Immunoglobulin G against Whitewater Arroyo virus or lymphocytic choriomeningitis virus was found in 41 (3.5%) of 1,185 persons in the United States who had acute central nervous system disease or undifferentiated febrile illnesses. The results of analyses of antibody titers in paired serum samples suggest that a North American Tacaribe serocomplex virus was the causative agent of the illnesses in 2 persons and that lymphocytic choriomeningitis virus was the causative agent of the illnesses in 3 other antibody-positive persons in this study. The results of this study suggest that Tacaribe serocomplex viruses native to North America, as well as lymphocytic choriomeningitis virus, are causative agents of human disease in the United States.

The arenaviruses (family Arenaviridae, genus Arenavirus) known to occur in North America include Whitewater Arroyo virus (WWAV), 7 other members of the Tacaribe serocomplex (Table 1), and lymphocytic choriomeningitis virus (LCMV, the prototypic member of the lymphocytic choriomeningitis–Lassa serocomplex). Specific members of the order Rodentia are the principal hosts of the arenaviruses, for which natural host relationships have been well characterized. For example, the hispid cotton rat (Sigmodon hispidus) in Florida is the principal host of Tamiami virus (6,7), and the ubiquitous house mouse (Mus musculus) is the principal host of LCMV (9).

Five South American members of the Tacaribe serocomplex, LCMV, and Lassa virus are etiologic agents of severe febrile illnesses in humans (10,11). The human health significance of the North American Tacaribe serocomplex viruses has not been rigorously investigated (12).

Studies since the mid-1990s have shown that Tacaribe serocomplex viruses are widely distributed in the United States and Mexico and that woodrats (Neotoma spp.) and other members of the family Cricetidae are natural hosts of these viruses (1–5,8,13,14). The purpose of this study was to investigate whether humans have been infected with North American Tacaribe serocomplex viruses.

Materials and Methods

Samples of serum (n = 1,305), plasma (n = 2), and cerebrospinal fluid (n = 70) from 1,185 persons in the United States with acute central nervous system disease or undifferentiated febrile illnesses were tested for immunoglobulin (Ig) G against the WWAV prototype strain AV 9310135 and LCMV strain Armstrong by using an ELISA as described (15). The samples were diagnostic specimens submitted to the Arbovirus Diseases Branch, Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC) (Fort Collins, CO, USA) during 1989–2000 by public health laboratories in the United States. The samples had been tested selectively by CDC laboratorians for evidence of infection with St. Louis encephalitis virus, western equine encephalomyelitis virus, and other arthropod-borne agents of human disease. These tests had not yielded a specific diagnosis for any of the cases in this study.

Information about each case was limited to patient age, sex, date of illness onset, and state from which the samples were submitted. Most (634 [53.5%]) of the 1,185 case-patients were male. Ages at illness onset ranged from 0.2 months to 93 years (median 35 years), and 982 (82.0%) of the case-patients were ≥10 years of age at illness onset.
A 1:80 dilution and 1:320 dilution of each sample was tested against the WWAV antigen, LCMV antigen, and corresponding comparison (negative-control) antigens. The adjusted optical density (AOD) of a sample-antigen reaction was the optical density of the well coated with the test antigen minus the optical density of the well coated with the corresponding control antigen. A sample was considered positive if the AOD at 1:80 was \( \geq 0.250 \), the AOD at 1:320 was \( \geq 0.250 \), and the sum of the AOD at 1:80 and AOD at 1:320 was \( \geq 0.750 \). Endpoint titers against each antigen were measured in the positive samples by using serial 2-fold dilutions from 1:320 through 1:40,960. The antibody titer of a positive sample was the reciprocal of the highest dilution for which the AOD was \( \geq 0.250 \). Titers <320 were 160 in comparisons of titers to WWAV and LCMV in individual samples. The apparent homologous virus in an antibody-positive sample was the virus associated with the highest titer if the absolute value of the difference between the titers to WWAV and LCMV was \( \geq 4 \)-fold.

### Results

We detected antibody against an arenavirus in 41 (3.5%) of the 1,185 case-patients. Of the antibody-positive case-patients, most (27 [65.9%]) were male. Ages ranged from 4 years to 85 years (median 39 years). Antibody-positive samples were submitted from Florida, Massachusetts, and Wyoming (3 samples each) and Arizona, Idaho, Kansas, Maryland, Michigan New Mexico, New York, North Carolina, Ohio, Rhode Island, Tennessee, Washington, and Wisconsin (1 sample each). For 19 samples, state of submission was unknown.

Twelve persons had positive test results for WWAV but not LCMV; 28 for LCMV but not WWAV; and 1 for WWAV and LCMV (Table 2). In the positive samples, endpoint titers against WWAV and LCMV ranged from \( <320 \) to 10,240 and from \( <320 \) to 20,480, respectively. The apparent homologous virus was WWAV in 10, LCMV in 24, and indeterminate in 7 of antibody-positive persons (Table 2).

Ages of the 10 persons in whom WWAV was the apparent homologous virus ranged from 5 to 70 years (median 43 years). Samples from these persons were submitted from Arizona, New Mexico, and North Carolina (1 sample each) and Florida and Wyoming (2 samples each); for 3 samples, state of submission was unknown.

The ELISA included paired samples from 8 antibody-positive persons. Time from onset of illness to the first samples from these persons ranged from 0 to 47 days. In side-by-side tests, the endpoint titer to WWAV in the second sample was \( \geq 4 \)-fold higher than that to WWAV in the first sample in paired samples from 2 persons, and the endpoint titer to LCMV in the second sample was \( \geq 4 \)-fold higher than that to LCMV in the first sample in paired samples from 3 of the 6 other antibody-positive persons (Table 3).

### Table 1. Natural hosts and geographic distribution of the North American Tacaribe serocomplex viruses

| Virus                     | Natural host(s)                                      | Location            | Reference |
|---------------------------|------------------------------------------------------|---------------------|-----------|
| Bear Canyon               | Large-eared woodrat (Neotoma macrotis), California mouse (Peromyscus californicus) | California, USA     | (1)       |
| Big Brushy Tank           | White-throated woodrat (N. albigua)                  | Arizona, USA        | (2)       |
| Catarina                  | Southern plains woodrat (N. micropus)                | Texas, USA          | (3)       |
| Rio Catorce               | White-toothed woodrat (N. leucodon)                  | San Luis Potosí, Mexico | (4)     |
| Skinner Tank              | Mexican woodrat (N. mexicana)                        | Arizona, USA        | (5)       |
| Tamiami                   | Hidist cotton rat (Sigmodon hispidus)                | Florida, USA        | (6, 7)    |
| Tonto Creek               | White-throated woodrat (N. albigua)                  | Arizona, USA        | (2)       |
| Whitewater Arroyo         | White-throated woodrat (N. albigua)                  | New Mexico, USA     | (8)       |

### Table 2. Antibody (immunoglobulin G) titers against WWAV and LCMV in 1,185 cases of acute central nervous system disease or undifferentiated febrile illnesses, United States*

| No. cases | WWAV  | LCMV  | Apparent homologous virus |
|-----------|-------|-------|---------------------------|
| 5         | 640   | <320  | WWAV                      |
| 1         | 1,280 | <320  | WWAV                      |
| 3         | 2,560 | <320  | WWAV                      |
| 1         | 10,240| <320  | WWAV                      |
| 7         | <320  | 640   | LCMV                      |
| 3         | <320  | 1,280 | LCMV                      |
| 5         | <320  | 2,560 | LCMV                      |
| 4         | <320  | 5,120 | LCMV                      |
| 2         | <320  | 10,240| LCMV                      |
| 3         | <320  | 20,480| LCMV                      |
| 2         | 320   | <320  | Indeterminate             |
| 1         | 640   | 1,280 | Indeterminate             |
| 4         | <320  | 320   | Indeterminate             |
| 1,144     | <320  | <320  | None                      |

*WWAV, Whitewater Arroyo virus; LCMV, lymphocytic choriomeningitis virus.

The period between illness onset and sample collection ranged from 0 days to 10.1 years (median 31 days). At least 1 sample from each of 580 case-patients was collected before the end of week 4 of illness; for 108 case-patients multiple samples, representing different time points, were available. Cases were geographically distributed as follows: New England, 72 cases; Mid-Atlantic, 50; South Atlantic, 141; East North Central, 96; West North Central, 73; East South Central, 78; West South Central, 42; Mountain, 177; Pacific, 96; and unknown, 360.

The ELISA included paired samples from 8 antibody-positive persons. Time from onset of illness to the first samples from these persons ranged from 0 to 47 days. In side-by-side tests, the endpoint titer to WWAV in the second sample was \( \geq 4 \)-fold higher than that to WWAV in the first sample in paired samples from 2 persons, and the endpoint titer to LCMV in the second sample was \( \geq 4 \)-fold higher than that to LCMV in the first sample in paired samples from 3 of the 6 other antibody-positive persons (Table 3).
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 8, August 2011 1419

Some of these include de

the North American Tacaribe serocomplex viruses should

illness onset.

10,240 in a serum sample collected on day 22 day after

in the antibody-positive person from New Mexico was

serocomplex or by LCMV. The antibody titer to WWAV

these illnesses were caused by a North American Tacaribe

in this study were limited to single specimens. Perhaps

maintained at CDC.

clinical laboratories could not be determined from records

were tested for anti-LCMV antibody (IgM or IgG) by

that the illnesses in case-patients 4–6 (Table 3) were

disseminated disease (18).

The results of this study suggest

The severity of human disease caused by LCMV

ranges from mild febrile illness to severe encephalitis and

and disseminated disease (18). The results of this study suggest

that the illnesses in case-patients 4–6 (Table 3) were

caused by LCMV. Whether samples from these 3 persons

were tested for anti-LCMV antibody (IgM or IgG) by

clinical laboratories could not be determined from records

maintained at CDC.

Specimens from 33 of the antibody-positive persons

in this study were limited to single specimens. Perhaps

these illnesses were caused by a North American Tacaribe

serocomplex or by LCMV. The antibody titer to WWAV

in the antibody-positive person from New Mexico was

10,240 in a serum sample collected on day 22 day after

illness onset.

Future studies on the relevance to human health of the

North American Tacaribe serocomplex viruses should

include defining the clinical spectrum and epidemiology

of human disease caused by these viruses. Some of these

viruses may cause aseptic meningitis, encephalitis, or

meningoencephalitis. Thus, human disease caused by North

American Tacaribe serocomplex viruses may be confused

with severe encephalitis caused by LCMV, especially in

persons who report recent exposure to rodents.

Acknowledgments

We thank Amanda Panella, Nick Karabatsos, and Stacey

Bartlett for technical support.

Financial support for the work done by M.L.M. and C.F.F.

was provided by National Institutes of Health grant AI-41435,

“Ecology of emerging arenaviruses in the southwestern United

States.”

Ms Milazzo is a senior research associate at the University of

Texas Medical Branch, Galveston. Her scientific interests include

the epidemiology and ecology of New World rodent–borne RNA

viruses.

References

1. Cajimat MNB, Milazzo ML, Hess B, Rood M, Fulhorst CF. Principal

host relationships and evolutionary history of the North

American arenaviruses. Virology. 2007;367:255–43. doi:10.1016/j.

virol.2007.05.031

2. Milazzo ML, Cajimat MNB, Haynie ML, Abbott KD, Bradley RD,

Fullhorst CF. Diversity among Tacaribe serocomplex viruses (family

Arenaviridae) naturally associated with the white-throated woodrat

(Notomys albivaga) in the southwestern United States. Vector Borne

Zoonotic Dis. 2008;8:523–40. doi:10.1089/vbz.2007.0239

3. Cajimat MNB, Milazzo ML, Bradley RD, Fullhorst CF. Catarina

virus, an arenaviral species principally associated with

Neotoma mexicana (southern plains woodrat) in Texas. Am J Trop Med Hyg.

2007;77:732–6.

4. Inizan CC, Cajimat MNB, Milazzo ML, Barragán-Gomez A, Brad-

ley RD, Fullhorst CF. Genetic evidence for a Tacaribe serocomplex

virus, Mexico. Emerg Infect Dis. 2010;16:1007–10.

5. Cajimat MNB, Milazzo ML, Borchert JN, Abbott KD, Bradley RD,

Fullhorst CF. Diversity among Tacaribe serocomplex viruses (fam-

ily Arenaviridae) naturally associated with the Mexican woodrat

(Notomys mexicana). Virus Res. 2008;133:211–7. doi:10.1016/j.

viruses.2008.01.005

6. Calisher CH, Ziaiabos T, Lord RD, Coleman PH. Tamiami virus,

a new member of the Tacaribe group. Am J Trop Med Hyg.

1970;19:520–6.

Table 3. Antibody (immunoglobulin G) against WWAV and LCMV in paired serum samples from humans with acute central nervous system disease or undifferentiated febrile illnesses, United States*

| Case-patient no. | Age, y, at illness onset | Days after illness onset | Antibody titer, WWAV | Antibody titer, LCMV | Apparent homologous virus |
|------------------|-------------------------|-------------------------|----------------------|---------------------|--------------------------|
|                  | S1                      | S2                      | S1                   | S2                  |                          |
| 1                | 32                      | 14                      | <320                 | 640                 | WWAV                     |
| 2                | 65                      | 15                      | <320                 | 2,560               | WWAV                     |
| 3                | 38                      | 14                      | <320                 | <320                | LCMV                     |
| 4                | 51                      | 2                       | <320                 | <320                | LCMV                     |
| 5                | 59                      | 24                      | <320                 | <320                | LCMV                     |
| 6                | 72                      | 0                       | <320                 | <320                | LCMV                     |
| 7                | 12                      | 25                      | <320                 | 320                 | LCMV                     |
| 8                | 25                      | 47                      | <320                 | 320                 | LCMV                     |

*WWAV, Whitewater Arroyo virus; LCMV, lymphocytic choriomeningitis virus; S1, first sample; S2, second (last) sample in paired samples.

Discussion

Previously, antibody to Tamiami virus was found in

5 (3.8%) of 131 Seminole Indians sampled in southern

Florida (16), and antibody to a Tacaribe serocomplex virus

was found in 2 (0.24%) of 829 persons who had worked

with cricetid rodents in North America (15,17). The results

of our current study strengthen the notion that Tacaribe

serocomplex viruses enzootic in North America are

infectious in humans. The increase in antibody titer against

WWAV in cases 1 and 2 in this study (Table 3) suggests

that a North American Tacaribe serocomplex virus caused

the illnesses in these persons.

The WWAV strain AV 9310135 was originally

isolated from a white-throated woodrat (N. albigula)
captured in northwestern New Mexico (8). A recent study

demonstrated a high level of diversity among the amino acid

sequences of the structural proteins of the North American

Tacaribe serocomplex viruses (5). Hypothetically, human

IgG against some North American Tacaribe serocomplex

viruses is not strongly reactive against WWAV in ELISA.

If so, the prevalence of antibody to Tacaribe serocomplex

viruses in this study actually might be >3.5%.

The severity of human disease caused by LCMV

ranges from mild febrile illness to severe encephalitis and

Acknowledgments

We thank Amanda Panella, Nick Karabatsos, and Stacey

Bartlett for technical support.

Financial support for the work done by M.L.M. and C.F.F.

was provided by National Institutes of Health grant AI-41435,

“Ecology of emerging arenaviruses in the southwestern United

States.”

Ms Milazzo is a senior research associate at the University of

Texas Medical Branch, Galveston. Her scientific interests include

the epidemiology and ecology of New World rodent–borne RNA

viruses.

References

1. Cajimat MNB, Milazzo ML, Hess B, Rood M, Fulhorst CF. Principal

host relationships and evolutionary history of the North

American arenaviruses. Virology. 2007;367:255–43. doi:10.1016/j.

virol.2007.05.031

2. Milazzo ML, Cajimat MNB, Haynie ML, Abbott KD, Bradley RD,

Fullhorst CF. Diversity among Tacaribe serocomplex viruses (family

Arenaviridae) naturally associated with the white-throated woodrat

(Notomys albivaga) in the southwestern United States. Vector Borne

Zoonotic Dis. 2008;8:523–40. doi:10.1089/vbz.2007.0239

3. Cajimat MNB, Milazzo ML, Bradley RD, Fullhorst CF. Catarina

virus, an arenaviral species principally associated with

Neotoma microps (southern plains woodrat) in Texas. Am J Trop Med Hyg.

2007;77:732–6.

4. Inizan CC, Cajimat MNB, Milazzo ML, Barragán-Gomez A, Brad-

ley RD, Fullhorst CF. Genetic evidence for a Tacaribe serocomplex

virus, Mexico. Emerg Infect Dis. 2010;16:1007–10.

5. Cajimat MNB, Milazzo ML, Borchert JN, Abbott KD, Bradley RD,

Fullhorst CF. Diversity among Tacaribe serocomplex viruses (fam-

ily Arenaviridae) naturally associated with the Mexican woodrat

(Notomys mexicana). Virus Res. 2008;133:211–7. doi:10.1016/j.

viruses.2008.01.005

6. Calisher CH, Ziaiabos T, Lord RD, Coleman PH. Tamiami virus,

a new member of the Tacaribe group. Am J Trop Med Hyg.

1970;19:520–6.
7. Jennings WL, Lewis AL, Sather GE, Pierce LV, Bond JO. Tamiami virus in the Tampa Bay area. Am J Trop Med Hyg. 1970;19:527–36.
8. Fulhorst CF, Bowen MD, Kisazek TG, Rollin PE, Nichol ST, Kosoy MY, et al. Isolation and characterization of Whitewater Arroyo virus, a novel North American arenavirus. Virology. 1996;224:114–20. doi:10.1006/viro.1996.0512
9. Childs JE, Peters CJ. Epidemiology and ecology of arenaviruses and their hosts. In: Salvato MS, editor. The Arenaviridae. New York: Plenum Press; 1993. p. 331–84.
10. Delgado S, Erickson BR, Agudo R, Blair PJ, Vallejo E, Albariño CG, et al. Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. PLoS Pathog. 2008;4:e1000047. doi:10.1371/journal.ppat.1000047
11. Peters CJ. Human infection with arenaviruses in the Americas. Curr Top Microbiol Immunol. 2002;262:65–74.
12. Centers for Disease Control and Prevention. Fatal illnesses associated with a New World arenavirus—California, 1999–2000. MMWR Morb Mortal Wkly Rep. 2000;49:709–11.
13. Milazzo ML, Barragán-Gomez A, Hanson JD, Estrada-Franco JG, Arellano E, González-Cózatl FX, et al. Antibodies to Tacaribe serocomplex viruses (family Arenaviridae, genus Arenavirus) in cricetid rodents from New Mexico, Texas, and Mexico. Vector Borne Zoonotic Dis. 2010;10:629–37. doi:10.1089/vbz.2009.0206
14. Musser GG, Carleton MD. Family Cricetidae. In: Wilson DE, Reeder DM, editors. Mammal species of the world. A taxonomic and geographic reference. 3rd ed. Baltimore: Johns Hopkins University Press; 2005. p. 955–1189.
15. Fulhorst CF, Milazzo ML, Armstrong LR, Childs JE, Rollin PE, Khabbaz R, et al. Hantavirus and arenavirus antibodies in persons with occupational rodent exposure, North America. Emerg Infect Dis. 2007;13:532–8. doi:10.3201/eid1304.061509
16. Tamiami (TAM) strain. W-10777. Am J Trop Med Hyg. 1970;19(Suppl):1157–8.
17. Fritz CL, Fulhorst CF, Enge B, Winthrop KL, Glaser CA, Vugia DJ. Exposure to rodents and rodent-borne viruses among persons with elevated occupational risk. J Occup Environ Med. 2002;44:962–7. doi:10.1097/00043764-200210000-00016
18. Peters CJ. Lymphocytic choriomeningitis virus—an old enemy up to new tricks. N Engl J Med. 2006;354:2208–11. doi:10.1056/NEJMp068021

Address for correspondence: Charles F. Fulhorst, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0609, USA; email: cfulhors@utmb.edu