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ORIGINAL ARTICLE

A Large-scale, Rapid Public Health Response to Rabies in an Organ Recipient and the Previously Undiagnosed Organ Donor

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Impacts

- Human-to-human transmission of rabies is thought to be a rare event. However, because rabies is invariably fatal once symptoms occur, public health investigations of human rabies cases are necessary to prevent further cases of this high-consequence disease.
- Delays in the diagnosis of rabies can obfuscate the recognition of an exposure, often resulting in more conservative treatment recommendations and increased use of rabies biologics.
- Good working inter-agency relationships across local, state, and federal lines are critical for the effective protection of public health in large, complex investigations.

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Summary

This article describes and contrasts the public health response to two human rabies cases: one organ recipient diagnosed within days of symptom onset and the transplant donor who was diagnosed 18 months post-symptom onset. In

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response to an organ-transplant-related rabies case diagnosed in 2013, organ donor and recipient investigations were conducted by multiple public health agencies. Persons with potential exposure to infectious patient materials were assessed for rabies virus exposure. An exposure investigation was conducted to determine the source of the organ donor's infection. Over 100 persons from more than 20 agencies spent over 2700 h conducting contact investigations in healthcare, military and community settings. The 564 persons assessed include 417 healthcare workers [5.8% recommended for post-exposure prophylaxis (PEP)], 96 community contacts (15.6% recommended for PEP), 30 autopsy personnel (50% recommended for PEP), and 21 other persons (4.8% recommended for PEP). Donor contacts represented 188 assessed with 20.2% recommended for PEP, compared with 5.6% of 306 recipient contacts recommended for PEP. Human rabies cases result in substantial use of public health and medical resources, especially when diagnosis is delayed. Although rare, clinicians should consider rabies in cases of encephalitis of unexplained aetiology, particularly for cases that may result in organ donation.

Introduction

Rabies is a neurotropic virus with the highest mortality rate of known infectious diseases (Rupprecht and Peterson, 2011). Globally, more than 55 000 persons die of rabies annually; however, human rabies is rare in the United States (Rupprecht and Peterson, 2011; Blanton et al., 2012). When a human rabies case is identified in the US, public health investigations must be conducted to identify persons who had contact with the patient, to provide appropriate recommendations for post-exposure prophylaxis (PEP) and prevent disease (Manning et al., 2008).

Most rabies infections are acquired from the bite of an infected animal; however, tissue and organs from patients who died of undiagnosed rabies have resulted in death several weeks after transplantation (Srinivasan et al., 2005; Bronnert et al., 2007). While organ and tissue transplantation is the only mechanism of human-to-human transmission that has been laboratory confirmed, it is theoretically possible for human-to-human transmission to occur if mucous membranes or non-intact skin come in contact with the saliva, neural tissue, cerebrospinal fluid (CSF) or tears from a person infected with rabies (Fekadu et al., 1996; Manning et al., 2008). Symptoms typically develop 3–12 weeks after infection, although longer incubation periods of over 1 year have been noted. PEP is not effective after symptom onset and must be initiated as soon after exposure as possible (Manning et al., 2008; Rupprecht and Peterson, 2011). Thus, all persons potentially exposed to a patient with rabies need to be rapidly identified and assessed.

In February 2013, a Maryland resident was diagnosed with rabies following a 4-week clinical illness that presented as hip pain and progressed to weakness, ataxia and rapid neurologic decline (Vora et al., 2013). No animal exposures were identified. The patient had received a kidney transplant 17 months prior to symptom onset, a potential incubation period much longer than the 6 weeks previously reported for transplant-associated rabies infections (Srinivasan et al., 2005; Bronnert et al., 2007). However, the possibility of transplant-acquired infection was considered, and organ donor tissue stored since 2011 was obtained for testing. Within 5 days of the recipient's diagnosis, rabies antigen was identified in archived brain tissue from the kidney donor. Genetic sequences were identical to virus from the recipient, confirming kidney transplantation as the source of infection. The genetic sequence was closely associated with a raccoon variant circulating in North Carolina, the donor's state of residence. The donor's heart, liver and second kidney had been transplanted into three other recipients. Given the high consequences of rabies infection, the long incubation period observed in the kidney recipient and the limited data regarding raccoon rabies pathogenesis in humans, the Centers for Disease Control and Prevention (CDC) recommended contact investigations be conducted for persons with exposures to the organ donor and donor tissues and the deceased kidney recipient (Centers for Disease C, Prevention, 2003; Affairs UDoV, 2012).

We describe a well-coordinated, intensive multiagency effort to perform these contact investigations among the numerous healthcare workers, family and community members potentially exposed to rabies virus.

Methods

Investigation coordination and communications

An incident command-like structure was implemented at the CDC whereby individuals were assigned specific roles. This structure allowed the coordination of multiple rabies

exposure investigations between local, state and federal public health agencies, the Department of Defense (DoD), an organ procurement organization, and clinical entities. Coordination was achieved through multiple daily conference calls in which topics such as risk assessment, PEP recommendations and updates regarding the progress of the investigation were discussed. State health departments managed in-state investigational activities in coordination with local health officials. Because both the organ donor and recipient received some of their care at military medical facilities, the DoD facilitated military hospital contact investigations. CDC provided overall coordination, situational awareness, risk assessment and PEP guidance, and educational materials.

Exposure investigation – organ donor

Representatives from the state health department of the donor's state of residence and from the DoD notified the family of the organ donor's post-humous diagnosis of rabies. Family and friends were interviewed to assess the organ donor's potential rabies exposures in the 5 years prior to death and to determine his travel history to facilitate contact investigations during the potential infectious period.

Contact investigations – organ donor, deceased organ recipient and asymptomatic recipients

Contact investigations were conducted using standardized questionnaires that assessed mucous membrane or broken skin exposure to infected saliva, neural tissue, CSF or tears. The risk assessment tools were adapted to assess unique exposures that might exist within certain risk groups. For example, healthcare workers were additionally queried about high-risk procedures (e.g. intubation, tracheal tube maintenance, lumbar puncture, nasogastric tube insertion, and other procedures involving the oral cavity) and the type of personal protective equipment (PPE) worn. For community contacts, the questionnaire specifically addressed social activities such as sharing of food, drink or utensils, intimate contact and other interactions that could result in exposure to infectious materials. Additional assessment tools were created for special circumstances, including for morticians, laboratory and autopsy personnel, and airline passengers in adjacent seats (Centers for Disease C, Prevention, 2010a, 2012a). The infectious period was determined to be the 14 days prior to symptom onset until death and decontamination of infectious materials. This infectious period was based on studies which have shown viral shedding up to 10 days prior to symptom onset in dogs, cats and ferrets (Tepsumethanon et al., 2004; Brown et al., 2011). The asymp-

tomatic shedding period has not been established in other species, and therefore, a more conservative period of 14 days was applied.

Healthcare workers involved in the medical care of the two patients with rabies were identified through review of medical records and interviews. Community contacts were identified through interviews with family members, community leaders, military instructors and classmates. Social media, including Google searches and Facebook, was used to help identify contacts and to determine the dates of social gatherings, commercial flights and other important events that occurred during the infectious period.

Healthcare facilities involved in the patients' care assumed primary responsibility for conducting risk assessments of potentially exposed hospital staff. State, local and DoD public health personnel conducted risk assessments of community contacts and other non-hospital employees. Public health departments assisted healthcare facilities with recommendations for PEP based on the results of risk assessments. The organ procurement organization provided information on all organs that were procured as well as contact information for the recipients. Medical facilities involved in the transplantation procedures worked with CDC and state health departments to notify recipients of the rabies exposure, oversee administration of PEP and obtain samples for serologic follow-up. Each group involved in conducting risk assessments provided an estimation of time spent on contact tracing and risk assessment activities.

In cases of animal bite transmission of rabies, urine has not been shown to harbour infectious virus. However, in a 2004 transplant-associated rabies case, a kidney recipient was found to have rabies antigen present throughout the kidney. This prompted concern for the possibility of shedding live virus in urine, and in that investigation, CDC issued expanded criteria for risk assessments in which urine, under certain conditions, was considered infectious (Baer, 1975; Centers for Disease C, Prevention, 2004a). In this current investigation, renal tissue from the donor and both kidney recipients was tested for rabies virus and guidance regarding the potential infectiousness of urine and renal tissue was developed based on these results.

Results

Investigation coordination and communications

Daily conference calls with local, state and federal partners ensured coordination and expedited contact tracing, problem solving and confirmation of information obtained through multiple sources. Regular conference call coordination was more efficient than communicating via confidential faxes and was not subject to public access requirements applicable in some states, which could poten-

tially violate the confidentiality of personal health information. For the intrastate responses, the responsible state health departments also coordinated detailed, real-time assessments through daily calls with involved partners, including local health departments and clinical facilities. Press releases were coordinated among local, state and federal partners using electronic mail and conference calls to ensure unified messaging to the public.

Exposure investigation – organ donor

The organ donor was an avid hunter and trapper with extensive exposures to wildlife. Family and friends reported two instances in which the donor was bitten by

raccoons: a bite on the right hand in February 2010 and a bite on an unspecified hand in January 2011 (Fig. 1). The second raccoon was reportedly healthy up to 4 weeks post-bite. The donor did not seek medical attention for either of his reported bite wounds. Neither raccoon was available for testing at the time of the exposure investigation.

Contact investigation – organ donor, infectious period August to September, 2011

The organ donor investigation was initiated 18 months after symptom onset (Fig. 2). Reported donor symptom onset began with bilateral hand paresthesias and nausea in
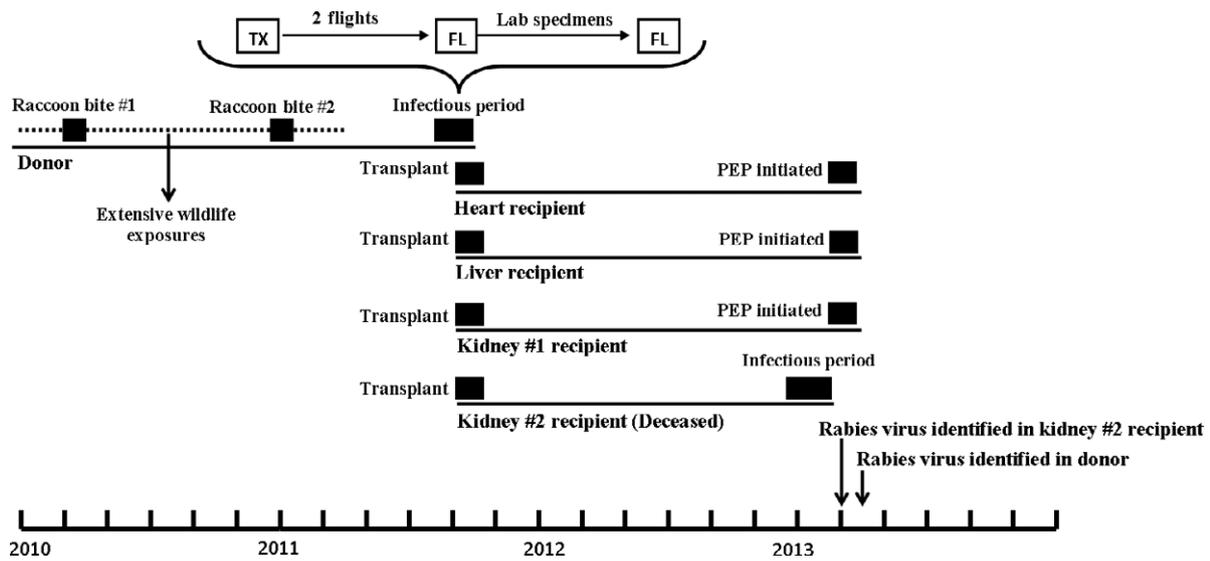

Fig. 1. Timeline of organ donation, organ transplantation and rabies diagnosis.
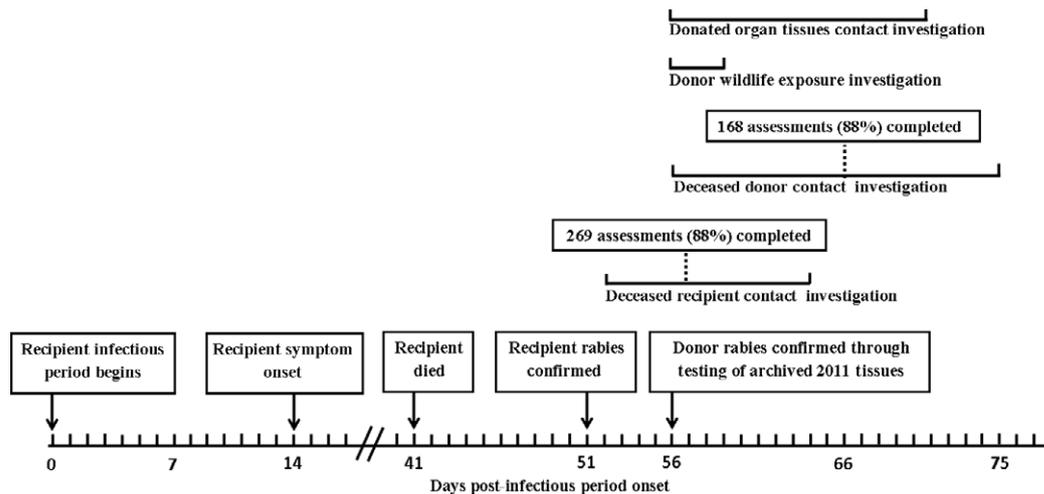

Fig. 2. Timeline of organ recipient's infectious period, rabies diagnosis and subsequent public health investigation.

August, 2011, which, at the time, was attributed to a jelly-fish sting and consumption of raw fish during the prior day's fishing trip. On day one of his infectious period, the donor flew to Florida on two commercial flights, during which time he was seated next to one passenger. The passenger was identified through military flight records and located through the use of social media. Risk assessment was performed, and no PEP was recommended. The donor remained on a Florida military base for days 2–18. Sixteen service members were identified who had interactions with the donor during this period. The service members were identified by reviewing the military death investigation report, a routine investigation conducted after any active duty military death. All 16 service men were contacted; three were recommended for PEP.

During days 16–20 of his infectious period, the donor sought care at a single military clinic four times and a military emergency department once. Fifty-two healthcare workers at the military medical facilities received risk assessments, and 14 were recommended for PEP. Four emergency medical services (EMS) personnel from two different services were involved in the donor's transport; none were recommended for PEP. On day 20, the patient was transferred to a civilian hospital, where his condition deteriorated. He was declared brain dead, and organs were recovered on day 35 post-onset. During hospitalization at civilian facilities, 69 healthcare workers and 10 community contacts were potentially exposed. Two healthcare workers and three community contacts were recommended for PEP.

Twenty-five people were present for the donor autopsy, during which an oscillating saw was used to expose the brain and neural tissues were potentially aerosolized. Fifteen of those involved in the autopsy were recommended for PEP due to potential exposure to neural tissue or saliva. The donor's body was sent to a funeral home where two morticians prepared the body for burial; one reported not routinely using appropriate PPE and was recommended for PEP.

An organ procurement organization was involved in procuring the donor's organs and matching them with prospective recipients. Prior to transplantation, a questionnaire was administered to the organ donor's family to identify potential infectious disease risks. The questionnaire addressed rabies risk by inquiring about animal bite events occurring in the 6 months prior to illness. Both bite events reported by the family occurred more than 6 months prior to illness, and therefore, this question did not capture those potential rabies exposures. The only disease that would definitively render a potential organ donor ineligible is HIV infection. There is no current regulation to exclude a donor with unexplained encephalitis or mental status changes.

Contact investigation – deceased organ recipient – infectious period January to February, 2013

The deceased kidney recipient's onset of symptoms began in late January 2013 with hip pain (Fig. 1). The patient presented to emergency departments at two different facilities on days 15 and 17 of his infectious period. On day 19, the patient returned to the emergency department at the first facility and was admitted. The patient remained hospitalized at that facility until death on day 41. Within 2 h of the recipient's definitive diagnosis, 8 days after death, a rabies risk screening clinic was set up at the facility where the patient was hospitalized. A total of 236 risk assessments were conducted for healthcare workers, pathologists and laboratorians affiliated with the two medical facilities in which the recipient received care (Table 1). Eight were recommended for PEP following reported broken skin or mucous membrane contact with saliva or tears during examination, intubation, or while cleaning up intubation trays. Twenty-one surgical team members, ward and intensive care unit staff involved in the kidney transplant in 2011 were assessed; none were recommended for PEP.

Through interviews with family members and community contacts, 69 individuals were identified as potentially exposed and received risk assessments. Nine individuals, primarily family, were recommended to receive PEP because of known saliva or tear contact with mucous membranes (such as kissing the patient on the lips) or because saliva contact could not be ruled out.

Rabies virus was not detected in pre- and post-mortem kidney or urine from the deceased kidney recipient nor from the asymptomatic kidney recipient; thus, CDC recommended that urine did not present a risk of transmission. Tissue antigen results and accompanying guidance were not available until 19 days after initial recipient diagnosis. In the interim, 113 healthcare personnel were preliminarily evaluated for possible urine exposure; 94 healthcare workers, most (79%) of whom worked in nursing, reported possible contact with the patient's urine or renal tissue. One nurse, who reported high-risk exposure to urine, was already getting PEP based on earlier assessments. Solid tissue containing nerves, such as renal tissue from post-transplant biopsies, was considered infectious, consistent with published recommendations (Manning et al., 2008).

Contact investigation – asymptomatic organ recipients

The organ procurement organization provided contact information for the three additional recipients who received the donor's heart, other kidney and liver. No other donor tissues, including cornea, were transplanted. Rabies

Table 1. Contact investigation summary table for contacts of the deceased organ recipient, deceased organ donor, and donor tissue, by risk group

	Deceased organ recipient contact investigation					Deceased organ donor contact investigation					Organ transplantation teams investigation					Total assessed
	Potential contacts	Number assessed (%)	PEP recommended (%)	PEP recommended, received (%)	PEP without exposure	Potential contacts	Number assessed (%)	PEP recommended (%)	PEP recommended, received (%)	PEP without exposure	Potential contacts	Number assessed (%)	PEP recommended (%)	PEP recommended, received (%)	PEP without exposure	
Healthcare Workers, N (%)	227	227 (100)	8 (3.5)	8 (100)	1	125	123 (98.4)	16 (13.0)	11 (68.8)	6	68	67 (98.5)	0 (0.0)	0	0	417
Autopsy staff, N (%)	5	5 (100)	0 (0.0)	0	0	25	25 (100)	15 (60.0)	15 (100)	3						30
Laboratorians, N (%)	4	4 (100)	0 (0.0)	0	0	11	11 (100)	0 (0.0)	0	0						15
Morticians, N (%)	1	1 (100)	0 (0.0)	0	0	2	2 (100)	1 (50.0)	1 (100)	0						3
Community contacts, N (%)	69	69 (100)	9 (13.0)	9 (100)	1	27	27 (100)	6 (22.2)	6 (100)	2						96
Asymptomatic organ recipients, N (%)											3	3 (100)	3 (100)	3 (100)	0	3
Total	306	306 (100)	17 (5.6)	17 (100)	2	190	188 (98.9)	38 (20.2)	33 (86.8)	11	71	70 (98.6)	3 (4.3)	3 (100)	0	564

PEP, post-exposure prophylaxis.

PEP was started in the three asymptomatic solid organ recipients to prevent disease. All were seronegative for rabies virus neutralizing antibodies at the initiation of PEP. After completion of the five-dose ACIP-recommended PEP schedule for immunocompromised persons, all three recipients showed evidence of appropriate serum antibody response. Fifty-eight hospital personnel involved in the recipient transplant surgeries were identified; none were recommended for PEP. Ten people who handled post-surgical biopsy samples were identified; none were recommended for PEP.

Investigation summary

Based on estimates provided by each public health agency and healthcare facility involved in contact tracing and conducting risk assessments, we conservatively estimate that over 100 local and state public health officials, clinicians, CDC and DoD representatives spent over 2700 h conducting contact investigation activities. These activities do not include time spent on diagnosis by laboratories, communications and outreach efforts, and other activities that were not directly part of the contact investigations. The rabies investigation of the deceased organ recipient identified and completed risk assessments for 269 of 306 (88%) potential contacts within 6 days of confirmation of the recipient rabies diagnosis (Fig. 2). All risk assessments were completed within 13 days. The organ donor investigation identified and conducted risk assessments for 165 of 190 (88%) potential contacts within 10 days of confirmation of rabies diagnosis. All risk assessments were completed within 19 days.

Upon completion of the contact investigations, data collected from risk assessments and PEP recommendations were reviewed to characterize the exposures. Healthcare workers represented 417 (74%) of the 564 persons assessed; 5.8% of healthcare workers were recommended for PEP (Table 1). Of the 96 community contacts identified, 15.6% were recommended for PEP. Fifteen of 25 (60%) people associated with the donor autopsy were recommended for PEP. In total for all investigations, 58 people were recommended for PEP.

Of those potentially exposed to the donor or donor tissues in 2011, 41 of 258 (15.9%) were recommended for PEP, compared with 17 of 306 (5.6%) potentially exposed in 2013 to the deceased recipient. Of those potentially exposed in 2011, 11 (5.8%) received PEP outside of recommendations compared with 2 (0.7%) who were exposed in 2013. In total, persons exposed in 2011 were 3-fold more likely to receive PEP compared with persons exposed in 2013. Of the 41 recommended for PEP, twelve were healthcare workers who reported routinely using appropriate PPE and who had not filed incident reports during the donor's

Table 2. Types of exposure by source of infectious material

Type of exposure	Deceased organ donor contact investigation PEP recommended, N (%)	Deceased organ recipient contact investigation PEP recommended, N (%)
Saliva contact	6 (15.8)	11 (64.7)
Tears contact	1 (2.6)	1 (5.9)
Saliva and tears contact	4 (10.5)	5 (29.4)
Neural tissue contact	15 (39.5)	0 (0.0)
Involved in patient care, unable to recall details	12 (31.6)	0 (0.0)
Total PEP	38 (100)	17 (100)

PEP, post-exposure prophylaxis.

hospitalization, but could not recall details about potential exposures after such an extended period (Table 2). All who received PEP in this response tolerated the regimen well, and no severe adverse events were reported.

Discussion

The public health response involved partnerships and coordinated communications among CDC, DoD, 13 state health departments, nine local health departments, three foreign Ministries of Health, five federal and civilian hospitals, pathologists, morticians, EMS technicians, laboratorians and a commercial airline. The large and well-coordinated effort resulted in the rapid assessment of hundreds of potentially exposed individuals, despite the challenges that arose as a result of delayed rabies diagnosis in the donor (Fig. 3). This rapid response was critical to allay concerns and anxiety and to ensure the timely administration of PEP, particularly for healthcare workers who accounted for three quarters of the case contacts. The development of generic and tailored risk assessment templates prior to an exposure event can facilitate a more rapid public health response.

Despite the overall speed and consistency with which the response was conducted, there were notable differences between the contact investigation for the deceased recipient, which began 7 weeks after symptom onset, and that of the donor, which began 18 months after symptom onset. The organ donor contact investigation took nearly 50% longer than the recipient investigation, primarily due to difficulties in locating persons such a long time after exposure. Military affiliation aided in expedited identification of contacts due, in part, to the extensive communication network and electronic health record. However, overseas travel among military service members delayed risk assessment completion and accounted for those who were not contacted until the third week of the donor investigation. In addition, given the long delay between exposure and
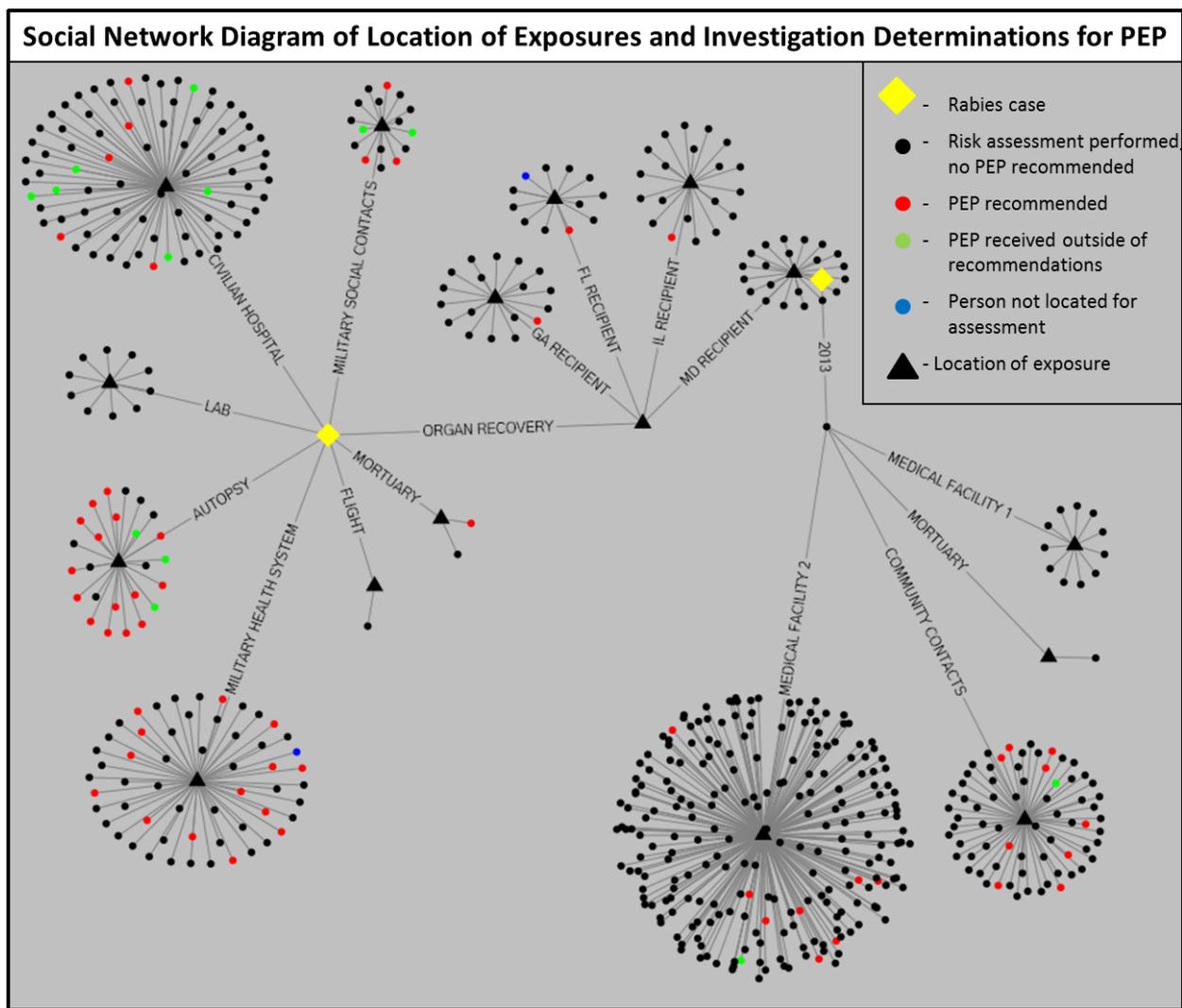
Fig. 3. Contact investigation social network diagram.

diagnosis, some contacts had moved to other geographic locations, complicating contact tracing.

Severe adverse events related to PEP are rare; however, they are possible (Dobardzic et al., 2007; Mattner et al., 2007a; Mattner et al., 2007b; Manning et al., 2008; Mahamat et al., 2012). Therefore, unnecessary administration of PEP during a contact investigation should be avoided. Organ donor contacts were more likely to seek PEP outside of recommendations compared with contacts of the deceased organ recipient. This proportion was also higher than has been documented in other rabies investigations (Centers for Disease C, Prevention, 2010b, 2011, 2012b, 2012c, 2012d). Concerns about being able to recall exposures, which occurred 18 months prior to risk assessment, were cited as an indication for PEP, particularly among healthcare workers for whom PEP was recommended. As a result of these more conservative PEP recom-

mendations based on potential but unconfirmed exposures, persons identified as contacts of the organ donor were more likely to be recommended for PEP. Other rabies investigations have also reported higher PEP recommendation rates when risk assessments were delayed (Centers for Disease C, Prevention, 2012a).We are not aware of any severe adverse events in those who received PEP during this response. However, with increased PEP administration, the potential for adverse events rises; therefore, timely risk assessments should be conducted to ensure proper administration of PEP. It is also important to note that in instances where exposures occurred well in the past and more people are likely to receive PEP, regionally available supplies of rabies biologics could be strained.

Mass media have been used in past rabies investigations following exposures to rabid animals (Centers for Disease C, Prevention, 1995, 1999), although it was not required to

identify potential contacts in this investigation. Social media, however, did play an invaluable role in identifying and contacting contacts. While the utility of rapidly evolving technologies such as social media for public health purposes must be acknowledged, it is imperative that investigators who use social media for public health purposes stay mindful of maintaining protections for patient privacy and confidentiality (Eysenbach, 2009).

Community contacts were far more likely to report an exposure that warranted PEP than healthcare workers. This may be because family members are more likely to engage in intimate behaviours, such as kissing, that could result in saliva contact (Munoz et al., 2002; Siegel et al., 2007). Standard precautions are recommended to prevent transmission of rabies in the healthcare setting and include hand hygiene, use of gloves, gown, mask, eye protection, or face shield, depending on the anticipated exposure, and safe injection practices (Siegel et al., 2007). The appropriate use of PPE, good infection prevention practices, and technologies such as closed suctioning systems that reduce healthcare provider contact with patient secretions in the healthcare setting undoubtedly contributed to the fewer number of recommendations for PEP in the healthcare community.

Many trainees were present for the donor's autopsy as part of routine forensic training, which resulted in more exposures than a typical autopsy. Persons involved in autopsies can be exposed to a multitude of infectious agents and must take care to prevent exposure, especially when the cause of death is unknown. Autopsy examinations were conducted using standard biosafety level two precautions to protect against commonly encountered pathogens (Nolte et al., 2002). Proper PPE, including use of N95 respirators and face protection, has been reported to offer sufficient protection for aerosolized brain matter, as may have occurred when the oscillating saw was used during the donor's autopsy (Centers for Disease C, Prevention, 2010a). The universal use of N95 masks in all autopsy exams has been recommended (Froede, 2003). However, in practice, this recommendation has not been widely adopted. This event demonstrates why these recommendations should be routinely implemented.

Although risk questionnaires administered to next of kin included items meant to elucidate rabies exposure, a more standardized approach for assessing rabies exposures among potential organ donors is warranted. As part of continued approaches to improve transplant safety, future efforts may include recommending post-mortem rabies diagnosis on CNS tissue from potential donors with unexplained encephalitis. In instances where rabies is found to be the cause of death, all organ and tissue recipients should be considered for PEP per published guidelines. This case highlights the need for a more standardized approach to recognizing organ donors with unexplained infectious encephalitis or where rabies is considered a differential diagnosis.

During investigation of a previous transplant-associated cluster of rabies, rabies virus antigen was detected in high concentrations throughout kidney tissue from one recipient, and thus in contrast to standard recommendations, renal tissue and concentrated urine containing cellular debris were considered potentially infectious (Manning et al., 2008; Centers for Disease C, Prevention, 2004b). In this investigation, no evidence of rabies virus was detected in donor kidney tissues or urine from kidney recipients, and urine was not considered infectious. Reaching this determination, in addition to assessing exposures to urine from the kidney recipients, increased the burden of the response in comparison with more routine investigations following bite-acquired rabies.

Conclusion

When faced with an urgent need to respond to this low incidence, high-consequence disease, public health agencies and their clinical partners acted quickly to mitigate the risk of rabies transmission from two human rabies patients. Specific concerns unique to this investigation included identification and assessment of contacts following an extended time since exposure, determination of whether tissues and fluids not routinely considered infectious for rabies presented a risk to contacts, management of asymptomatic recipients who had received rabies virus-infected organs, and implementation of a single, rapid and coordinated response through the efforts of multiple distinct jurisdictional and geographic boundaries. These challenges were successfully met with the critical goal of ensuring prompt and appropriate PEP administration.

Acknowledgements

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