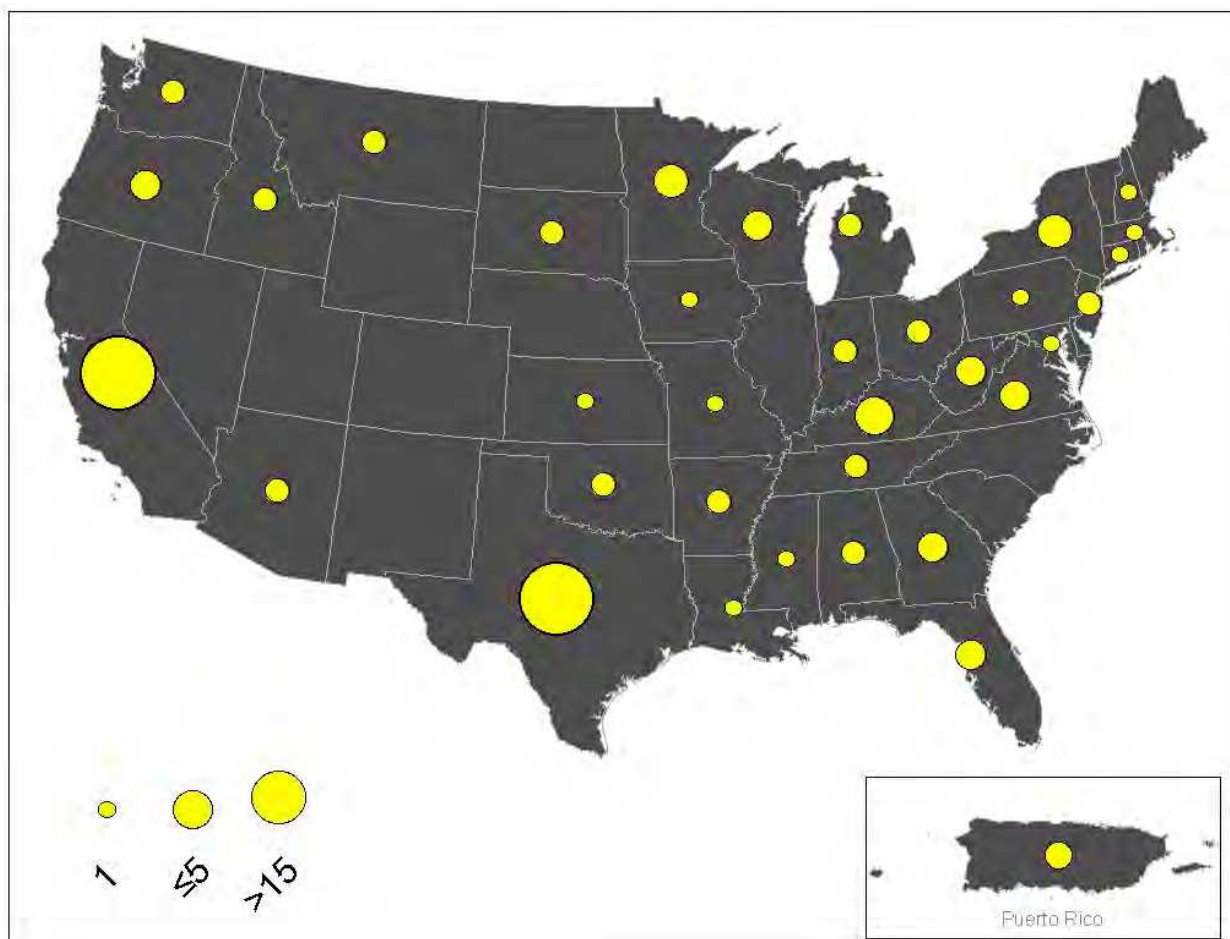
Fig. 1. Geographic Distribution of Human Rabies Cases in the United States, 1960–2010

3.2 Source of infection

The majority of human rabies cases (78/108; 72%) resulted from exposures that occurred within the United States and its territories. However, exposures in 12 foreign countries were responsible for a total of 30 imported cases. Exposures in Mexico were the most common and accounted for 13 imported cases. Animals were linked epidemiologically to 98 cases (91%) either by exposure history or RABV variant typing. Transplantation of infected organs or tissue was responsible for 5 cases (5%) and exposure to a laboratory RABV was implicated in two cases (2%). In 3 cases (3%) there was no history of exposure and no RABV variant identified to suggest a likely source of infection. The animal species linked epidemiologically to human rabies were bats (48/98; 49%), dogs (37/98; 38%), skunks (5/98; 5%), foxes (2/98; 2%), a cat (1/98; 1%), a bobcat (1/98; 1%), and a raccoon (1/98; 1%). The species responsible for infection was unclear in three cases in which the RABV variant identified did not match the exposure history; patient 24 reported a bite from a stray cat while a RABV variant associated with skunks was identified, patient 55 reported contact with a sick cow that later died while a RABV variant associated with bats was identified, and patient 101 had a history of exposure to a dog and a fox while the RABV variant identified was most closely related to viruses found in bats. These appear to have been spillover infection from a primary reservoir species to another animal. In all other cases where an animal exposure was reported the RABV variant identified matched the species of the exposing animal.

3.3 Exposure history

A definite history of exposure to RABV was reported in 54 cases; 47 reported an animal bite, 2 involved exposures to laboratory RABV, and 5 had undergone transplantation of infected organs or tissue. A probable exposure was reported in 26 cases, 21 of which involved a probable exposure to a bat and 5 described a probable exposure to a dog. Of the 28 cases with an unknown exposure, a bat RABV variant was identified in 16 cases, a dog RABV variant was identified in 8 cases, and RABV variants associated with raccoons and skunks were identified in 1 case each. Among the definite exposures involving animal bites, 27 cases were indigenous cases involving bites from 12 bats, 7 dogs, 4 skunks, 2 foxes, 1 cat, and 1 bobcat. Only 2 of the 20 imported cases involved a RABV variant not associated with a domestic animal species. Only 9 animals involved in exposures were available for diagnostic testing, though all tested positive for RABV antigen. With respect to seasonality, rabies cases associated with bats (either by exposure or by identification of a bat RABV variant) were more likely to have onset of illness during the fall when compared to all other cases excluding those acquired through transplantation (OR 3.30; 95% CI 1.45–7.54). Exposures to bats were also more likely to occur during fall months when compared to exposures to other animals (OR 16.50; 95% CI 1.83–148.61).

3.4 Prophylaxis

Sixteen patients received PEP prior to the onset of symptoms. All of these cases occurred prior to 1980 and before the introduction of modern cell culture vaccines. Only two cases completed the PEP regimen according to recommended guidelines and can be considered true failures. The failure of PEP to prevent disease in the remaining 14 patients was attributed to either a delay in administration (i.e. administered greater than 72 hours after exposure), receipt of too few doses of vaccine, or failure to administer rabies immune globulin. Two patients had received rabies vaccine prior to their exposure: patient 22

received four doses of an experimental rabies vaccine 13 years prior to illness onset, however subsequent serologic testing failed to detect antibodies in serum; patient 29 received pre-exposure prophylaxis and regular booster doses with duck embryo vaccine and had a positive RABV antibody titer 6 months before exposure. Patient 22 died of his illness, while patient 29 survived.

3.5 Clinical course

Excluding cases acquired through laboratory exposures and tissue and organ transplantation, specific dates of definite and probable exposures reported for 28 cases were used to calculate a median incubation period of 41.5 days (range 8–701 days). Fifty patients had sought healthcare prior to admission with a median of one day (range 0–6 days) between illness onset and presentation for medical evaluation. Hospital admission dates were reported in 94 cases with a median of 4 days (range 0–16 days) from the onset of illness to hospital admission. Median time from onset of illness to admission to an intensive care unit (ICU) was also 4 days (range 1–13 days) in 14 cases reporting ICU admission date. Similarly, in 65 cases reporting the date of intubation the median time from onset of illness to intubation was 5 days (range 1–19 days). Time from onset of illness to development of fever was reported in 30 cases giving a median of 2 days (range 0–11 days); time from onset of illness to development of coma was reported in 33 cases giving a median of 7 days (range 1–28 days). The median length of illness (defined as days from illness onset until death) was 13.5 days (range 1–133 days).

3.6 Comparison of rabies cases and non-rabies cases
3.6.1 Demographics

Data available from 108 confirmed human rabies cases and 144 encephalitis cases where rabies was ruled out by laboratory diagnostic testing were compared (Table 2). Rabies cases were older on average than non-rabies cases with a mean of 34.4 years (range 2–82 years) versus 30.7 years (range <1–78 years). However, this result was not statistically significant. Male gender was nearly 2 times more likely among rabies cases than non-rabies cases (P-value 0.019).

Variable	Positive, N=108 n (%)	Negative, N=144 n (%)	Odds Ratio (95% CI*)	P-value
Mean age (range)	34.35 (2–82)	30.72 (<1–78)		0.173
Aerophobia	10 (9.3%)	1 (0.7%)	14.59 (1.84–115.83)	0.001†
Hydrophobia	36 (33.3%)	9 (6.3%)	7.50 (3.42–16.43)	<0.001†
Paresthesia or localized pain	54 (50.0%)	21 (14.6%)	5.86 (3.22–10.64)	<0.001†
Priapism or spontaneous ejaculation	4 (3.7%)	2 (1.4%)	2.73 (0.50–15.19)	0.41
Dysphagia	53 (49.1%)	43 (29.9%)	2.26 (1.35–3.80)	0.003†
Localized weakness	44 (40.7%)	34 (23.6%)	2.22 (1.29–3.83)	0.004†
Male gender	83 (76.9%)	87 (62.6%)	1.98 (1.13–3.49)	0.019†
Fever	90 (83.3%)	113 (78.5%)	1.37 (0.72–2.61)	0.422
Muscle spasm	45 (41.7%)	59 (41.0%)	1.03 (0.62–1.71)	1

Variable	Positive, N=108 n (%)	Negative, N=144 n (%)	Odds Ratio (95% CI*)	P-value
Hypersalivation	28 (25.9%)	38 (26.4%)	0.98 (0.55–1.72)	1
Anxiety	33 (30.6%)	51 (35.4%)	0.80 (0.47–1.37)	0.50
Hallucinations	26 (24.1%)	42 (19.2%)	0.77 (0.44–1.36)	0.39
Autonomic instability	29 (26.9%)	47 (32.6%)	0.76 (0.44–1.31)	0.34
Agitation or combativeness	55 (50.9%)	86 (59.7%)	0.70 (0.42–1.16)	0.20
Nausea or vomiting	38 (35.2%)	66 (45.8%)	0.64 (0.38–1.07)	0.09
Ataxia	20 (18.5%)	38 (26.4%)	0.63 (0.34–1.17)	0.17
Anorexia	19 (17.6%)	37 (25.7%)	0.62 (0.33–1.15)	0.17
Insomnia	11 (10.2%)	27 (18.8%)	0.49 (0.23–1.04)	0.08
Confusion or delirium	67 (62.0%)	123 (85.4%)	0.28 (0.15–0.51)	<0.001†
Seizures	27 (25.0%)	79 (54.9%)	0.27 (0.16–0.47)	<0.001†
Malaise or fatigue	39 (36.1%)	101 (70.1%)	0.24 (0.14–0.41)	<0.001†
Headache	29 (26.9%)	90 (62.5%)	0.22 (0.13–0.38)	<0.001†
* CI = Confidence interval, † Statistically significant				

Table 2. Signs and Symptoms Among Cases Testing Positive and Negative for Rabies

3.6.2 Seasonality

The onset of illness of rabies cases was more likely to occur during summer or fall months (May through October) when compared to non-rabies cases (OR 1.77; 95% CI 1.04–3.01). While no significant difference was observed between indigenous rabies cases and non-rabies cases in the seasonal pattern of exposures to animals, the limited number of cases reporting a definite animal exposure was a limiting factor in this analysis.

3.6.3 Signs and symptoms

The presenting signs and symptoms of human rabies in the United States were often nonspecific such as fever, malaise, headache, weakness, fatigue, sore throat, and anorexia. The most commonly reported signs and symptoms reported among rabies cases during the course of illness were fever (83%), confusion or delirium (62%), agitation or combativeness (51%), paresthesia or localized pain (50%), and dysphagia (49%). In contrast, the most common signs and symptoms reported among non-rabies cases were confusion or delirium (85%), fever (78%), malaise or fatigue (70%), headache (63%), and agitation or combativeness (60%). When comparing these two groups, aerophobia, hydrophobia, and paresthesia or localized pain were more likely to be reported among rabies cases than non-rabies cases with an OR of 14.59, 7.50, and 5.86 respectively (P-values ≤ 0.001). Dysphagia and localized weakness were also more likely to occur among rabies cases with ORs of 2.73 and 2.26 (P-values ≤ 0.004). Priapism or spontaneous ejaculation was reported more commonly among rabies cases (OR 2.73) but this finding did not reach statistical significance. Among non-rabies cases, headache, malaise or fatigue, seizures, and confusion or delirium were more frequent than in rabies cases with ORs of 0.22–0.28 (P-values <0.001). Although not statistically significant, insomnia was also seen more often in non-rabies cases. Fever, muscle spasm, hypersalivation, anxiety, hallucinations, autonomic instability, agitation or

combativeness, nausea or vomiting, and ataxia all appeared to occur with equal likelihood in rabies and non-rabies cases.

3.6.4 Laboratory values

Laboratory values reported for the first collected samples of serum and CSF from rabies and non-rabies cases were compared. The serum white blood cells of rabies cases were elevated higher than non-rabies cases with mean values of 14.8 x 10^3 cells/µL (range 7.0–46.6 x 10^3 cells/µL) and 12.1 x 10^3 cells/µL (range 2.9–29.4 x 10^3 cells/µL) for rabies and non-rabies cases respectively (P-value 0.009). Over 95% of both rabies and non-rabies cases reporting CSF values had an abnormal CSF white blood cell count, red blood cell count, protein, or glucose. The percentage of abnormal values for each of these tests was similar between rabies and non-rabies cases. The white blood cell count in CSF was elevated in both rabies cases and non-rabies cases with mean values of 61.3 cells/µL (range 0–1000 cells/µL) and 89.0 cells/µL (range 0–980 cells/µL) respectively though this difference was not statistically significant (P-value 0.213). A lymphocytic predominance in CSF was seen in the majority of rabies cases. Rabies cases also demonstrated higher percentages of lymphocytes with a mean of 79% lymphocytes (range 31–100%) compared to a mean of 66% lymphocytes (range 0–100%) in non-rabies cases (P-value 0.034). Segmented neutrophils in CSF were also found to be higher in rabies cases with a mean of 30% (range 1–99%) compared to a mean of 15% (range 0–97%) in non-rabies cases (P-value 0.013). Protein in CSF was elevated in both groups with mean values of 72.8 mg/dL (range 15.0–178.0 mg/dL) in rabies cases and 86.2 mg/dL (range 4.0–1140.0) in non-rabies cases. This difference was not statistically significant (P-value 0.460). The mean value of glucose in CSF was elevated in rabies cases (85.8 mg/dL, range 24.0–211.0 mg/dL) while the mean of non-rabies cases was within the normal range (73.2 mg/dL, range 14.0–157.0 mg/dL) (P-value 0.004). No significant differences between rabies and non-rabies cases were found in CSF red blood cell counts, serum lymphocyte counts, serum segmented neutrophil counts, or serum glucose (P-values 0.193-0.781).

3.7 Treatment

Treatment of human rabies was successful in 4 cases. Of these, 2 had received rabies vaccine before the onset of illness. The first survivor (patient 18) became ill 2 days after completing a 14-day course of duck embryo vaccine following a bat bite. The diagnosis of rabies was based on CSF RABV antibody detection and serum antibody titers most consistent with clinical infection in combination with compatible epidemiologic and clinical histories. This patient required intensive supportive care but recovered fully within 6 months after onset. The second survivor (patient 29) had onset of symptoms ~2 weeks after spraying suspensions of a modified live RABV strain while performing research as a laboratory technician. Diagnosis was confirmed by detection of CSF antibodies and rising RABV serum antibody titers. The patient had received pre-exposure prophylaxis with annual boosters and had demonstrated RABV antibodies in response to these vaccinations. It is hypothesized that the strain he was exposed to may have developed increased infectivity following passage through animal and cell culture systems (Gibbons, 2002). Following intensive medical care, the patient survived but was left with severe neurologic sequelae. The third survivor (patient 94) developed rabies after being bitten by a bat. RABV antibodies were found in both serum and CSF. She was treated with an experimental treatment protocol (later termed the Milwaukee Protocol) involving induction of coma and administration of antiviral agents and recovered with only minor residual deficits (Hu,

2007). The last survivor in this series (patient 103) showed clinical signs and symptoms of encephalitis 2 months after exposure to bats and RABV antibodies were detected in both serum and CSF prior to the administration of a single dose of rabies vaccine and rabies immune globulin. This patient made a full recovery without the need for intensive care. No RABV was identified from any of the surviving patients.

Excluding the surviving cases, a total of 31 cases reported treatment after the onset of symptoms consisting of either administration of rabies immune globulin, immunization with rabies vaccine, induction of coma via the Milwaukee Protocol, or receipt of one or more antiviral medications including acyclovir, ganciclovir, amantadine, ribavirin, interferon, cytarabine, or adenine arabinoside. Thirteen patients were administered rabies immune globulin, 8 patients were immunized with rabies vaccine, 23 patients received antiviral therapy, and 5 patients underwent treatment with the Milwaukee Protocol during the course of illness. The median length of illness among all of those treated was longer when compared to those who did not receive any of the specified treatments (23.0 days vs. 13.0 days, P-value 0.029 by Log-rank test). It may be that those who received treatment were also more likely to receive supportive care which has previously been seen to increase the length of illness (Anderson, 1984). When treatments were compared individually, the median length of illness was longer for patients receiving rabies vaccine (14.0 day versus 13.5 days), the Milwaukee Protocol (28.0 days versus 13.0 days), or antiviral therapy (17.0 day versus 13.0 days) but shorter for patients receiving rabies immune globulin (13.0 days versus 14.0 days). However, none of the differences for individual treatments reached statistical significance (P-value 0.198-0.537 by Log-rank test). Overall, the median length of illness was 13.5 days (range 1–133 days).

3.8 Postexposure prophylaxis of contacts of cases

Data on administration of PEP was available in 71 cases (Table 1). A minimum of 3,359 individuals received PEP due to contact with a human rabies patient with a median of 39 individuals per case (range 1–180). The average number of individuals receiving PEP was greater in cases diagnosed postmortem compared to cases diagnosed antemortem (51 vs. 54) though this result was not statistically significant (P-value 0.453). The number of total risk assessments performed was reported for 22 cases. Typically 33% of individuals evaluated for RABV exposure received PEP per case (range 3–69%).

3.9 Rabies virus diagnostic testing
3.9.1 Antemortem test results

Results of RABV laboratory diagnostic testing were collected and summarized for 62 patients where specimens were collected prior to death (Table 3). When available, the number of days after illness onset the sample was collected (i.e. the sample collection date – illness onset date) is reported in parentheses following the test result. The cutaneous nerves of nuchal skin biopsies were tested for RABV antigen in 41 cases. A positive result was obtained in 24 cases (59%) with the first positive sample occurring a median of 7 days (range 2-12 days) after illness onset. RABV was detected in corneal impressions in 9 of 19 cases (47%) with 3 (16%) reporting inconclusive results and 7 (37%) reporting negative results. RABV antigen was first detected in corneal impressions a median of 11 days (range 2-13 days) after onset of rabies. Samples of brain were tested in 6 cases; 1 was inconclusive, 1 was negative, and 4 were first found positive a median of 12 days (range 7-21 days)

Patient	Detection of Antigen			Saliva Virus Isolation	Saliva RNA Detection	Detection of Antibody	
	Cutaneous Nerve	Cornea	Brain			Serum	CSF
9*	--†	--	--	Negative	--	--	--
13	--	--	--	--	--	Negative	--
14	--	--	--	--	--	Positive (11, 54, 64,65‡)	--
15	--	Negative (18–27)	Positive (21)	Negative (27)	--	Positive (6,13,17,21,45)	Positive (10,21)
16	--	Negative	--	Negative	--	--	--
18	--	--	Negative (16)	Negative (14)	--	Positive (14)	Positive (14)
19	--	--	--	Positive (3–5,7,9,11), Negative(6,13,16)	--	Positive (7–9,11,13,16,20,23), Negative (2,3,5,6)	Negative (4,6,11)
23	--	Positive	--	Positive (13)	--	--	--
26	Positive (9)	Negative (7,8)	--	Positive (7,11), Negative (16)	--	Positive (9–11,14,15,18)	Positive (17)
27	Positive (11)	Positive (11)	--	--	--	Positive (10,12,18)	--
28	Negative	Negative	--	--	--	--	--
29*	Negative (33)	Negative (33)	--	--	--	Positive (7,11,21)	Positive (28)
34*	Negative (6,10)	Positive (10), Negative (6)	--	--	--	Positive (6,10)	Negative (6,10)
35*	--	Inconclusive (5)	--	--	--	Positive (5)	Negative (5)
36	--	--	--	--	--	Positive (7)	Positive (6)
37	--	--	--	--	--	Positive (7,8,13)	Negative (7)
38	Negative (8)	Positive (8)	--	Negative (8)	--	Negative (8)	Negative (8)
40*	Positive (7)	--	--	Positive (10,14)	--	Negative (7–23)	Negative (7–23)
41	Positive (6,11)	Negative (6,18)	Positive (8)	Positive (9–13), Negative (16–25)	--	Positive (16–27), Negative (6–14)	Negative (8–19)
42	Negative (18,22)	--	--	Negative (18)	--	Positive (18,23,27)	Positive (27), Negative (18,23)
43	--	--	Positive (16)	Negative (17)	--	Positive (17), Negative (10)	Positive (14)
44	Positive (6)	--	--	--	Positive	Negative (6)	Negative (6)
49	Negative (5)	--	--	Negative (5)	--	Negative (5)	Negative (5)

| Patient | Detection of Antigen | | | Saliva Virus Isolation | Saliva RNA Detection | Detection of Antibody | |
	Cutaneous Nerve	Cornea	Brain			Serum	CSF
50	Positive (12)	--	--	Positive (5)	Positive (5)	Negative (5)	Negative (5)
53*	Positive (7,13), Negative (3)	Negative (2)	--	Negative (7,11,13)	Positive (7,11,13,16)	Positive (7,16), Negative (2)	Negative (13)
55	--	--	--	--	--	Negative (6)	--
56	Positive (5)	Inconclusive (5–9)	--	Positive (5)	Positive (5)	Negative (5–9)	Negative (8)
60	Positive (4)	--	Positive (7)	Negative (4)	Positive (4)	Positive (4)	--
61	--	Positive (13)	--	--	--	--	--
62	Positive (10)	--	--	Positive (10)	Positive (10)	Negative (10)	Negative (10)
63	Positive (7)	--	--	Positive (8)	Positive (8)	--	--
64	Negative (5)	Inconclusive (5)	--	--	--	Positive (11,13), Negative (5)	Negative (4)
Patient	Detection of Antigen			Saliva Virus Isolation	Saliva RNA Detection	Detection of Antibody	
	Cutaneous Nerve	Cornea	Brain			Cutaneous Nerve	Cornea
65	--	Positive (13)	--	Negative (9)	Positive (9)	Positive (7,11,14)	Negative (10)
67	Positive (8)	--	--	Positive (8)	Positive (8)	Negative (8)	--
68	Negative (5,6)	--	--	Positive (5)	Positive (5)	Positive (6), Negative (5)	Negative (5)
69	--	--	--	--	--	Positive (12), Negative (4)	--
70	Negative (13)	--	--	--	Positive (13)	Positive (13)	--
73	--	--	--	--	--	Negative (9)	--
74	Positive (5)	--	--	--	Positive (5)	Negative (5)	Negative (5)
75	Positive (7)	--	--	--	Positive (7)	Positive (7,14)	Positive (7)
76	Positive	Positive	--	--	Positive	--	--
77	Positive	--	--	--	Positive	--	--
79	Positive	--	--	--	Positive	--	--
80	--	--	--	--	--	Negative (6)	--
81	--	--	--	--	Positive	Positive (12,15)	Negative
82	Negative (9)	Positive (11), Inconclusive (9)	--	--	Positive (9)	Positive (12,13), Negative (9)	--
83	Negative (6)	--	--	--	Positive (8)	Positive (8), Negative (6)	Positive (8), Negative (6)

Patient	Detection of Antigen			Saliva Virus Isolation	Saliva RNA Detection	Detection of Antibody	
	Cutaneous Nerve	Cornea	Brain			Serum	CSF
84	Positive (11)	--	Inconclusive (7)	--	--	Positive (9)	Negative (8)
87*	--	--	--	--	Positive	Positive (19,21)	Negative (17)
94	Negative (5)	--	--	Negative (5)	Negative (5,27)	Positive (5,12,20,59,56,70)	Positive (5,12,20,59,56,70)
96	--	--	--	--	--	Positive (5,10)	Positive (10), Negative (5)
97	Positive (2)	--	--	--	Positive (2)	Negative (3)	Negative (2)
98	Positive (10)	--	--	--	Positive (10,19,23,26)	Positive (10,19,23,26)	Positive (19,23,26), Negative (10)
99	Positive (5,21)	Positive (2)	--	--	Positive (4)	Positive (13), Negative (2–12)	Positive (15), Negative (2)
100	Negative	--	--	--	Negative	Positive	Positive (10 or 16)
102	Positive (5)	--	--	--	Positive (5)	Positive (5)	Negative (5)
103	Negative (14)	--	--	--	Negative (14)	Positive (14,18,22,32)	Positive (14,18,22,37)
104	Negative (14)	--	--	--	Positive (14)	Positive (14)	Negative (6)
105	Negative (21)	--	--	--	Negative (21)	Positive (21)	Positive (21)
106	Positive (5)	--	--	--	Positive (5)	Positive (18), Negative (5–17)	Negative
107	Negative (17)	--	--	--	Negative (17)	Positive (12)	Positive (12)
108	Positive (10)	--	--	--	Positive (8)	Negative (8)	--

* Patient received immunization, † -- = Sample not collected, testing not performed, or results not reported, ‡ When known, the number of days after illness onset the sample was collected (i.e. sample collection date – illness onset date) is indicated in parentheses

Table 3. Summary of Antemortem Diagnostic Test Results for 62 Patients with Human Rabies in the United States, 1960–2010

following onset of illness. Virus isolation from saliva was attempted in 23 cases and successful in 11 (48%) in samples collected a median of 8 days (range 3-13 days) after illness onset. RABV RNA was detected in 27 of 32 cases tested (84%) with the first positive results obtained from samples a median of 7 days (range 2-14 days) after the appearance of symptoms. Serum was tested for antibodies in 48 patients with no history of vaccination at the time of sample collection and was positive in 33 cases (69%). Antibodies in serum were first detected a median of 10.5 days (range 4-21 days) from the onset of illness in these unvaccinated patients. In contrast, antibodies in CSF were found in only 17 of 40 cases tested (43%) and first appeared a median of 14 days (range 5-28 days) following illness onset.

3.9.2 Postmortem test results

Confirmation of rabies through laboratory testing of postmortem samples was reported in 81 cases. The confirmation came shortly after death in the majority of cases. However, in at least 14 cases rabies was not suspected prior to death and was diagnosed as part of a postmortem investigation. Notable among these cases were all of the cases involving transplantation of infected organs or tissue (patients 30-31 and 89-93), 2 cases (patient 71 and patient 72) initially evaluated for suspected Creutzfeldt-Jakob disease, 1 case (patient 76) referred for testing of an undiagnosed encephalitis to the California Encephalitis Project, 1 case (patient 96) referred for testing to CDC's Unexplained Deaths Project, and 1 case (patient 59) originally attributed to disseminated candidiasis and mucormycosis in a pregnant female. The delay in diagnosis for these cases ranged from 1 to 6 months after death.

4. Conclusion

Despite being indigenous in wildlife, human rabies was a rarely reported disease in the United States during 1960–2010. An average of 2 cases per year was recorded during this time period, a trend that remained largely stable throughout each decade. While this should be considered a great success of public health efforts towards prevention and control, the true incidence of human rabies is likely higher due to under recognition. The disease occurs so infrequently that most clinicians have little direct experience with rabies and therefore may not consider it in the differential diagnosis of patients presenting with encephalitis. The lack of a clear animal exposure preceding illness in increasing numbers of cases leaves clinicians without a significant clue that might prompt consideration of rabies. The myriad of other possible etiologies of encephalitis further compounds this problem. For these reasons, a clear diagnosis cannot be found in the majority of cases of encephalitis even when extensive testing to identify the cause of illness is employed (Glaser, 2003). In fact, between 1979 and 1998 there was an average of over 1,000 deaths per year from encephalitis due to unknown cause reported in the United States (Khetsuriani, 2007). It is interesting to note that 1 of the 334 cases of encephalitis (0.3%) investigated by the California encephalitis project was diagnosed with rabies (Glaser, 2003). Rabies was not previously suspected in this patient and would almost certainly have remained unrecognized without the extensive testing performed as part of the study. Applying this rate of unrecognized rabies cases to the annual number of reported deaths due to encephalitis of unknown cause suggests there could be over 3 cases of human rabies that go unrecognized each year in the United States alone. This review provides a comprehensive summary of epidemiologic and clinical data of

all of the known cases within the last 5 decades which can be used as an aid in recognizing and identifying rabies among patients with encephalitis.

The epidemiology of human rabies in the United States has undergone striking changes over the last century. Prior to the 1960s, the vast majority of human rabies cases in the United State were due to bites from an infected dog. Worldwide, dogs remain the primary source of human rabies (WHO, 2004; Knobel, 2005). However, a dramatic decline in human rabies cases in the United States occurred during the 1940s and 1950s as illustrated in Figure 2. This decrease in cases paralleled the improvement and application of new rabies vaccines for both humans and animals. Key to this approach was the targeting of domestic animals for vaccination to create a barrier of protection from RABV transmission to humans, a strategy that was ultimately successful in eliminating the canine RABV variant from the United States (Velasco-Villa, 2008). Throughout the 1940s and 1950s the number of human rabies cases attributed to domestic animals (primarily dogs) far exceeded those involving wildlife animals. However, a reversal in this relationship took place in the 1960s when the number of human rabies cases associated with wildlife surpassed those due to domestic animals, a trend that continues to this day. Currently the most frequently reported rabid animals in the United States are raccoons, bats, skunks, and foxes (Blanton, 2010). Clinicians should be aware that these species can therefore be considered high risk though must also be careful not to discount exposures to other known vector species.
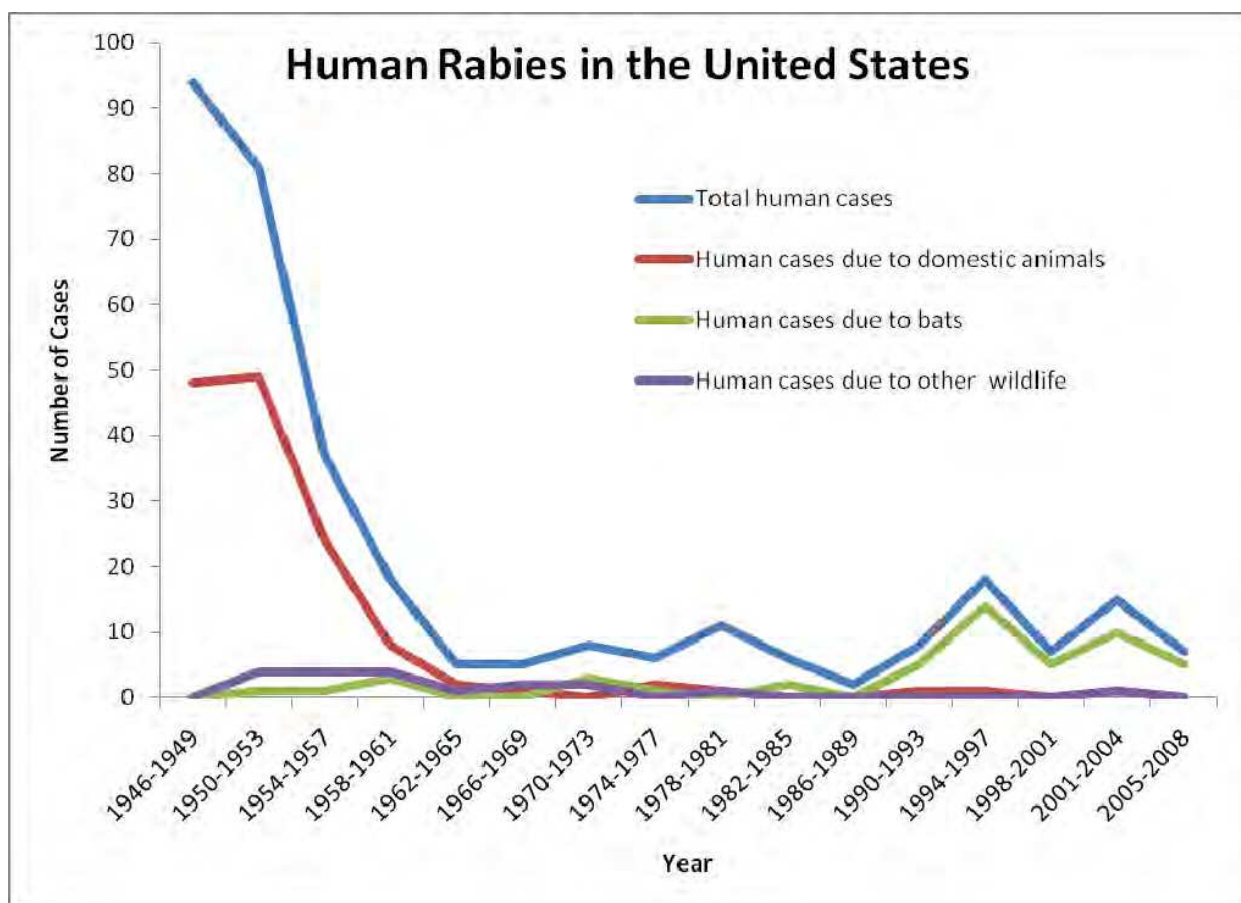
Fig. 2. Human Rabies Cases in the United States, 1946–2008

The increasing number of cases associated with bats illustrates the growing importance of this species in the epidemiology of rabies (Figure 2). The advancement and increased utilization of RABV variant typing methods has led to a greater understanding of rabies epidemiology, particularly with regards to the role of bats (Smith, 1992). Excluding cases acquired through transplantation of infected tissue, a total of 42 RABV variants associated with bats were identified in this series, yet 16 (38%) of these cases had no reported exposure history. Without the availability of antigenic and molecular typing, this epidemiologic link to bats likely would have remained unrecognized in these cases. Many times, possible contact between the patient and a bat was recalled only after a bat RABV variant had been identified. Excluding cases acquired through transplantation, a total of 41/46 (89%) indigenous cases have been associated with bats either through a reported bat exposure or identification of a bat variant. The most common species of bats associated with human cases through variant typing were the silver-haired bat and the tricolored bat (*Lasionycteris noctivagans* and *Perimyotis subflavus*). This is a somewhat curious finding considering that these species of insectivorous bats are considered to be solitary tree-dwelling bats and are infrequently submitted to public health laboratories for rabies diagnostic testing (Krebs, 2000; Messenger, 2002; Blanton, 2010). However, there is some evidence suggesting that the RABV variants in these species have evolved genetic changes that may increase their infectivity (Morimoto, 1996; Dietzschold, 2000). Additional studies of bat RABV will undoubtedly improve understanding of the emergence, perpetuation, and epizootiology of this disease (Streicker, 2010).

Classically, one expects human rabies cases to be preceded by an animal bite exposure. However, a definite history of a recent animal bite was reported in less than half of the cases in this series. The epidemiologic shift in the source of infection of human rabies in the United States provides one possible explanation for this observation. Bites from dogs or other carnivores are more likely to be recognized simply due to the size of the animal. A larger bite wound is also more likely to require medical treatment at which time consideration can be given to the need for rabies PEP. In contrast, North American bats are small and produce bite wounds that are superficial by comparison and less likely to require medical attention. With the advent of modern cell culture vaccines in 1980 and rabies immune globulin, no PEP failures have been reported in the United States. Unless the victim was previously aware of the risk of rabies from a bat bite, the opportunity for lifesaving PEP may be lost. A survey among cavers (spelunkers) in the United States found that 15% indicated a bat bite was not a risk for rabies, suggesting that a significant proportion of the public at large may also be unaware of the risk posed by bats (Gibbons, 2002). Some bat bites go unnoticed entirely because bat teeth are small and sharp (Feder, 1997). If the victim were engaged in an outdoor activity it is not hard to imagine a bat bite being confused for an insect bite or other minor trauma if the bat remained hidden in a tree or crevice (Gibbons, 2002). Furthermore, due to the extended incubation period a patient may not link the symptoms of the disease with an exposure that occurred months before the onset of illness. The median incubation in this series was nearly six weeks with evidence suggesting that long incubation periods on the order of years are possible (Smith, 1991). Thus, it is essential that the public be informed of the risk of rabies from all mammals and to remain vigilant for potential exposures, particularly when engaging in activities that put them at risk for contact with bats and other wildlife animals. Clinicians must also recognize that rabies should not be excluded from the differential diagnosis of a

patient with acute progressive encephalitis due to the absence of a recent animal exposure history.

The initial signs and symptoms of human rabies are largely nonspecific and include fever, malaise, headache, nausea, and vomiting. Not surprisingly, almost half of the patients in this series were evaluated for their symptoms at least once prior to being admitted to the hospital without the diagnosis of rabies being considered. Thus, it may be very difficult to diagnose rabies during the prodromal phase in the absence of an animal exposure to alert one to the possibility. However, the progression of illness is rapid with most patients seeking medical care within one day of the appearance of symptoms and requiring hospitalization within 4 days of illness onset. Furthermore, most patients succumbed to their illness within 2 weeks of the onset of symptoms. These data suggest that rabies would be less likely in patients who do not require hospitalization within one week of developing symptoms or in hospitalized patients surviving longer than 2 weeks. Prioritization of testing for other etiologies over rabies would be prudent in these situations. However, several signs and symptoms were found to occur more frequently in patients with rabies when compared to patients with encephalopathy who tested negative for rabies. Aerophobia and hydrophobia were the most specific findings associated with rabies cases despite the fact that these symptoms were found in relatively few cases. Intubation and sedation have become common components of modern medical management of critically ill patients, a practice that may mask these symptoms unless specifically noted by patients early in their course. The neurologic findings of paresthesias or localized pain, dysphagia, and focal weakness were also positively linked to rabies cases. In contrast, headache, malaise or fatigue, seizures, and confusion or delirium were observed more frequently in non-rabies cases than in rabies cases.

The clinical presentation of human rabies is often classified as either encephalitic (furious) or paralytic (dumb) rabies. The encephalitic form of the disease is characterized by overall hyperexcitability with episodes of confusion, agitation or aggressive behavior, and hallucinations. In the paralytic form, localized weakness and/or paralysis are the most prominent feature and are commonly accompanied by paresthesias, pruritis, or localized pain at the site of the bite and a normal mental status. The signs and symptoms associated with rabies cases in this series are those classically used to describe the paralytic rather than the encephalitic form. In general, 80% of human rabies patients are thought to manifest the encephalitic form while 20% have a paralytic form (Jackson, 2002)(Jackson, 2007). As such, clinicians may be more likely to submit cases for testing that resemble their preconceived notion of the more common furious form of human rabies and less likely to consider rabies with the more rare paralytic form. A connection between the paralytic form of rabies and transmission by vampire bats has been noted in several human rabies outbreaks (Nehaul, 1955; Hurst, 1959; Hurst, 1959; Pawan, 1959; Verlinde, 1975; da Rosa, 2006). However, vampire bats do not cause exclusively paralytic disease as the encephalitic form has been described with a vampire bat human rabies outbreak in Peru (Lopez, 1992). Host factors most certainly play a role also as two individuals bitten by the same dog were seen to develop encephalitic rabies in one and paralytic rabies in the other (Hemachudha, 1988). Nevertheless, it is unclear whether the overall preponderance of cases linked to bats may have affected the clinical syndrome observed in this series. Regardless of the source of infection, clinicians should be aware that the clinical presentation of human rabies is a spectrum that can include features of either the encephalitic or paralytic forms. Positive indicators such as hydrophobia, aerophobia, paresthesias or localized pain, focal weakness,

and dysphagia in a patient with acute progressive encephalitis should alert the clinician to the possibility of rabies.

The age and sex of a patient in addition to the month of illness onset may also provide clues to the diagnosis of rabies in patients with encephalitis. Globally, human rabies is most likely to be seen in children less than 15 years old (WHO, 2004). However, patients in this series were more likely to be older with a median age of 29 years. The disproportionate number of cases linked with bats and other wildlife species as opposed to dogs is likely responsible for this discrepancy. Children are more likely to unintentionally incite a dog attack through provoking behaviors and inexperience or because their size and movements may be similar to prey. With respect to wildlife, one might expect older age groups to be more likely to engage in outdoor activities or other behaviors that would put them at higher risk of exposure to bats and wildlife animals. Similarly, the predominance of males in this case series may also be due in part to males engaging in these activities more frequently than females. Limited data on the administration of PEP suggests that males may have higher rates of PEP (Helmick, 1983) though this trend was not confirmed in other studies of state level data (Blanton, 2005; O'Bell, 2006). Furthermore, males may be less likely to seek PEP after an exposure occurs. In support of this claim is evidence suggesting that the perception and awareness of health-related risks may be lower in males compared to females (Naslund, 1997; Gustafson, 1998). The observation that most cases occurred during fall months corresponds well with the observation that most contact with wildlife, particularly bats, occurs during the late summer months (Messenger, 2002). Assuming an incubation period of 1-3 months, exposures occurring during summer would then be expected to become ill during the fall. This pattern was particularly significant when analyzing cases associated with bats. Most bat exposures occurred during the early fall months and is consistent with previous research demonstrating that the incidence of rabies-infected bats peaks in August (Constantine, 1979; Pape, 1999). Furthermore, the illness onset month in cases associated with bats was most common during the late fall months. Both exposures and onset of illness were more likely to occur in fall months in cases associated with bats compared with those not associated with bats. Based on these findings, a typical human rabies case in the United States would be a young adult male presenting with signs and symptoms of encephalitis in the fall.

When human rabies is suspected it is important to initiate diagnostic testing as early as possible. Current guidelines for antemortem testing of human patients recommend the collection of samples of skin, serum, saliva, and CSF. In this series, the earliest positive results were found with detection of viral RNA in saliva and viral antigen in skin after a median of 7 days following onset of illness. The earliest diagnosis occurred in patient 98 with both saliva and skin collected 2 days after illness onset reported positive by PCR and DFA respectively on the sixth day of illness. Virus isolation from saliva was also fairly rapid with positive results obtained as early as 3 days after illness onset (median 8 days). The development of a humoral immune response lags behind the secretion of virus in saliva and antibodies were detected in serum and CSF a median of 10 and 14 days respectively following the appearance of symptoms. The earliest detection of rabies specific antibodies after illness onset was 4 days in serum and 5 days in CSF. With respect to sensitivity, identification of viral RNA in saliva was the most sensitive testing modality with 84% of rabies cases tested giving positive results. Detection of antibodies in serum and viral antigens in brain and cutaneous nerves were also relatively sensitive with positive results in 69%, 67%, and 59% of cases tested respectively. Though isolation of RABV from saliva was

successful in fewer than half of cases, the utility of virus isolates for variant typing, comparative analyses, investigations of pathogenesis, and other studies is invaluable. Similarly, while antibodies in CSF were found relatively infrequently, their detection is significant as this finding alone is considered diagnostic for rabies regardless of history of rabies vaccination (Moore, 2010). Examination of corneal impressions was positive in only 47% of cases tested and is no longer routinely used for antemortem diagnostic testing given the risk of damage to the eyes when performed by inexperienced practitioners and the relatively poor sensitivity. While the sensitivity of viral antigen detection in antemortem brain samples is high, routine testing of these samples is not recommended due to the invasiveness of the collection procedure. The best approach for maximizing the sensitivity and accuracy of antemortem diagnostic rabies testing is through submission of skin, saliva, serum, and CSF for evaluation with multiple modalities including detection of viral antigen, viral nucleic acid, and rabies specific antibodies, especially because some test results become available in less than 24 hours.

The diagnosis of human rabies can be essential in preventing further cases. Identifying human cases allows for a public health response to investigate the source of infection and provide risk assessments of contacts with potential exposures. If a suspected animal source infestation is discovered, these animals can be removed to avert any further exposures and tested to confirm whether additional animals are rabid. Any individuals with contact with potentially rabid animals can then be assessed for exposures and given PEP when indicated. Public education can also be targeted to increase awareness of the risk of rabies transmission from reservoir species and the importance of seeking medical attention promptly if an exposure does occur. Contacts of rabies patients should also be identified and evaluated for exposures. Although human-to-human transmission of rabies has only been well documented in cases of organ or tissue transplantation, transmission following exposure to human saliva or nervous tissue remains a theoretical possibility (Helmick, 1987). Rare anecdotal reports of direct human to human transmission of rabies through bites, kissing, lactation, intercourse, transplacental transmission, and delivery of healthcare have been reported though possible animal exposures were difficult to exclude and none of these cases were laboratory confirmed (Helmick, 1987; Gibbons, 2002). Healthcare providers can be reassured by the fact that no case of rabies has ever been confirmed in a caregiver of any of the estimated 55,000 cases occurring each year. Moreover, early recognition and contact isolation of suspected cases are effective means of limiting exposures in healthcare settings (Helmick, 1987). Given these facts, the median of 39 individuals receiving PEP per case found in this series may seem excessive. Though the higher rate of PEP of contacts among cases diagnosed postmortem compared to antemortem was not statistically significant, it is still likely that early diagnosis of human rabies will lead to fewer exposures and decrease unnecessary PEP. Lastly, identification of human rabies can avoid transmitting the virus through organ and tissue transplantation. Even if the diagnosis is made after transplantation has already taken place, removal of the transplanted tissue and administration of PEP has been successful in preventing infection in two recipients of corneas from an infected donor (Vetter, 2011).

The early diagnosis of rabies also provides the best opportunity for experimental therapy of victims. The 4 survivors reported in this series demonstrate that survival is rare but does occur. In addition, patient 95 was the first report of a patient recovering from rabies without receiving any vaccination against rabies through the use of the Milwaukee Protocol. Two subsequent survivors attributed to the application of this protocol have been reported

among 24 attempts to give an estimated 9% survival by intention-to-treat analysis (Willoughby, 2009). As knowledge is gained from both treatment failures and successes, further refinement of this approach may increase the rate of success. The recovery of patient 104 without application of the Milwaukee Protocol or even need for intensive care is the only well documented case of a presumed human abortive rabies infection. This case hints at the possibility that there may be a much larger spectrum of disease in rabies cases that has not been previously appreciated. It may be only recently recognized due to improved laboratory diagnostic techniques, greater availability of laboratory testing, or increased awareness of the possibility of rabies after several high profile cases in the United States including the survival of patient 95 and the cases transmitted through transplantation (patients 90-93). The association of both of these survivors with exposures to bats has also led to the hypothesis that canine RABV variants may be more virulent than bat variants (Lafon, 2005). However, one case of documented human rabies of canine origin in Equatorial Guinea purportedly survived infection with application of the Milwaukee Protocol, but later succumbed (Rubin, 2009). The patient's death on hospital day 22 was thought to be due to complications of malnutrition. Irrespective of the source of infection, the limited success of treatment attempts emphasizes the importance of prevention. Current treatment protocols require considerable expense and advanced medical facilities making practical application unrealistic in many countries. In contrast, rabies prevention strategies implementing safe, efficacious, and affordable human and animal vaccines have proven to be highly effective, particularly in combination with community outreach and education programs (Rupprecht, 2008; Cleaveland, 2010).

The results of this study are subject to several limitations. Given the relative rarity of human rabies in the United States despite the abundance of the disease in nature, this case series represents a relatively small sample size and several cases had only limited data available. In addition, all of the data from cases were collected retrospectively and are therefore subject to recall bias. Histories of potential animal exposures may be particularly sensitive to poor memory given the lengthy incubation period seen with rabies; this may be exacerbated in cases where rabies was not initially considered or the diagnosis was delayed. In all cases there is a short window of opportunity to communicate directly with patients due to the rapid progression of disease and nearly universal fatal outcome. In the confirmed rabies cases additional clinical and laboratory data were gained through public health investigations. In contrast, data from non-rabies cases relied primarily on patient information forms completed at the time of submission for diagnostic testing. As such, those data represent only a snapshot of the clinical picture making comparisons of temporal patterns in rabies and non-rabies cases unfeasible. Moreover, no follow-up of clinical outcomes (i.e. survival or death) was available for non-rabies cases. Though statistically significant results were obtained, it is possible that other significant findings may have been missed due to the small sample size.

This review complements previous reports of smaller series of human rabies cases in the United States (Held, 1967; Anderson, 1984; Noah, 1998; CDC, 2006). Significant changes in the epidemiology of rabies include the increasing role of bats in human rabies and the concomitant rise in cases with no clear history of animal exposure. These findings underscore the need to increase public awareness of the risk of rabies from wildlife, particularly bats, and the importance of prompt medical evaluation if contact with such animals occurs. Advances in the treatment of human rabies have led to the first reported cases of recovery without immunization with rabies vaccine. These survivors raise hope

for continued advancements in the efforts to develop a treatment for rabies. Identification of the first presumptive abortive human rabies case suggests an expanded view of the continuum of disease caused by lyssaviruses is necessary. Our knowledge of human rabies will continue to grow as more cases are identified. As such, increasing the recognition and diagnosis of human rabies will not only enhance our understanding of the disease but ultimately will save human lives as well. Early diagnosis allows the institution of proper biosafety and isolation precautions of rabies patients as well as the initiation of public health action to identify potential exposures to evaluate their need for PEP. Insights gained from human rabies may also prove to be applicable to other zoonoses. As one of the earliest known zoonotic diseases, rabies can be used as a prototype in investigating the interplay between animals and their impact on human health. This relationship is becoming increasingly important as the majority of emerging infectious diseases are now recognized to be zoonotic in nature. Lyssavirus infections and human rabies due to bats should be considered emerging infectious threats themselves. Research into bats and human disease is particularly relevant given the identification of bats as the reservoir of numerous other human pathogens including Ebola virus, Marburg virus, nipah virus, hendra virus, and SARS-like coronaviruses among others (Calisher, 2006). Clearly, the health of humans, animals, and the environment are interconnected and lessons learned from rabies are extremely valuable in relation to this concept of "One Health."

5. Acknowledgements

6. References

Anderson, L. J., K. G. Nicholson, et al. (1984). "Human rabies in the United States, 1960 to 1979: epidemiology, diagnosis, and prevention." Ann Intern Med 100(5): 728-735.

Blanton, J. D., N. Y. Bowden, et al. (2005). "Rabies postexposure prophylaxis, New York, 1995-2000." Emerg Infect Dis 11(12): 1921-1927.

Blanton, J. D., D. Palmer, et al. (2010). "Rabies surveillance in the United States during 2009." J Am Vet Med Assoc 237(6): 646-657.

Calisher, C. H., J. E. Childs, et al. (2006). "Bats: important reservoir hosts of emerging viruses." Clin Microbiol Rev 19(3): 531-545.

CDC (2006).

CDC (2006). Protocol for Postmortem Diagnosis of Rabies in Animals by Direct Fluorescent Antibody Testing.

Christian, K. A., J. D. Blanton, et al. (2009). "Epidemiology of rabies post-exposure prophylaxis--United States of America, 2006-2008." Vaccine 27(51): 7156-7161.

Cleaveland, S., P. Costa, et al. (2010). "Catalysing action against rabies." Vet Rec 167(11): 422-423.

Constantine, D. G. (1979). "An updated list of rabies-infected bats in North America." J Wildl Dis 15(2): 347-349.

da Rosa, E. S., I. Kotait, et al. (2006). "Bat-transmitted human rabies outbreaks, Brazilian Amazon." Emerg Infect Dis 12(8): 1197-1202.

Dietzschold, B., K. Morimoto, et al. (2000). "Genotypic and phenotypic diversity of rabies virus variants involved in human rabies: implications for postexposure prophylaxis." J Hum Virol 3(1): 50-57.

Feder, H. M., Jr., R. Nelson, et al. (1997). "Bat bite?" Lancet 350(9087): 1300.

Gibbons, R. V. (2002). "Cryptogenic rabies, bats, and the question of aerosol transmission." Ann Emerg Med 39(5): 528-536.

Gibbons, R. V., R. C. Holman, et al. (2002). "Knowledge of bat rabies and human exposure among United States cavers." Emerg Infect Dis 8(5): 532-534.

Glaser, C. A., S. Gilliam, et al. (2003). "In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000." Clin Infect Dis 36(6): 731-742.

Gustafson, P. E. (1998). "Gender differences in risk perception: theoretical and methodological perspectives." Risk Anal 18(6): 805-811.

Held, J. R., E. S. Tierkel, et al. (1967). "Rabies in man and animals in the United States, 1946-65." Public Health Rep 82(11): 1009-1018.

Hellenbrand, W., C. Meyer, et al. (2005). "Cases of rabies in Germany following organ transplantation." Euro Surveill 10(2): E050224 050226.

Helmick, C. G. (1983). "The epidemiology of human rabies postexposure prophylaxis, 1980-1981." Jama 250(15): 1990-1996.

Helmick, C. G., R. V. Tauxe, et al. (1987). "Is there a risk to contacts of patients with rabies?" Rev Infect Dis 9(3): 511-518.

Hemachudha, T., P. Phanuphak, et al. (1988). "Immunologic study of human encephalitic and paralytic rabies. Preliminary report of 16 patients." Am J Med 84(4): 673-677.

Houff, S. A., R. C. Burton, et al. (1979). "Human-to-human transmission of rabies virus by corneal transplant." N Engl J Med 300(11): 603-604.

Hu, W. T., R. E. Willoughby, Jr., et al. (2007). "Long-term follow-up after treatment of rabies by induction of coma." N Engl J Med 357(9): 945-946.

Hurst, E. W. and J. L. Pawan (1959). "A further account of the Trinidad outbreak of acute rabic myelitis: histology of the experimental disease." Caribb Med J 21: 25-45.

Hurst, E. W. and J. L. Pawan (1959). "An outbreak of rabies in Trinidad without history of bites, and with the symptoms of acute ascending myelitis." Caribb Med J 21: 11-24.

Jackson, A. C., M. J. Warrell, et al. (2003). "Management of rabies in humans." Clin Infect Dis 36(1): 60-63.

Jackson, A. C. and W. H. Wunner (2002). Rabies. Amsterdam ; Boston, Academic Press.

Javadi, M. A., A. Fayaz, et al. (1996). "Transmission of rabies by corneal graft." Cornea 15(4): 431-433.

Khetsuriani, N., R. C. Holman, et al. (2007). "Trends in encephalitis-associated deaths in the United States." Epidemiol Infect 135(4): 583-591.

Knobel, D. L., S. Cleaveland, et al. (2005). "Re-evaluating the burden of rabies in Africa and Asia." Bull World Health Organ 83(5): 360-368.

Krebs, J. W., J. S. Smith, et al. (2000). "Mammalian reservoirs and epidemiology of rabies diagnosed in human beings in the United States, 1981-1998." Ann N Y Acad Sci 916: 345-353.

Kusne, S. and J. Smilack (2005). "Transmission of rabies virus from an organ donor to four transplant recipients." Liver Transpl 11(10): 1295-1297.

Kuzmin, I. V., I. S. Novella, et al. (2009). "The rhabdoviruses: biodiversity, phylogenetics, and evolution." Infect Genet Evol 9(4): 541-553.

Lafon, M. (2005). "Bat rabies--the Achilles heel of a viral killer?" Lancet 366(9489): 876-877.

Lopez, A., P. Miranda, et al. (1992). "Outbreak of human rabies in the Peruvian jungle." Lancet 339(8790): 408-411.

Messenger, S. L., J. S. Smith, et al. (2002). "Emerging epidemiology of bat-associated cryptic cases of rabies in humans in the United States." Clin Infect Dis 35(6): 738-747.

Moore, S. M. and C. A. Hanlon (2010). "Rabies-specific antibodies: measuring surrogates of protection against a fatal disease." PLoS Negl Trop Dis 4(3): e595.

Morimoto, K., M. Patel, et al. (1996). "Characterization of a unique variant of bat rabies virus responsible for newly emerging human cases in North America." Proc Natl Acad Sci U S A 93(11): 5653-5658.

Naslund, G. K. (1997). "Relationships between health behavior, knowledge, and beliefs among Swedish blue-collar workers." Scand J Soc Med 25(2): 100-110.

Nehaul, B. B. (1955). "Rabies transmitted by bats in British Guiana." Am J Trop Med Hyg 4(3): 550-553.

Noah, D. L., C. L. Drenzek, et al. (1998). "Epidemiology of human rabies in the United States, 1980 to 1996." Ann Intern Med 128(11): 922-930.

O'Bell, S. A., J. McQuiston, et al. (2006). "Human rabies exposures and postexposure prophylaxis in South Carolina, 1993-2002." Public Health Rep 121(2): 197-202.

Pape, W. J., T. D. Fitzsimmons, et al. (1999). "Risk for rabies transmission from encounters with bats, Colorado, 1977-1996." Emerg Infect Dis 5(3): 433-437.

Pawan, J. L. (1959). "Rabies in the vampire bat of Trinidad, with special reference to the clinical course and the latency of infection." Caribb Med J 21: 137-156.

Rubin, J., D. David, et al. (2009). "Applying the Milwaukee protocol to treat canine rabies in Equatorial Guinea." Scand J Infect Dis 41(5): 372-375.

Rupprecht, C. E., J. Barrett, et al. (2008). "Can rabies be eradicated?" Dev Biol (Basel) 131: 95-121.

Smith, J. S., D. B. Fishbein, et al. (1991). "Unexplained rabies in three immigrants in the United States. A virologic investigation." N Engl J Med 324(4): 205-211.

Smith, J. S., L. A. Orciari, et al. (1992). "Epidemiologic and historical relationships among 87 rabies virus isolates as determined by limited sequence analysis." J Infect Dis 166(2): 296-307.

Srinivasan, A., E. C. Burton, et al. (2005). "Transmission of rabies virus from an organ donor to four transplant recipients." N Engl J Med 352(11): 1103-1111.

Streicker, D. G., A. S. Turmelle, et al. (2010). "Host phylogeny constrains cross-species emergence and establishment of rabies virus in bats." Science 329(5992): 676-679.

Velasco-Villa, A., S. A. Reeder, et al. (2008). "Enzootic rabies elimination from dogs and reemergence in wild terrestrial carnivores, United States." Emerg Infect Dis 14(12): 1849-1854.

Verlinde, J. D., E. Li-Fo-Sjoe, et al. (1975). "A local outbreak of paralytic rabies in Surinam children." Trop Geogr Med 27(2): 137-142.

Vetter, J. M., L. Frisch, et al. (2011). "Survival after transplantation of corneas from a rabies-infected donor." Cornea 30(2): 241-244.

WHO (2004). WHO Expert Consultation on Rabies. First Report. WHO technical report series No 931. Geneva, WHO. 2005: 121.

Willoughby, R. E., Jr. (2009). ""Early death" and the contraindication of vaccine during treatment of rabies." Vaccine 27(51): 7173-7177.

7. Case references

[1] CDC (1960). Human rabies. Morbidity and Mortality Weekly Report, Vol.9, No.31, p.2

[2] Ross, E.; Armentrout, S. (1962). Myocarditis Associated with Rabies: Report of a Case. New England Journal of Medicine, Vol.266, No.21, pp.1087-1089

[3] CDC (1961). Human Rabies — Kentucky. Morbidity and Mortality Weekly Report, Vol.10, No.2, p.2

[4] CDC (1961). Human Rabies — California. Morbidity and Mortality Weekly Report, Vol.10, No.3, p.2

[5] CDC (1961). Human Rabies — Kentucky. Morbidity and Mortality Weekly Report, Vol.10, No.26, p.8

[6] CDC (1962). Rabies in Man — Texas. Morbidity and Mortality Weekly Report, Vol.11, p.258

[7] CDC (1962). Human Rabies — Idaho. Morbidity and Mortality Weekly Report, Vol.11, pp.395,400

[8] CDC (1963). Human Rabies Death — Alabama. Morbidity and Mortality Weekly Report, Vol.12, p.300

[9] Gomez M.; Siekert R. & Hermann E. (1965). A Human Case of Skunk Rabies. Journal of the America Medical Association, Vol.194, , pp.333-335

[10] CDC (1965). Human Rabies Death — West Virginia. Morbidity and Mortality Weekly Report, Vol.14, p.195

[11] Bell, G. (1967). Death from Rabies in a Ten-Year-Old Boy (One of Two Cases in United States in 1966). South Dakota Journal of Medicine, Vol.20, pp.28-30

[12] CDC (1967). Case of Imported Rabies — New York. Morbidity and Mortality Weekly Report, Vol.16, p.258

[13] Cereghino, J.; Mason, L. & Sheehan, T. (1968). A Case of Rabies Encephalitis. Northwest Medcine, Vol.67, pp.857-860

[14] Rubin, R.; Sullivan, L.; Summers, R.; Gregg, M. & Sikes, K. (1970). A Case of Human Rabies in Kansas: Epidemiologic, Clinical, and Laboratory Considerations. Journal of Infectious Diseases, Vol.122, pp.318-322

[15] Emmons, R.; Leonard, L.; Degenaro, F.; Protas, E.; Bazeley, P.; Giamonna, S. & Sturckow, K. (1973). A Case of Human Rabies with Prolonged Survival. Intervirology, Vol.1, pp.60-72

[16] Hattwick, M.; Hochberg, F.; Landrigan, P. & Gregg, M. (1972). Skunk-Associated Human Rabies. Journal of the American Medical Association, Vol.122, No.1, pp.44-47

[17] Hattwick, M.; Weis, T.; Stechschulte, C.; Baer, G. & Gregg, M. (1972). Recovery from Rabies: A Case Reprt. Annals of Internal Medicine, Vol.76, pp.931-942

[18] Bhatt, D.; Hattwick, M.; Gerdsen, R.; Emmons, R. & Johnson, H. (1977). Human Rabies: Diagnosis, Complications, and Management. American Journal of Diseases of Children, Vol.127, pp.862-869

[19] CDC (1971). Human Rabies — New Jersey. Morbidity and Mortality Weekly Report, Vol.20, No.51, pp.459-460

[20] CDC (1972). Human Rabies — California. Morbidity and Mortality Weekly Report, Vol.21, No.9, pp.73-74

[21] Winkler, H.; Fashinell, T.; Leffingwell, L.; Howard, P. & Conomy, J. (1973). Airborne Rabies Transmission in a Laboratory Worker. Journal of the American Medical Association, Vol.126, No.10, pp.1219-1221

[22] CDC (1973). Human Rabies — Kentucky. Morbidity and Mortality Weekly Report, Vol.22, No.39, pp.325-326

[23] Sung, J.; Hayano, M.; Mastri, A. & Okagaki, T. (1976). A Case of Human Rabies and Ultrastructure of the Negri Body. Journal of Neuropathology and Experimental Neurology, Vol.35, pp.541-559

[24] CDC (1976). Human Rabies — Puerto Rico. Morbidity and Mortality Weekly Report, Vol.24, pp.94,99

[25] Baraff, L.; Hafkin, B.; Wehrle, P.; Emmons, R.;Gunn, R.; Overturf, G. & Steinberg, E. (1978). Human Rabies. The Western Journal of Medicine, Vol.128, pp.159-164

[26] CDC (1976). Human Rabies — Maryland. Morbidity and Mortality Weekly Report, Vol.25, pp.235-236

[27] CDC (1977). Human Rabies — Texas. Morbidity and Mortality Weekly Report, Vol.26, pp.31-32

[28] CDC (1977). Rabies in a Laboratory Worker — New York. Morbidity and Mortality Weekly Report, Vol.26, pp.183-184

[29] Houff, S.; Burton, R.; Wilson, R.; Henson, T.;London, W.; Baer, G.;Anderson, L.; Winkler, W.; Madden, D. & Sever, J. (1979). Human-To-Human Transmission of RABV by Corneal Transplant. The New England Journal of Medicine, Vol.300, No.11, pp.603-604

[30] CDC (1978). Human Rabies — Texas. Morbidity and Mortality Weekly Report, Vol.27, p.267

[31] CDC (1979). Human Rabies — Pennsylvania. Morbidity and Mortality Weekly Report, Vol.28, pp.75-76,81

[32] CDC (1979). Two Suspected Cases of Human Rabies — Texas, Washington. Morbidity and Mortality Weekly Report, Vol.28, p.292,297-298

[33] CDC (1979). Human Rabies — United States. Morbidity and Mortality Weekly Report, Vol.28, pp.315-316,321

[34] CDC (1979). Human Rabies — California. Morbidity and Mortality Weekly Report, Vol.28, pp.435-436

[35] CDC (1979). Human Rabies — Oklahoma. Morbidity and Mortality Weekly Report, Vol.28, pp.476-481

[36] CDC (1979). Human Rabies — Kentucky. Morbidity and Mortality Weekly Report, Vol.28, pp.590-591

[37] CDC (1981). Human Rabies — Oklahoma. Morbidity and Mortality Weekly Report, Vol.30, pp.343-344,349

[38] CDC (1981). Human Rabies Acquired Oustide the United States from a Dog Bite. Morbidity and Mortality Weekly Report, Vol.30, No.43, pp.537-540

[39] CDC (1983). Imported Human Rabies. Morbidity and Mortality Weekly Report, Vol.32, No.6, pp.78-80,85-86

[40] CDC (1983). Human Rabies — Michigan. Morbidity and Mortality Weekly Report, Vol.32, No.12, pp.159-160

[41] CDC (1984). Human Rabies — Texas. Morbidity and Mortality Weekly Report, Vol.33, No.33, pp.469-470

[42] Smith, J.; Fishbein, D.; Rupprecht, C. & Clark, K. (1991). Unexplained Rabies in Three Immigrants in the United States. The New England Journal of Medicine, Vol.324, pp.205-211

[43] CDC (1984). Human Rabies — Pennsylvania. Morbidity and Mortality Weekly Report, Vol.33, No.45, pp.633-635

[44] CDC (1985). Human Rabies Acquired Outside the United States. Morbidity and Mortality Weekly Report, Vol.34, No.17, pp.235-236

[45] CDC (1985). Human Rabies Diagnosed 2 Months Postmortem — Texas. Morbidity and Mortality Weekly Report, Vol.34, No.46, pp.700,705-707

[46] CDC (1988). Human Rabies — California, 1987. Morbidity and Mortality Weekly Report, Vol.37, No.19, pp.305-308

[47] Dempsey, D. (1990). The Case of the Missing Animal. The Pediatric Infectious Diseases Journal. Vol.9, No.1, pp.49-50

[48] CDC (1989). Human Rabies — Oregon, 1989. Morbidity and Mortality Weekly Report, Vol.38, No.19, pp.335-337

[49] CDC (1991). Human Rabies — Texas, 1990. Morbidity and Mortality Weekly Report, Vol.40, No.8, pp.132-133

[50] CDC (1991). Human Rabies — Texas, Arkansas, and Georgia, 1991. Morbidity and Mortality Weekly Report, Vol.40, No.44, pp.765-769

[51] CDC (1992). Human Rabies — California, 1992. Morbidity and Mortality Weekly Report, Vol.41, No.26, pp.461-463

[52] CDC (1993). Human Rabies — New York, 1993. Morbidity and Mortality Weekly Report, Vol.42, No.41, pp.799,805-806

[53] CDC (1994). Human Rabies — Texas and California, 1993. Morbidity and Mortality Weekly Report, Vol.43, No.6, pp.93-96

[54] CDC (1994). Human Rabies — California, 1994. Morbidity and Mortality Weekly Report, Vol.43, No.25, pp.455-457

[55] CDC (1994). Human Rabies — Miami, 1994. Morbidity and Mortality Weekly Report, Vol.43, No.42, pp.773-775

[56] CDC (1995). Human Rabies — Alabama, Tennessee, and Texas, 1994. Morbidity and Mortality Weekly Report, Vol.44, No.14, pp.269-272

[57] CDC (1995). Human Rabies — West Virginia, 1994. Morbidity and Mortality Weekly Report, Vol.44, No.5, pp.86-87,93

[58] CDC (1995). Human Rabies — Washington, 1995. Morbidity and Mortality Weekly Report, Vol.44, No.34, pp.625-627

[59] CDC (1996). Human Rabies — California, 1995. Morbidity and Mortality Weekly Report, Vol.45, No.17, pp.353-356

[60] CDC (1996). Human Rabies — Connecticut, 1995. Morbidity and Mortality Weekly Report, Vol.45, No.10, pp.207-209

[61] CDC (1996). Human Rabies — Florida, 1996. Morbidity and Mortality Weekly Report, Vol.45, No.33, pp.719-720,727

[62] CDC (1997). Human Rabies — New Hampshire, 1996. Morbidity and Mortality Weekly Report, Vol.46, No.12, pp.267-270

[63] Scully, R.; Mark, E.; Mcneely, W.; Ebeling, S. & Phillips, L. (1998). Case 21-1998 — A 32-Year-Old Woman with Pharyngeal Spasms and Paresthesias after a Dog Bite. The New England Journal of Medicine, Vol.339, No.2, pp.105-112

[64] CDC (1997). Human Rabies — Kentucky and Montana, 1996. Morbidity and Mortality Weekly Report, Vol.46, No.18, pp.397-400

[65] CDC (1997). Human Rabies — Montana and Washington, 1997. Morbidity and Mortality Weekly Report, Vol.46, No.33, pp.770-774

[66] CDC (1998). Human Rabies — Texas and New Jersey, 1997. Morbidity and Mortality Weekly Report, Vol.47, No.1, pp.1-5

[67] CDC (1999). Human Rabies — Virginia, 1998. Morbidity and Mortality Weekly Report, Vol.48, No.5, pp.95-97

[68] CDC (2000). Human Rabies — California, Georgia, Minnesota, New York, and Wisconsin, 2000. Morbidity and Mortality Weekly Report, Vol.49, No.49, pp.1111-1115

[69] Soun, V.; Eidson, M.; Trimarchi, C.; Drabkin, P; Leach, R.; Wallace, B.; Jones, G.; Cantiello, K.; Qian, J. (2006). Antemortem Diagnosis of New York Human Rabies Case and Review of U.S. Cases. *International Journal of Biomedical Science*. Vol. 2, No. 4, (December 2006), pp.433-444

[70] Krebs, J.; Noll, H.; Rupprecht, C.; Childs, J. (2002). Rabies surveillance in the United States during 2001. *Journal of the American Veterinary Medical Association*. Vol. 221, No. 12, (December 2002), pp.1690-1701

[71] CDC (2002). Human Rabies — California, 2002. Morbidity and Mortality Weekly Report, Vol.51, No.31, pp.686-688

[72] CDC (2002). Human Rabies — Tenessee, 2002. Morbidity and Mortality Weekly Report, Vol.51, No.37, pp.828-829

[73] CDC (2003). Human Rabies — Iowa, 2002. Morbidity and Mortality Weekly Report, Vol.52, No.3, pp.47-48

[74] CDC (2003). First Human Death Associated with Raccoon Rabies — Virginia, 2003. Morbidity and Mortality Weekly Report, Vol.52, No.45, pp.1102-1103

[75] Krebs, J.; Mandel, E.; Swerdlow, D.; Rupprecht, C. (2004). Rabies surveillance in the United States during 2003. *Journal of the American Veterinary Medical Association*. Vol. 225, No. 12, (December 2004), pp.1837-1849

[76] CDC (2004). Human Rabies Death Associated with Bat Rabies — California, 2003. Morbidity and Mortality Weekly Report, Vol.53, No.2, pp.33-35

[77] CDC (2005). Human Rabies — Florida, 2004. Morbidity and Mortality Weekly Report, Vol.54, No.31, pp.767-769

[78] CDC (2004). Investigations of Rabies Infections in Organ Donor and Transplant Recipients — Alabama, Arkansas, Oklahoma, and Texas, 2004. Morbidity and Mortality Weekly Report, Vol.53, pp.1-3

[79] Srinivasan, A.; Burton, E.; Kuehnert, M.; et al (2005). Transmission of RABV from an organ donor to four transplant recipients. The New England Journal of Medicine, Vol.352, No.11, pp.1103-1111

[80] Willoughby, R.; Tieves, K.; Hoffman, G.; Ghanayem, N.; Amlie-Lefond, C.; Schwabe, M.; Chusid, M. & Rupprecht, C. (2005). Survival After Treatment of Rabies with Induction of Coma. The New England Journal of Medicine, Vol.352, No.24, pp.2508-2514

[81] CDC (2004). Recovery of a Patient from Clinical Rabies — Wisconsin, 2004. Morbidity and Mortality Weekly Report, Vol.53, No.50, pp.1171-1173

[82] Krebs, J.; Mandel, E.; Swerdlow, D.; Rupprecht, C. (2005). Rabies surveillance in the United States during 2004. *Journal of the American Veterinary Medical Association*. Vol. 227, No. 12, (December 2005), pp.1912-1925

[83] CDC (2006). Human Rabies — Mississippi, 2005. Morbidity and Mortality Weekly Report, Vol.55, No.8, pp.207-208

[84] Blanton, J.; Hanlon, C.; Rupprecht, C. (2006). Rabies surveillance in the United States during 2006. *Journal of the American Veterinary Medical Association*. Vol. 231, No. 4, (August 2007), pp.540-556

[85] Shah, U. (2007). Rabies Investigation & Response: A Multi-Disciplinary Approach, Proceedings of the 135th APHA Annual Meeting & Exposition, Washington, DC, USA, November 3-7, 2007

[86] CDC (2007). Human Rabies — Indiana and California, 2006. Morbidity and Mortality Weekly Report, Vol.56, No.15, pp.361-365

[87] CDC (2008). Human Rabies — Minnesota, 2007. Morbidity and Mortality Weekly Report, Vol.57, No.17, pp.460-462

[88] CDC (2009). Imported Human Rabies — California, 2008. Morbidity and Mortality Weekly Report, Vol.5, No.26, pp.713-716

[89] CDC (2009). Human Rabies — Missouri, 2008. Morbidity and Mortality Weekly Report, Vol.58, No.43, pp.1207-1209

[90] CDC (2010). Presumptive Abortive Human Rabies — Texas, 2009. Morbidity and Mortality Weekly Report, Vol.59, No.7, pp.185-190

[91] CDC (2010). Human Rabies — Kentucky/Indiana, 2009. Morbidity and Mortality Weekly Report, Vol.59, No.13, pp.393-396

[92] CDC (2011). Human Rabies — Michigan, 2009. Morbidity and Mortality Weekly Report, Vol.60, No.14, pp.437-440

[93] CDC (2010). Human Rabies — Virginia, 2009. Morbidity and Mortality Weekly Report, Vol.59, No.38, pp.1236-1238

[94] CDC (2011). Human Rabies from Exposure to a Vampire Bat — Louisiana, 2010. Morbidity and Mortality Weekly Report, Vol.60, No.31, pp.1050-1052

[95] CDC (2011). Human Rabies — Wisconsin, 2010. Morbidity and Mortality Weekly Report, Vol.60, No.34, pp.1164-1166